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Prognosis and Outcomes of COVID-19 infection During Pregnancy

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Susceptibility to infection: At the beginning of the pandemic, there was a controversy whether the immunological changes occurring in pregnancy would make the pregnant woman more vulnerable to contract SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) or not, and whether or not would the maternal COVID-19 (Coronavirus Disease, 2019) be more severe. Some authors initially argued that pregnancy could be protective against COVID-19 cytokine storm by lowering TNF- α (tumor necrosis factor-alpha) through downregulation of the proinflammatory activity of Th1 (T-helper cell type 1). It is now established that the pregnant population are, in general, not more vulnerable to acquire SARS-CoV-2; however, the clinical course of the disease may be more severe during pregnancy, and rapid deterioration may occur, especially after 28 weeks. Pregnancy increases a woman's chance of severe disease, hospitalization, ICU (intensive care unit) admission, and mechanical ventilation. Having severe COVID-19 increases the odds of preterm and cesarean delivery (CD) (Allotey et al., 2020; Badr et al., 2020; Delahoy et al., 2020; Ellington et al., 2020; Elshafeey et al., 2020; Hanna et al., 2020; Hessami et al., 2020; Khoury et al., 2020; Mor and Cardenas, 2010; Panagiotakopoulos et al., 2020; Poon et al., 2020; Zambrano et al., 2020a).

Clinical course of the disease and disease severity during pregnancy: The overall characteristics of the disease in pregnant women are similar to nonpregnant women, but with differences in the course of the disease and its severity. The commonest reported symptoms are fever and cough with rates 32.8% and 41.3% respectively, compared with 77% and 68% in the general population. Average duration of symptoms is approximately 1 month, although a quarter of patients can have some persistent symptoms for more than 2 months. Asymptomatic infection is hard to calculate: the Centers for Disease Control and Prevention (2020) gives an estimate of 40% in the general population, and the calculated range of asymptomatic infection for pregnant women in a very recent metaanalysis is 9%–30.9%. Initially asymptomatic pregnant women can present with subsequent severe COVID-19 and deteriorate rapidly. Pregnant women are less likely to report symptoms, which mimic physiological changes of pregnancy such as dyspnea, fatigue, myalgia, gastrointestinal symptoms, and even fever, which contributes in the delayed diagnosis amongst the pregnant population and first presentation in a severe form of the disease (Afshar et al., 2020; Allotey et al., 2020; Breslin et al., 2020; Centers for Disease Control and Prevention, 2020; Matar et al., 2021; Papapanou et al., 2021; World

Health Organization, 2020a; Xie et al., 2020; Zambrano et al., 2020a).

Commonest laboratory findings among COVID-19 pregnant women are lymphopenia (35%–69.6%), elevated C-reactive protein levels (48%–69%), and elevated D-dimers (82%–84.6%). However, interpretation of D-dimer levels differs during pregnancy due to the normally elevated levels during pregnancy. Regarding radiological findings, abnormal chest CT (computed tomography) scans are observed in 68.6% of pregnant women with COVID-19, with the most common patterns being ground glass opacities, almost always bilaterally (Allotey et al., 2020; Papapanou et al., 2021; Righini et al., 2008; Szecsi et al., 2010).

Severe disease and hospitalization: Definitions of severe and critical COVID-19 in pregnant women follow those of the general population (Table 6.1). Pneumonia occurs in 40%–49% of pregnant women with COVID-19. Around 31.9% of pregnant women are hospitalized, which is a high fraction knowing that hospitalization rate in nonpregnant women is 5.8%. However, it should be taken in consideration while interpreting these figures that part of the reported hospital admissions could be for the mere reason of delivery and not the disease severity itself. Severe illness necessitating hospital admission usually starts around 7 days after the onset of symptoms and requires an average hospital stay of 6 and 12 days for severe and critical disease, respectively (Allotey et al., 2020; Berghella and Hughes, 2021; Ellington et al., 2020; Narang et al., 2020; National Institutes of Health, 2020; Pierce-Williams et al., 2020; World Health Organization, 2020a).

It is not fully comprehended why pregnant women show a higher trend of having severe form of the disease. Angiotensin-converting enzyme 2 (ACE2) receptors have been verified to be the way through which SARS-CoV-2 gains access to the human cell. Perhaps the upregulation of ACE2 receptors, which occurs during pregnancy, could be an explanation of the different course of the illness in the unique pregnant population. Other contributing factors are increased oxygen consumption and reduced functional residual capacity normally occurring, which could aggravate the severity in patients with pneumonia (Ahlberg et al., 2020; Narang et al., 2020; Pringle et al., 2011; Stephens et al., 2020).

Black women seem more prone to SARS-CoV-2, along with Asian and other minority races. Risk factors for severe COVID-19 in the pregnant population include maternal age above 35 years, comorbidities such as hypertension and diabetes, obesity, and gestational diabetes. It is possible that comorbidities and COVID-19 share synergistic immunological and

TABLE 6.1
Definitions of Severe and Critical COVID-19.

	WHO: COVID-19 Disease Severity	NIH: Clinical Classification of COVID-19
Severe	<ul style="list-style-type: none"> Clinical signs of pneumonia (i.e., fever, cough, dyspnea, fast breathing) + <ul style="list-style-type: none"> One of the following: <ul style="list-style-type: none"> Respiratory rate >30 breaths/minute Severe respiratory distress SpO₂ <90% on room air 	One of the following: <ul style="list-style-type: none"> Respiratory frequency >30 breaths per minute SpO₂ <94% on room air at sea level PaO₂/FiO₂ <300 mmHg Lung infiltrates >50%
Critical	<ul style="list-style-type: none"> Presence of ARDS, sepsis, or septic shock Other complications include acute pulmonary embolism, acute coronary syndrome, acute stroke, and delirium 	<ul style="list-style-type: none"> People who have respiratory failure, septic shock, and/or multiple organ dysfunction

ARDS, acute respiratory distress syndrome; NIH, National Institutes of Health; PaO₂/FiO₂, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; SpO₂, saturation of peripheral oxygen; WHO, World Health Organization.

inflammatory pathways (Allotey et al., 2020; Ellington et al., 2020; Knight et al., 2020; Narang et al., 2020).

ICU admission and mechanical ventilation: ICU admission rates in maternal COVID-19 range between 3% and 13%, and rates of mechanical ventilation are between 1.5% and 4.3%. Risk factors for ICU admission are similar to the ordinary population, including obesity and preexisting morbidities such as diabetes and hypertension. Tables 6.2 and 6.3 show rates of ICU admission and mechanical ventilation in pregnant women with COVID-19, respectively (Allotey et al., 2020; Capobianco et al., 2020; Juan et al., 2020; Khalil

et al., 2020a; Matar et al., 2021; Segars et al., 2020; Smith et al., 2020; Trippella et al., 2020; Zaigham and Andersson, 2020). A systematic review by Turan et al. (2020) specifically reported the percent of mechanically ventilated patients among SARS-CoV-2-positive pregnant women admitted in the ICU and was as high as 83.6% (51 ventilated out of 61 admitted). The COVID-19 Response Pregnancy and Infant Linked Outcomes Team of the Centers for Disease Control and Prevention (CDC) reports a large study comparing 23,434 SARS-CoV-2 positive pregnant women to 386,028 positive nonpregnant women in their

TABLE 6.2
Frequency and Percent of ICU Admission in Pregnant Women With COVID-19.

Study (First Author, Year)	n/N	Percent (%)
Allotey (2020)	232/10901	3.0
Capobianco (2020)	—	13.0
Juan (2020)	12/253	4.7
Khalil et al. (2020a)	—	7.0
Smith (2020)	1/23	4.3
Trippella (2020)	10/275	3.6
Zaigham (2020)	3/108	2.8

ICU, intensive care unit; n, the number of patients admitted in ICU; N, the total number of pregnant women with COVID-19 in the study.

TABLE 6.3
Frequency and Percent of Pregnant Women With COVID-19 Who Needed Mechanical Ventilation.

Study (First Author, Year)	n/N	Percent (%)
Allotey (2020)		
Invasive ventilation	155/10713	1.5
ECMO	16/1935	0.8
Juan (2020)	3/170	1.8
Khalil et al. (2020a)		
Invasive ventilation	—	3.4
ECMO	—	0.7
Matar et al. (2021)	2/136	1.5
Segars (2020)	4/162	2.5
Smith (2020)	1/23	4.3
Trippella (2020)	5/275	1.8

ECMO, extracorporeal membrane oxygenation; *n*, the number of patients who needed mechanical ventilation; *N*, the total number of pregnant women with COVID-19 in the study.

reproductive age: the pregnant women showed a higher risk of ICU admission (10.5 vs. 3.9 per 1000 cases), invasive ventilation (2.9 vs. 1.1 per 1000 cases), ECMO (extracorporeal membrane oxygenation) (0.7 vs. 0.3 per 1000 cases), and death (1.5 vs. 1.2 per 1000 cases) (Zambrano et al., 2020a).

Complications of COVID-19 in pregnancy: All complications of COVID-19 that occur in the nonpregnant population can occur in pregnant women, including respiratory, cardiovascular, thromboembolic, renal, neurological, gastrointestinal, hepatic, hematologic and cutaneous complications, psychiatric illness, secondary infections, and post-COVID syndrome. In this section, emphasis is on complications with specific maternal impact or specific presentation.

Acute respiratory failure occurs in up to 8% of COVID-19 patients and is considered the principal cause of death in COVID-19. The vulnerability of a pregnant woman lies in their increased oxygen consumption, decreased functional residual capacity, and physiological hyperventilation with compensated respiratory alkalosis, which can make the progress rapidly if pneumonia occurs. Moreover, due to different anatomy and physiology of the pregnant woman, and also the presence of a fetus, there are some special considerations in management of ARDS in pregnant women. Unlike nonpregnant patients in who SpO₂ (saturation of peripheral oxygen) should be above 90%, it should be above 95% and maintained between 92% and 95% once stabilized in pregnant women, which is to ensure PaO₂ (partial pressure of oxygen) above

70 mmHg with the aim of preserving adequate oxygen diffusion across the placenta to the fetus. The prone position, which is encouraged in COVID-19 patients, might be challenging in pregnant ladies especially in the late trimester and can be substituted by the semi-prone or left lateral positions. Also, the uterus can be displaced to minimize aortocaval compression by applying pads above and below the level of the uterus. Lines such as permissive hypercapnia, high PEEP (positive end-expiratory pressure), and ECMO should be used with close fetal surveillance especially that studies on fetal effect are not abundant (Campbell and Klocke, 2001; Caputo et al., 2020; Chen et al., 2020c; Liu et al., 2020a; Pacheco and Saad, 2018; Ruan et al., 2020; Soma-Pillay et al., 2016; Stephens et al., 2020; Syeda et al., 2020; Tolcher et al., 2020; Webster et al., 2020; World Health Organization, 2020b).

Thromboembolic complications: COVID-19 has been described to cause microthromboembolism and DIC and also to increase the risk of venous thromboembolism (VTE) due to the classic components of the Virchow's triad: (1) endothelial injury (2) imbalance between procoagulants and anticoagulants caused by the inflammatory and immunological course of the disease, and (3) immobilization in hospitalized patients. VTE can occur in one-third of COVID-19 ICU patients, mainly deep venous thrombosis and pulmonary embolism. Pregnancy is typically known to induce a hypercoagulable state, which increases chances of VTE in COVID-19 patients especially if hospitalized. Therefore, hospitalized pregnant women with COVID-19 should

be prescribed prophylactic anticoagulation—unless contraindicated—during their hospital stay. Whether to utilize unfractionated or low-molecular-weight heparin should be guided by the time frame to delivery. Therapeutic anticoagulation should only be administered according to VTE risk scores and presence of other indications (Begbie et al., 2000; James, 2010; Jose and Manuel, 2020; Libby and Lüscher, 2020; Lowenstein and Solomon, 2020; Maier et al., 2020; National Institutes of Health, 2020; Panigada et al., 2020; Ranucci et al., 2020; Tang et al., 2020b; Teuwen et al., 2020; Turan et al., 2020; Zhou et al., 2020).

Cardiac complications that can occur in COVID-19 patients include acute myocardial injury, cardiomyopathy, acute coronary syndrome, arrhythmias, and acute heart failure. Causes may be the direct viral myocarditis, the indirect cytokine-mediated cardiac injury, microvascular thrombosis, the cardiac overload during infection, or as a part of multiple organ system failure. Acute myocardial injury—defined as elevation of troponin level above the 99th centile—can occur in up to 16% of hospitalized patients with COVID-19. Myocardial injury has been described in pregnant women with COVID-19, with a high mortality rate of 13%, mainly due to associated fatal arrhythmias. The vulnerability of the pregnant women lies in their hyperdynamic circulation, increased blood volume, and cardiac output. Aggravating cofactors include advanced maternal age, preexisting comorbidities, and obesity. Cardiomyopathy, which may occur in nonpregnant COVID-19 patients, has also been described in pregnant women with guarded prognosis (Juusela et al., 2020; de Lorenzo et al., 2020; Guo et al., 2020; Hendren et al., 2020; Long et al., 2020; Mercedes et al., 2021; Prasiolumkum et al., 2020; Verity et al., 2020; Williams, 2003).

Acute kidney injury (AKI) has been described in COVID-19 patients with an incidence of 10.6%, which is higher than that in non-COVID-19 hospitalized patients. The pathophysiology of AKI in COVID-19 patients is not fully understood. Suggested mechanisms include (1) hypovolemia and hemodynamic changes—secondary to shock or multiple organ system failure—leading to acute tubal necrosis (ATN), (2) renal microvascular thromboembolism, (3) rhabdomyolysis, (4) direct viral effect on the kidney, as viral evidence in renal tissue has been confirmed in autopsy, and/or (5) side effect to the antiviral remdesivir is under study. So hypothetically, the pregnant women due to the normal physiological changes during pregnancy, which include extravascular fluid shift and procoagulopathic changes, are more vulnerable to AKI. A 33-year-old woman from Iran has been described who was 34 weeks pregnant

and was diagnosed to be SARS-Co-V-2 positive by nasopharyngeal reverse-transcription polymerase chain reaction (RT-PCR) and developed severe form of the disease necessitating mechanical ventilation; during her hospital stay, she developed ATN, which—with no other possible etiology—resolved after improvement of the disease (European Medicines Agency, 2020; Farkash et al., 2020; Lin et al., 2020; Mitchell and Chiwele, 2021; Naicker et al., 2020; National Institute for Health and Care Excellence, 2020; Taghizadieh et al., 2020; Zaim et al., 2020).

Hematological conditions, which can complicate COVID-19, include SARS-Co-V-2-induced immune thrombocytopenia or immune thrombocytopenic purpura (ITP). These cases need meticulous diagnostic approach to exclude other possible causes. Contributing factors are advanced age and disease severity. ITP has been diagnosed in asymptomatic patients and during recovery. Proposed theories include immunological changes and genetic mutations. Some reports have described ITP newly diagnosed in pregnancy with COVID-19. Flare of previously known ITP occurring in pregnancy with COVID-19 has been also described (Bhattacharjee and Banerjee, 2020; Nesr et al., 2020; Tang et al., 2020a).

Maternal death: Although pregnancy is associated with higher odds of hospitalization, ICU admission, and mechanical ventilation compared with the nonpregnancy state, fortunately, maternal mortality due to COVID-19 is below 2%. In the large systematic review conducted by Allotey et al. (2020), the maternal mortality was 0.6% (73 out of 11,580 mothers). The initial report issued by the CDC in June 2020 stated that COVID-19 pregnant women do not have a higher mortality compared with their nonpregnant peers; however, this was later followed by an update in November 2020 calculating that the pregnant population have a slightly higher risk of death compared with the nonpregnant (1.5 vs. 1.2 per 1000 cases) population with an adjusted risk ratio of 1.7. Mortalities are mostly due to ARDS (acute respiratory distress syndrome) with its cardiopulmonary consequences and venous thromboembolism. Unfortunately, mortalities happen to be more in middle- and low-income countries where healthcare facilities are more limited (Allotey et al., 2020; Ellington et al., 2020; Hantoushzadeh et al., 2020; Hessami et al., 2020; Nakamura-Pereira et al., 2020; Takemoto et al., 2020; Zambrano et al., 2020a).

Maternal deaths amid different studies are summarized in Table 6.4 (Allotey et al., 2020; Capobianco et al., 2020; Juan et al., 2020; Khalil et al., 2020a; Matar et al., 2021; Segars et al., 2020; Smith et al., 2020; Trippella et al., 2020; Zaigham and Andersson, 2020).

TABLE 6.4
Frequency and Percent of Maternal Mortality in Pregnant Women With COVID-19.

Study (First Author, Year)	n/N	Percent (%)
Allotey (2020)	73/11580	0.6
Capobianco (2020)	—	0.0
Juan (2020)		
Case series and reports	9/324	2.8
Case series only	7/304	2.3
Khalil et al. (2020a)	—	0.0
Matar et al. (2021)	1/136	0.7
Segars (2020)	2/162	1.2
Smith (2020)	1/92	0.0
Trippella (2020)	10/275	0.4
Zaigham (2020)	0/108	0.0

n, the number of patients admitted in ICU; *N*, the total number of pregnant women with COVID-19 in the study.

In summary, pregnant women with COVID-19 are more probable to need hospitalization, ICU admission, and mechanical ventilation, compared with their nonpregnant counterparts, but their risk of death is similar or slightly higher (Ellington et al., 2020; Papanou et al., 2021; Zambrano et al., 2020a).

OBSTETRIC OUTCOMES AND MATERNAL, FETAL, AND NEONATAL PROGNOSIS IN COVID-19

CD rates: According to the National Center for Health Statistics, the overall CD rate in the United States was 31.7% in 2019 (Hamilton et al., 2020).

CD rates among pregnant women diagnosed with COVID-19 are very high with rates ranging between 48.3% and 94%. In several instances, being diagnosed with COVID-19 is the only indication for CD. The mere maternal COVID-19 diagnosis accounts for 7.7% and 60.4% of CDs, and being symptomatic for COVID-19 or not does not change the odds of having a CD. Other indications include severe/critical maternal disease and fetal compromise. Dubey et al. (2020) analyzed CD rates geographically and found rates to be considerably higher in China (91%) compared with the United States (40%) and Europe (38%). A Swedish study observed that SARS-CoV-2-positive women are less likely to undergo induction of labor with a percentage of 18.7% of deliveries compared with 29.6% in their matched SARS-CoV-2 negative controls. Table 6.5 summarizes CD rates along several different studies (Ahlberg et al., 2020; Allotey et al.,

2020; Capobianco et al., 2020; Di Mascio et al., 2020a; Dubey et al., 2020; Kasraeian et al., 2020; Khalil et al., 2020a; Matar et al., 2021; Muhidin et al., 2020; Smith et al., 2020; Trippella et al., 2020; Trocadero et al., 2020; Woodworth et al., 2020; Zaigham and Andersson, 2020).

Several factors interlace in the higher CD rates among pregnant women with COVID-19: (1) lack of recommendations and guidelines at the beginning of the pandemic, when reasons such as fear of maternal–fetal transmission were sometimes the only indication for CD, (2) the already higher CD rates in China where the pandemic first started and from where the most early publications, which were mainly case reports and case series were published, (3) the assumed higher incidence of prematurity among women with COVID-19, which under certain circumstances can necessitate CD, (4) despite induction of labor being safe and successful in mechanically ventilated pregnant women, sometimes the circumstances are challenging regarding the operating theater and intensive care staff and ease of equipment provision, (5) sometimes the reported indication for CD by many authors is the belief of rapid need for termination of pregnancy due to aggravation of maternal illness and rapid need for relief of abdominal distension and improving efficiency of mechanical ventilation, and (6) also, the need for rapid termination to safely allow maternal administration of possibly teratogenic investigational antiviral medications (Berghella and Hughes, 2021; Boerma et al., 2018; Ming et al., 2019; Papanou et al., 2021; Yang et al., 2020b).

TABLE 6.5
Frequency and Percent of Cesarean Deliveries in COVID-19 Pregnant Women.

Study (First Author, Year)	CS Rate (Percent) (%)
Allotey (2020)	54.8
Capobianco (2020)	88
Di Mascio et al. (2020a)	92.7
Dubey (2020)	72
Kasraeian (2020)	92
Khalil et al. (2020a)	48.3
Matar et al. (2021)	76.3
Muhidin (2020)	88.8
Smith (2020)	80
Trippella (2020)	75
Trocado (2020)	94
Woodworth (2020)	51.4
Zaigham (2020)	92

Preterm labor and preterm birth: The classic definition of preterm labor (PTL) is occurrence of regular uterine contractions accompanied by cervical changes before 37 weeks, while preterm birth (PTB) or preterm delivery means actual delivery before 37 weeks of gestation. Although a proportion of women with PL will go into preterm birth, this is not the condition in all cases. PTB rate in the United States was estimated to be 10.23% in 2019 (Hamilton et al., 2020; Howson et al., 2013; Rundell and Panchal, 2017).

PTL rates are estimated between 22.7% and 32.2%, and PTB rates in studies with ample sample sizes constitute 20.6%–25% of all deliveries. When observing studies with smaller samples rates reach as high as 63.8%. However, the PTB rates in the United States might not be affected; the CDC COVID-19 Response Pregnancy and Infant Linked Outcomes Team reports PTB rates of 12.9% (506/3912 infants). The proportion of preterm births, which are spontaneous among the overall preterm births in COVID-19 pregnant women, do not seem to be actually high and represent around 5%–6% of all preterm births. The larger fraction of preterm deliveries is in fact iatrogenic, and a study mentions being diagnosed with maternal COVID-19 to be the main indication for preterm delivery in half of the PTBs. Iatrogenic preterm deliveries with medically relevant indications could perhaps represent only 18% of births. In summary, COVID-19 mothers have higher chances of delivering preterm, although usually

spontaneous PTB would not be the cause. The mechanism by which spontaneous PTL and PTB occur is not fully understood yet; however, maternal hypoxia, maternal fever, placental pathological changes, and uteroplacental insufficiency could be responsible (Allotey et al., 2020; Khalil et al., 2020a; Papapanou et al., 2021; Smith et al., 2020; Turan et al., 2020; Woodworth et al., 2020).

Miscarriage: COVID-19 does not seem to raise the rates of miscarriage in pregnant women. Unlike SARS (severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome) in which miscarriage rates were approximately 25% and 18%, respectively, rates of miscarriage in SARS-CoV-2-positive women are below 2%. Woodworth et al. (2020) report pregnancy loss before 20 weeks to be as low as 0.3%. However, the paucity of data on women in early pregnancy must be kept in mind. There is some concern that placental infection and pathological changes—mentioned later in vertical transmission—could be responsible for midtrimester miscarriage. Anxiety and fear of “consequences of the novel disease on the unborn fetus” may increase women’s requests for abortion (Baud et al., 2020; Berghella and Hughes, 2021; Dashraath et al., 2020; Papapanou et al., 2021).

Preeclampsia: A case-control Swedish study demonstrated higher prevalence of preeclampsia (PE) among SARS-CoV-2-positive pregnant women compared with their matched negative controls with a prevalence of

7.7% the positive group compared with 4.3% in controls. Development of preeclampsia could be related to the immunological and inflammatory changes occurring in COVID-19 and involved in the pathophysiology of PE. Moreover, a possible explanation of development of preeclampsia in COVID-19 is that after SARS-CoV-2 uses the ACE2 receptor for cell entry, it causes its downregulation—after the initial upregulation mentioned before—thus decreasing conversion of angiotensin II to angiotensin-(1–7), thus resulting in a pathophysiology, which mimics preeclampsia. In addition to this shared mechanism, COVID-19 and preeclampsia share other pathophysiology such as endothelial cell dysfunction and complement activation. In conclusion, preeclampsia could be aggravated by COVID-19 or could worsen COVID-19 (Ahlberg et al., 2020; Alrahmani and Willrich, 2018; Ferrario et al., 2005; Narang et al., 2020; Pringle et al., 2011; Risitano et al., 2020; Varga et al., 2020).

COVID-19 and preeclampsia also share common abnormalities particularly thrombocytopenia, elevated transaminases, and evidence of disseminated intravascular coagulopathy (DIC) with prolonged prothrombin time, low fibrinogen, and elevated fibrinogen degradation products, which renders differentiation between COVID-19 related laboratory abnormalities and severe preeclampsia—especially with HELLP syndrome—difficult. Other interlacing aberrations are hemolysis and lupus anticoagulant positivity. Moreover, symptoms of COVID-19 and severe preeclampsia and eclampsia could intermingle, such as headache, and cerebrovascular and neurological manifestations (Berghele and Hughes, 2021; Futterman et al., 2020; Lippi et al., 2020; Narang et al., 2020; Zhang et al., 2020).

Vertical Transmission and Neonatal COVID-19 Infection

In general, vertical transmission of a virus refers to its transmission from the mother to her offspring. This can happen either intrauterine, intrapartum, or postpartum (Fermin, 2018).

The possibility of the vertical transmission of SARS-CoV-2 has been a major concern of the medical community. Theoretically, maternal–fetal transmission is possible because the ACE2 receptor—which is now established as the receptor of SARS-CoV-2—is expressed in the placental villi, in both cytotrophoblasts and syncytiotrophoblasts, in addition to extravillous trophoblasts (Gengler et al., 2021; Hanna et al., 2020; Hikmet et al., 2020; Li et al., 2020a; Pringle et al., 2011; Valdés et al., 2006).

It is assumed that SARS-CoV-2 can be transmitted from the mother to the fetus or neonate through several probable routes: (1) intrauterine, either transplacental, through ingestion or aspiration of infected amniotic fluid, or due to maternal viremia, (2) intrapartum, through contact with maternal blood or secretions, or (3) postpartum, through breast milk. The neonate could also get infected during the postpartum period through the conventional respiratory route from an infected mother or contact. However, transient positive neonatal nasopharyngeal swabs have been collected in the first 24 h with subsequent negative swabs and negative IgM antibodies, which could be explained by contamination of the newborn's mouth or airway with maternal secretions during resuscitation (Blumberg et al., 2020; Caparros-Gonzalez et al., 2020).

To prove the possibility of maternal–fetal transmission of the SARS-CoV-2, two factors should be fulfilled: (1) evidence of the presence of the virus in amniotic fluid, umbilical cord blood, placenta, cervical secretions, or breast milk by immunohistochemistry or nucleic acid methods such as in situ hybridization, and (2) evidence of neonatal COVID-19 infection by a positive RT-PCR within the first 12–72 h (Caparros-Gonzalez et al., 2020; Schwartz et al., 2021; Schwartz et al., 2020; Walker et al., 2020).

A handful of studies have assessed infection of the amniotic fluid by SARS-CoV-2 in COVID-19 positive mothers, all of which have disproved evidence of the virus (Chen et al., 2020b; Li et al., 2020b; Liu et al., 2020b; Peng et al., 2020; Stonoga et al., 2021; Vivanti et al., 2020; Wang et al., 2020b; Xiong et al., 2020; Yang et al., 2020b; Yu et al., 2020) except for one case report from Iran (Zamaniyan et al., 2020). It seems maternal–fetal transmission via the amniotic fluid is unlikely to occur (Caparros-Gonzalez et al., 2020; Salem et al., 2021).

Multiple studies also confirmed the absence of SARS-CoV-2 RNA in umbilical cord blood (Chen et al., 2020b; Khan et al., 2020; Li et al., 2020b; Liu et al., 2020b; Patanè et al., 2020; Peng et al., 2020; Wang et al., 2020a; Yang et al., 2020a; Yang et al., 2020b; Zambrano et al., 2020b). Only two studies demonstrated viral evidence, in one of which the sample was obtained from the umbilical cord stump; however, neonatal RT-PCR swabs were negative (Kulkarni et al., 2021; Stonoga et al., 2021).

Unlike the amniotic fluid which seems—according to current evidence—not infectious to the fetus of a COVID-19 mother, the placenta could be accused of in utero maternal–fetal transmission of SARS-CoV-2. While several studies have shown negative results

from placental tissues, other studies have demonstrated positive SARS-CoV-2 RNA on the placental fetal side. RNA belonging to SARS-CoV has been found in different types of cells of the placental barrier: cytotrophoblasts, syncytiotrophoblasts, villous endothelial cells, and extravillous trophoblasts. The histopathological examination of placentae from COVID-19 mothers has shown accelerated villous maturation, acute intervillitis, chronic histiocytic–lymphocytic intervillitis, necrosis of syncytiotrophoblasts, acute deciduitis and chorioamnionitis, decida capsularis thrombotic vasculopathy, chorangiomas, funisitis, subchorial hematoma, and perivillous fibrin deposition with infarctions. Moreover, [Algarroba et al. \(2020\)](#) were able to visualize SARS-CoV-2 virions in the villous syncytiotrophoblasts by the electron microscope. A handful of neonates born to mothers with these changes have tested positive for SARS-CoV, and the number is still rising. Also, [Kulkarni et al., 2021](#) report a term neonate delivered to a suspected COVID-19 mother, whose placenta tested positive for SARS-CoV. The mother although having a negative nasopharyngeal swab later on developed detectable antibodies, and the neonate developed symptomatic COVID-19. There is growing evidence that the two findings “trophoblast necrosis” and “chronic histiocytic intervillitis” when together are possible markers for placental infection with SARS-CoV with risk of fetal transmission ([Algarroba et al., 2020](#); [Baud et al., 2020](#); [Facchetti et al., 2020](#); [Hecht et al., 2020](#); [Hosier et al., 2020](#); [Hsu et al., 2021](#); [Kirtsman et al., 2020](#); [Kulkarni et al., 2021](#); [Patanè et al., 2020](#); [Penfield et al., 2020](#); [Stonoga et al., 2021](#); [Vivanti et al., 2020](#)).

On the contrary, other few studies have reported negative swabs from placentae of COVID-19 women, with delivery of healthy neonates with negative swabs. [Chen et al. \(2020e\)](#) performed histological examination on placentae from three COVID-19 mothers and were found to show no histopathologic changes, in addition to negative RT-PCR ([Chen et al., 2020d, 2020e](#); [Li et al., 2020b](#); [Peng et al., 2020](#); [Schwartz, 2020](#); [Schwartz et al., 2021](#); [Schwartz and Morotti, 2020](#); [Wang et al., 2020b](#); [Xiong et al., 2020](#)).

Regarding presence in breast milk, interpretation of results of studies may be more difficult. While several studies have negated the presence of viral evidence in breast milk ([Chen et al., 2020b](#); [Li et al., 2020b](#); [Liu et al., 2020b](#); [Peng et al., 2020](#); [Wang et al., 2020a](#); [Xiong et al., 2020](#)) SARS-CoV-2 RNA has been isolated from multiple samples in other studies ([Bastug et al., 2020](#); [Chambers et al., 2020](#); [Kirtsman et al., 2020](#); [Lugli et al., 2020](#); [Tam et al., 2021](#); [Zhu et al., 2020](#)).

However, the infectious potential of breast milk of COVID-19 infected mothers remains unclear till now ([Caparros-Gonzalez et al., 2020](#); [Chen et al., 2020a](#)), as it is hard to prove whether a previously negative breastfed neonate that transforms to positive acquired it from the breast milk of its COVID-19-infected mother or via the conventional respiratory route.

Whether vertically transmitted or not, newborns born to mothers with COVID-19 have a chance of testing positive for SARS-CoV-2 in their early neonatal life by RT-PCR for throat swabs. The incidence is not common, but some reviews support that vertical transmission is possible. [Table 6.6](#) summarizes the percent of newborns born to COVID-19-infected mothers, who tested positive for SARS-CoV-2 ([Amaral et al., 2020](#); [Ashraf et al., 2020](#); [Bellos et al., 2021](#); [Dhir et al., 2020](#); [Di Toro et al., 2021](#); [Figueiro-Filho et al., 2020](#); [Han et al., 2020](#); [Khalil et al., 2020a](#); [Trocado et al., 2020](#); [Turan et al., 2020](#); [Walker et al., 2020](#); [Yee et al., 2020](#); [Yoon et al., 2020](#)). The main drawback is that most of the publications included in these reviews are case series and case reports. Some publications have not accurately mentioned the time frame during which the neonatal nasopharyngeal RT-PCR was carried out. Also, there are some overlapping publications included in the reviews, not to mention the possibility of overlapping participants in the included publications. After conducting an analysis of systematic reviews, [Papapanou et al. \(2021\)](#) estimated the possibility of COVID-19 mothers to have an infected newborn to be around 2.5%.

In summary, congenital intrauterine transmission seems possible and cannot be excluded; however, neonatal COVID-9 is uncommon. The exact method of maternal–fetal transmission of SARS-CoV—if actually occurring—needs further meticulous studying ([Salem et al., 2021](#); [Schwartz et al., 2020](#); [Sheth et al., 2020](#); [Walker et al., 2020](#)).

Perinatal Morbidity and Mortality

At first glance, possible adverse perinatal outcomes to fetuses and neonates of mothers with COVID-19 that would jump in mind the obstetrician are fetal distress, fetal growth restriction (FGR), stillbirth, prematurity, low birth weight (LBW), low Apgar scores, and neonatal asphyxia, with subsequent NICU (neonatal intensive care unit) admission and probable neonatal mortality. It could be wrongfully guessed that newborns infected in utero or having early neonatal COVID-19 could have worse outcomes. Actually, there seems no difference in these outcomes between infected and normal neonates; however, an evident contributing factor is

TABLE 6.6
Percent of Newborns Who Tested Positive for SARS-CoV-2 Born to COVID-19 Infected Mothers.

Study (First Author, Year)	Publications Included	Total Neonates	Tested Neonates	Positive Neonates	% of Positive to Total	% of Positive to Tested
Amaral (2020)	70	1042	—	39	3.74	—
Ashraf (2020)	21	92	86	4	4.35	4.65
Bellos et al. (2021)	60	920	—	4	0.43	—
Dhir (2020)	86	1141	—	58	5.08	—
Di Toro et al. (2021)	5	444	—	19	4.28	—
Figueiro-Filho (2020)	8	1116	—	18	1.61	—
Han (2020)	30	559	—	21	3.76	—
Khalil et al. (2020a)	9	751	—	19	2.53	—
Trocado (2020)	8	51	—	1	1.96	—
Turan (2020)	63	479	405	8	1.67	1.98
Walker (2020)	49	666	—	28	4.20	—
Yee (2020)	11	338	154	5	1.48	3.25
Yoon (2020)	28	201	167	4	1.99	2.40

the severity of the maternal disease, with worse perinatal outcomes among severe and critically ill COVID-19 mothers. Other risk factors include gestational age at diagnosis, LBW, and need for maternal ventilatory support. To this date, there are no cases of neonatal mortalities due to early neonatal diagnosis of COVID-19 in newborns of COVID-19 mothers. Perinatal outcomes in hospitalized pregnant women are generally worse, being those with severe or critical COVID-19 (Allotey et al., 2020; Di Mascio et al., 2020b; Papapanou et al., 2021; Turan et al., 2020).

Fetal distress: The occurrence of fetal distress as one of the outcomes of neonates born to pregnant women with COVID-19 has shown a wide range of reporting. Systematic reviews have described frequencies ranging from 8.5% up to 61%. One of the largest neonatal samples is that reported by Allotey et al. (2020), in which 8.5% (25/293) of neonates had fetal distress. On the other end of the wide range, Smith et al. (2020) report a much higher frequency of fetal distress of 61% (11/18 neonates). However, the latter systematic review includes a smaller number of pregnancies, all from case reports and series, solely from China, and very early in the pandemic experience (Allotey et al., 2020; Papapanou et al., 2021; Smith et al., 2020). Also,

discrepancies could be attributed to different definitions used for fetal distress along different publications.

Cardiotocographic changes: A Spanish study retrospectively analyzed cardiotocograph (CTG) tracings of 12 pregnant women with COVID-19, 10 of which had abnormalities in their tracings. Abnormalities included elevated fetal heart rate baseline, absent accelerations, occurrence of late decelerations, and abnormal variability. The authors hypothesized that these alterations could be attributed to fetal response to maternal fever, transplacental passage of inflammatory and immunological mediators of the cytokine storm, or possible uteroplacental insufficiency and FGR (Gracia-Perez-Bonfils et al., 2020).

Fetal growth restriction and small for gestational age: Although FGR seems as an important outcome worth studying, it is still underreported. Available reviews report rates between zero and 9% of neonates born to COVID-19 mothers (Di Mascio et al., 2020a; Diriba et al., 2020; Segars et al., 2020). Restricted fetal growth could be explained by uteroplacental insufficiency, which could be due to severe maternal illness, maternal hypoxia, placental COVID-19-induced pathological changes, or maternal hypercoagulable state, leading to thrombosis and infarction in the placenta and

TABLE 6.7
Frequency and Percent of Newborns With Low Birth Weight (LBW) Born to COVID-19-Infected Mothers.

Study (First Author, Year)	Neonates with LBW (Number)	Total Neonates (Number)	Neonates with LBW (Percent) (%)
Chang (2020)	9	92	9.8
Dubey (2020)	41	548	7.5
Elshafeey (2020)	20	256	7.8
Juan (2020)	8	221	3.6
Muhidin (2020)	7	89	7.9
Smith (2020)	9	21	42.8

umbilical vessels (Gracia-Perez-Bonfils et al., 2020; Schwartz et al., 2020a). Woodworth et al. (2020) state in their report in November 2020 that out of 3486 live births of women with COVID-19 with known weight and gestational age at birth, 198 (5.7%) were small for gestational age.

Stillbirth: Rates of stillbirth in COVID-19 pregnant women are calculated to be as low as 0.6% by Allotey et al. (2020) and as high as 2.4% by Di Mascio et al. (2020a). Hospitalized pregnant women have a higher stillbirth rate, which could reach 3% (Panagiotakopoulos et al., 2020). Possible explanations of stillbirths in COVID-19 patients could be (1) the aforementioned uteroplacental changes, maternal hypoxia, placental and umbilical thrombosis, and infarctions, (2) the transient elevation of lupus anticoagulant observed in COVID-19 patients, (3) the severity of maternal illness, and (4) inadequate antenatal care, due to lockdowns, lack of face-to-face services, or fear of patients to visit healthcare facilities during the pandemic. Stillbirths being probably explained by the aforementioned uteroplacental changes, which could be more advanced as the maternal disease is more severe, hence the higher still birth rates amidst hospitalized pregnant women (Bowles et al., 2020; Devreese et al., 2020; Helms et al., 2020; KC et al., 2020; Khalil et al., 2020b; Reyes Gil et al., 2020).

Congenital anomalies/birth defects: There is no increase in frequency of birth defects in newborns of women with COVID-19 during pregnancy compared with non-COVID-19 mothers. Woodworth et al. (2020) report a frequency of 28 neonates with birth defects out of 4447 live births (0.6%) to mothers with COVID-19. However, till now, data on patients who were infected in their first trimester are still limited.

LBWs: The World Health Organization (2014) classically defines LBW as “weight at birth less than 2500 g.”

Like fetal distress, LBW rates show a wide discrepancy between currently available systematic reviews with rates ranging from around 3.6%–42.8%. Reviews with a small number of neonates are mainly those with high rates of LBW, so perhaps the small sample of the represented neonatal population could be the cause. Dubey et al. (2020) in their analysis report an LBW rate of 7.5% (41/548); however, when publications are divided into two main categories, case series and case reports, a discrepancy is seen with LBW rates of 5.3% (27/505) and 32.6% (14/43), respectively. The main contributing factor to LBWs of these neonates is prematurity, as suggested by Smith et al. (2020). Table 6.7 summarizes rates of LBW among neonates born to mothers with COVID-19 (Chang et al., 2020; Dubey et al., 2020; Elshafeey et al., 2020; Juan et al., 2020; Muhidin et al., 2020; Smith et al., 2020; Trocado et al., 2020).

Low/abnormal Apgar scores: Since first proposed by Virginia Apgar in 1953, the Apgar scoring system—now well established—has been a quick and efficient quantitative way for early assessment of neonates following delivery. Hence, one of the aspects to assess the probable effect of any maternal illness on pregnancy outcomes—especially neonatal outcomes—is to evaluate its effect on the Apgar score (Apgar, 1953, 2015; Finster and Wood, 2005). Since Apgar scores are generally lower in cases of fetal distress and prematurity, it is an obvious finding that when critically ill mothers are delivered prematurely due to fetal distress, their neonates would have abnormal scores (Pettirosso et al., 2020; Turan et al., 2020). As other neonatal outcomes, still some controversy exists; with most figures showing no abnormalities in Apgar scores of neonates delivered to diseased mothers and average scores of 8.8 and 9.5 at 1 and 5 min, respectively (Ashraf et al., 2020; Chang et al., 2020; Juan et al., 2020; Matar et al., 2021; Mustafa

and Selim, 2020; Smith et al., 2020; Trocado et al., 2020). An even larger systematic review including 500 neonates assessed with the Apgar scoring system at 5 min shows only 11 (2.2%) had scores less than 7 (Allotey et al., 2020). Collectively, Apgar scores seem to be affected in cases of fetal distress, prematurity, and severe/critical maternal disease.

Neonatal asphyxia: Factors predisposing to neonatal asphyxia include maternal hypoxia due to severe illness, fetal distress, and prematurity. Rates are reported to be around 0.6% and 1.8% of live born neonates in systematic reviews with reasonable number of neonates included (Juan et al., 2020; Yoon et al., 2020). Some extremes are also reported; several systematic reviews have found no cases at all (Di Mascio et al., 2020a; Matar et al., 2021; Trocado et al., 2020), while others show rates of 7.7% and 13% (Capobianco et al., 2020; Trippella et al., 2020). In the aforementioned reviews, neonatal asphyxia does not seem to be caused by neonatal COVID-19; Yoon et al. (2020) reported their 168 neonates to have one case of asphyxia out of their four SARS-CoV-2 positive neonates, with a total rate of 1.8% (3/168 neonates).

NICU admission: Overall, causes of ICU admissions of neonates born to COVID-19 mothers mostly are due to either prematurity, or the sole need for neonatal isolation—especially early in the pandemic when very little was understood regarding the new disease—while neonatal SARS-CoV-2 infection per se is not the actual cause necessitating NICU admission (Papapanou et al., 2021; Turan et al., 2020; Woodworth et al., 2020). Therefore, reports widely range in rates of NICU admissions. The largest available report till now is that of Woodworth et al. (2020), in which 279 term live-born neonates were admitted to the NICU out of 2995 with an admission rate of 9.3%, followed by the estimation of Allotey et al. (2020) with 1348 neonates of which 368 (27.3%) were admitted. Prematurity is the commonest cause of NICU admission—regardless of the SARS-CoV-2 neonatal status—where preterm SARS-CoV-2-negative neonates accounted for 96.3% (52/54) of the total NICU admissions in the systematic review of Turan et al. (2020). Dhir et al. (2020) estimated the admission rate solely among SARS-CoV-2-positive neonates and was 38% (22/58 positive neonates). Overall, admission rate to the NICU ranges between 3.1% and 76.9%; the large disparity is due to presence of studies with very small numbers of neonates and due to lack of universal standardized indications for NICU admission in neonates born to SARS-CoV-2 positive mothers, not to mention that a lot of studies do not mention the cause for NICU admission (Allotey et al., 2020; Della Gatta et al., 2020; Dhir

et al., 2020; Di Mascio et al., 2020a; Diriba et al., 2020; Elshafeey et al., 2020; Huntley et al., 2020; Juan et al., 2020; Matar et al., 2021; Smith et al., 2020; Turan et al., 2020; Zaigham and Andersson, 2020).

Neonatal mortality: Neonatal mortalities in cases maternal COVID-19 infection do not exceed 3.2%. Conclusions from available systematic reviews and metaanalyses suggest that mortalities are not related to neonatal SARS-CoV-2 positivity. Risk factors that could contribute to neonatal mortality are prematurity—on the top of the list—and the severity of maternal condition (Di Mascio et al., 2020b; Hessiani et al., 2020). Table 6.8 provides neonatal mortalities according to different studies (Allotey et al., 2020; Capobianco et al., 2020; Chang et al., 2020; Juan et al., 2020; Kasraian et al., 2020; Khalil et al., 2020a; Matar et al., 2021; Muhidin et al., 2020; Trippella et al., 2020; Trocado et al., 2020; Zaigham and Andersson, 2020).

In summary, fetal and neonatal outcomes appear to be favorable apart from higher incidence of prematurity, and higher NICU admissions, the latter possibly explained by prematurity and extraprecautionary measures (Papapanou et al., 2021).

Rare Reported Outcomes

Preeclampsia-like syndrome: Hosier et al. (2020) have described a 22-week-pregnant lady who contracted SARS-CoV-2 during pregnancy who developed hypertension, proteinuria, elevated transaminases, thrombocytopenia, and hypofibrinogenemia consistent with DIC, and hence was diagnosed as severe PE and terminated. Histopathological examination of the placenta revealed the COVID-19-related changes of histiocytic intervillitis and fibrin deposition, but lacked classic PE vasculopathy. Mendoza et al. (2020) name this condition “preeclampsia-like syndrome” and describe it as a PE-like condition developing in pregnant women infected with COVID-19 and that can resolve after resolution of manifestations of COVID-19. In their prospective study, 42 SARS-CoV-2 pregnant ladies were classified—as per presence of severe pneumonia—as severe and nonsevere COVID-19, with 8 and 34 ladies, respectively. Any lady suspected to have PE was evaluated for uterine artery pulsatility index (UtAPI) and sFlt-1/PlGF (soluble fms-like tyrosine kinase-1/placental growth factor) ratio. Of the eight with severe COVID-19, five developed PE. Abnormal sFlt-1/PlGF and UtAPI, which are predictors for PE, were confirmed only in one case, while the other four had normal parameters. One case continued her pregnancy after recovery from her severe pneumonia and her preeclampsia-like syndrome resolved (Hosier et al., 2020; Mendoza et al., 2020; Zeisler et al., 2016).

TABLE 6.8
Frequency and Percent of Neonatal Mortality in Neonates Born to COVID-19 Infected Mothers.

Review Study (First Author, Year)	Neonatal Death (Number)	Total Neonates (Number)	Neonatal Death (Percent) (%)
Allotey (2020)	6	1728	0.3
Capobianco (2020)	2	108	1.9
Chang (2020)	0	92	0.0
Juan (2020)	1	221	0.5
Kasraeian (2020)	0	86	0.0
Khalil et al. (2020a)	4	668	0.6
Matar et al. (2021)	3	94	3.2
Muhidin (2020)	2	89	2.2
Trippella (2020)	1	248	0.4
Trocado (2020)	1	51	2.0
Zaigham (2020)	1	87	1.1

Transient fetal skin edema: Garcia-Manau et al. (2020) describe a rare finding of two pregnant cases diagnosed with COVID-19: the first was severe and required ICU admission and mechanical ventilation, while the other one had mild symptoms, who were diagnosed by positive RT-PCR nasopharyngeal and oropharyngeal swabs for SARS-CoV-2. On fetal ultrasound examination, both revealed isolated fetal skin edema, without any other manifestations of fetal hydrops—fetal ascites, hydrothorax, placentomegaly. No other anomalies were evident, with normal fetal heart rate, echocardiography, and Doppler indices. Maternal serological tests for TORCH infections and antibodies were negative, and amniocentesis was also negative for known TORCH infections in addition to negative SARS-CoV-2 RT-PCR. Fetal skin edema was self-limited and resolved spontaneously on follow-up scans. Possible explanations could be congenital SARS-CoV-2 infection, effect of the maternal general condition, viral-induced immunological response, or mere coincidence.

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