

## Coronavirus Disease 2019 and the Fetus

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### Abstract

The outbreak of COVID-19 and its classification as a pandemic has raised many alarms. The impact of the SARS-CoV-2 virus on the pregnant woman and her unborn child is of utmost concern. Previous viral outbreaks taught us that this population is very vulnerable and among the most affected. Pregnant women infected with COVID-19 were associated with a higher rate of preterm birth, cesarean section, and perinatal death, though it appears that those who are critically ill are at an increased risk of such complications. One major concern is the transmission of this virus from the mother to her fetus during pregnancy. Although rare, review of the literature has indicated that it is possible, with some reporting that 30% of infections were likely due to vertical transmission. The impact of the infection in the neonate however has been reported to be mild and none worrying. A multitude of circumstantial factors may protect or harm the fetus such as the allogenic rejection of the decidua, the buffering nature of the placenta, the indirect effects of the lockdown and its repercussions, or the possible teratogenic effect of antiviral medications if used. Further studies are needed to assess not only short-term outcomes but also long-term outcomes, and particularly fetal programming.

**Keywords:** COVID-19; SARS-CoV-2; Maternal Infection; Fetal Infection; Pregnancy; Outcomes; Vertical Transmission; Fetal Programming

### Abbreviations

WHO: World Health Organization; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2; SARS: Severe Acute Respiratory Syndrome; MERS: Middle East Respiratory Syndrome; CDC: Centers for Disease Control; AAP: American Academy of Pediatrics; IUGR: Intrauterine Growth Restriction; PTL: Preterm Labor/Delivery; qRT-PCR: Quantitative Reverse Transcriptase Polymerase Chain Reaction; IgG: Immunoglobulin G; IgM: Immunoglobulin M; ACE2: Angiotensin-Converting Enzyme 2; TMPRSS2: Transmembrane Protease Serine 2; MSC: Mesenchymal Stem Cell; UKOSS: UK Obstetric Surveillance System; CRH: Corticotropin-Releasing Hormone; ACTH: Adreno-Corticotropin Hormone; p-CRH: Placental CRH; c-Section: Cesarean Section; WAPM: World Association of Perinatal Medicine; VLBW: Very Low Birth Weight; ELBW: Extremely Low Birth Weight; HCPs: Health Care Professionals; NAFTA: North American Fetal Therapy Network; CI: Confidence Interval; HR: Hazard Ratio; NTD: Neural Tube Defect

### Introduction

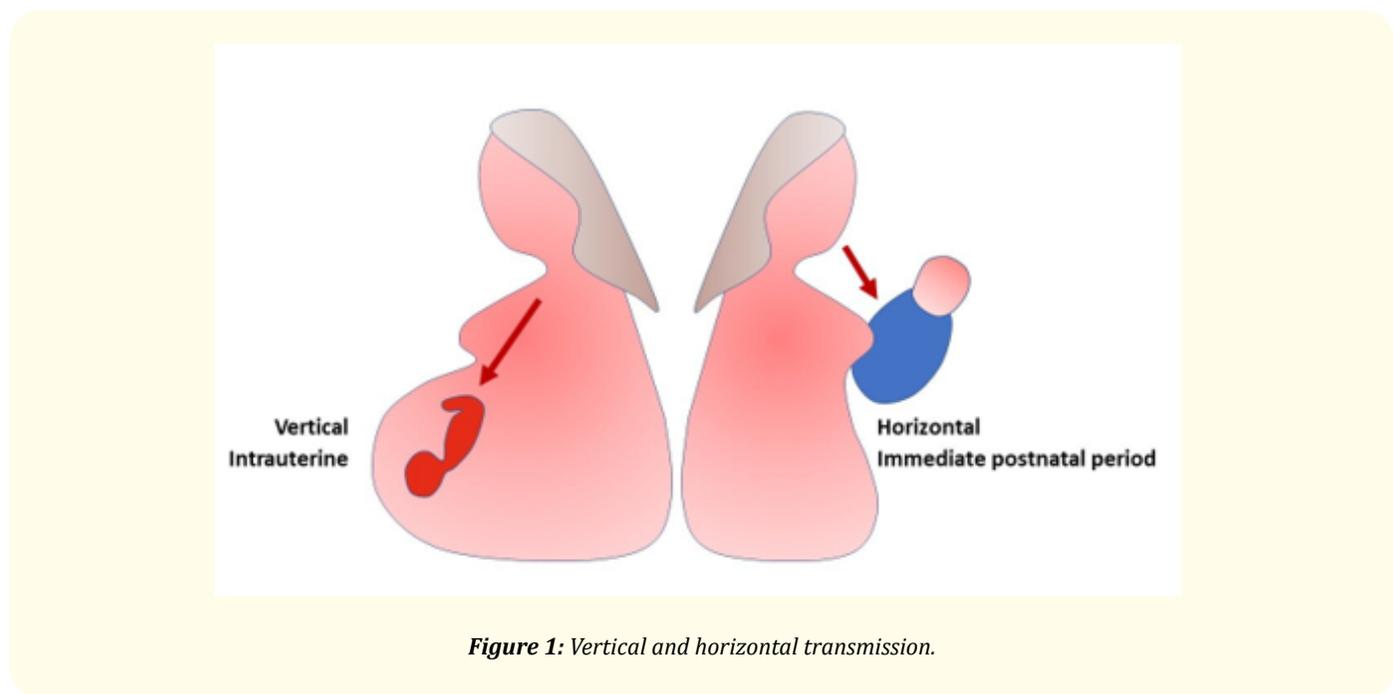
An outbreak of several cases of pneumonia of unknown etiology occurred in Wuhan, China towards the end of December 2019 and its rapid spread across continents lead the World Health Organization (WHO) to declare this disease a pandemic on March 11, 2020 [1]. The

disease, coined COVID-19, is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has become a threat to public health without a substantial reduction in its transmission.

The virus causes an acute respiratory distress syndrome of variable severity and is responsible for imbalances in the immune system and in the inflammatory condition characterized by a “cytokine storm” that leads to an exacerbated inflammatory state and may be associated with risk dysfunction of other organs, such as kidneys and heart, and eventually death [2].

When it comes to viral infections and global outbreaks such as Ebola, Zika, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), our memories are gloomy. As health care professionals caring for both mother and fetus, we have learnt from previous epidemics that this population is amongst those most affected and impacted with the poorest of outcomes [3]. The matter of most concern is the potential transmission of these infectious diseases from the pregnant woman to her unborn fetus, or vertical transmission whether congenital or intrapartum.

There are three potential patterns with regards to the vertical transmission of respiratory viruses from the mother to the child: transplacental during pregnancy, via the birth canal during labor and by breastfeeding postpartum [4]. As for horizontal transmission, which is the transmission from the mother to the neonate post-delivery, several guidelines by the Centers for Disease Control (CDC) and American Academy of Pediatrics (AAP) have detailed safe practices to limit such transfer (Figure 1).



**Figure 1:** Vertical and horizontal transmission.

It appears that irrefutably proving intrauterine transmission of COVID-19 is technically not feasible, as the required evidence would be to confirm the replication of SARS-CoV-2 in fetal pulmonary tissues. Practically speaking, the most convenient approach to investigate the occurrence of an intrauterine viral infection is to test for the presence of the said virus in placental tissue, amniotic-fluid, cord blood and neonatal pharyngeal swab samples. It is important to emphasize that all these samples need to be collected immediately after delivery using a sterile technique, to guarantee that the samples are not contaminated and that they represent intrauterine conditions [2].

Here we present an overall review of the impact of maternal COVID-19 infection on the fetus. We discuss the possibility of congenital infection, pathophysiology of vertical transmission and its consequences, maternal COVID-19 infection, effects of pandemic lifestyle and psychology on the fetus, fetal care during the pandemic, fetal outcome following COVID-19 infection, and fetal programming.

### **Congenital infection and effect on fetus**

There are several adverse outcomes associated with congenital viral infections and these range between intrauterine growth restriction (IUGR), congenital birth defects, particularly with adverse neurological outcomes, preterm labor/delivery (PTL), spontaneous abortion to stillbirth.

Currently, there are numerous controversies regarding whether SARS-CoV-2 can be transmitted from an infected mother to her fetus in utero. In the first study investigating the possibility of intrauterine vertical transmission of COVID-19 in 9 pregnant women with mild to moderate manifestation of laboratory-confirmed infection in their third trimester, matched amniotic fluid, cord blood, and neonatal pharyngeal swab samples from six neonates were tested for SARS-CoV-2, using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). All samples tested negative, suggesting that intrauterine fetal infection did not occur during the third trimester of pregnancy [5].

A case described by Vivanti, *et al.* might be the first report of confirmed transplacental transmission of COVID-19 from mother to fetus. Using a classification system of reliable COVID-19 diagnostic tests [6], the researchers reported that the mother who was infected in the last trimester, gave birth to a neonate presenting with neurological compromise. The infection was confirmed by comprehensive virological and pathological investigations [7]. A recent systematic review of neonatal SARS-CoV-2 infections by Raschetti, *et al.* reported that of 176 published cases, 30% were likely due to vertical transmission although only 5.7% were confirmed congenital infections [8].

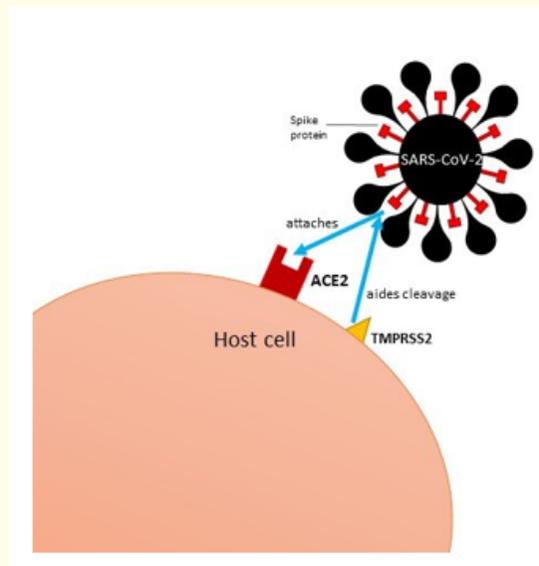
Some studies have reported the presence of serum specific immunoglobulin G (IgG) and immunoglobulin M (IgM) for the virus in neonates born to mothers with COVID-19, however researchers have suggested caution in interpreting this as vertical transmission or true congenital infection because of the lower sensitivity or specificity of IgM testing for congenital infections than molecular diagnostic tests based on nucleic acid amplification and detection [9].

According to a case report by Yu, *et al.* of two pregnant women diagnosed with COVID-19 in their second trimester of pregnancy, vertical transmission cannot be ruled out. Although both mothers tested positive for IgG in serum while only one mother tested positive for IgM in serum, qRT-PCR tests of amniotic fluid samples collected via ultrasound monitored amniocentesis returned negative. They argue however that the negative findings when testing amniotic fluid could be due to the instability of RNA in amniotic fluid as compared to DNA [10]. They also added that the virus might have been undetectable in amniotic fluid because the ultimate time to conduct amniocentesis is beyond 18 - 21 weeks of gestation. Previous studies with Zika virus infected pregnant women, another RNA virus, did report transient positive results in amniocentesis [11]. Therefore, they concluded that their sample size was insufficient to make conclusions and that they lacked cord blood samples [10].

### **Pathophysiology of vertical transmission**

Coronaviruses are single-stranded RNA, non-segmented, enveloped viruses, which cause illness ranging in severity from the common cold to severe and fatal illness. There have been reports of adverse outcomes such as miscarriage and stillbirth, albeit limited. Our knowledge of the basic pathophysiology of SARS-CoV-2 in pregnancy and the factors, which determine this virus' ability to infect a fetus is still inadequate. In general, pathogens are unable to cross the placenta during early pregnancy, but when they do, the outcomes are usually severe.

It appears that for SARS-CoV-2 to enter a cell, an interaction of its spike (s) protein with the cell's membrane-bound Angiotensin-Converting Enzyme 2 (*ACE2*), which is cleaved by the Transmembrane Protease Serine 2 (*TMPRSS2*), should take place (Figure 2). Blocking the activity of *TMPRSS2* protease leads to the blocking of *ACE2*-mediated entry of SARS-CoV-2 into the cell, thus suggesting that co-expression of both genes is required for infection [12]. Thus, cells in which *ACE2* and *TMPRSS2* are colocalized are possibly more prone to entry by SARS-CoV-2 [13]. Infection of the host cell is then followed by viral replication and release of the virus, causing programmed cell death, and an inflammation which may result in a cytokine storm that eventually leads to multisystem organ failure [13].



**Figure 2:** SARS-CoV-2 mechanism for host cell entry.

The expression and co-expression of these genes in the trophoblast of the blastocyst and placental villi and hypoblast of the early implantation stages. These cells eventually develop into the placental tissues that interact with the maternal blood supply for nutrient exchange. Consequently, the expression of *ACE2* and *TMPRSS2* in these tissues raises the possibility for vertical transmission and raises the question of transmission during early pregnancy [12].

Moreover, the evidence so far suggests that *ACE2* is highly expressed in the female reproductive system: uterus, vagina, ovary and placenta and in fetal tissue [14]. Looking at the placentas of women with COVID-19, studies found negative results for COVID-19 infection and no morphological changes related to infection in the placentas [15,16]. Taglauer, *et al.* however reported that of 15 placentas collected from mothers infected with COVID-19, all organs showed signs of SARS-CoV-2 infection, and in 5 (30%) cases, the virus was passed to their neonates [17].

An interesting feature in the scientist magazine reports the findings from a twin birth to a mother who tested positive during delivery. One placenta was heavily infected with the virus and severely inflamed while the other was mildly affected, both babies however tested negative for the virus. This could imply a buffering role for the placenta in preventing the vertical transmission of COVID-19 [18].

### Maternal COVID-19 infection and effect on fetus

Cellular studies reveal that the expression of COVID-19 receptor is attenuated in females, in keeping with the epidemiological observation that most COVID-19 infections to date have occurred in men [19]. However, pregnant women are likely to be at increased risk of severe infections, with the potential for adverse maternal and perinatal outcomes. This concern is based on previous reports from outbreaks of related coronaviruses which caused SARS and MERS. Both these syndromes were found to be associated with worse outcomes during pregnancy [20,21].

Moreover, although pregnant women have a weakened immune system due to the fetal allograft, it seems that they do not exhibit an increased susceptibility to COVID-19. A possible explanation has been hypothesized, after the major advancements in treatment of COVID-19 with mesenchymal stem cell (MSC) therapy and how it could help reverse the outcome of the 'cytokine storm'. Similarly, circulating fetal stem cells might have a protective impact on mothers and contribute to the observed mild and even asymptomatic COVID-19 infections during pregnancy [22].

Maternal infection with COVID-19 may have significant unfavorable impact on the fetus through its effects on maternal health per se or the placenta. A recent systematic review including all reports published on COVID-19, SARS and MERS coronaviruses in pregnancy, revealed that COVID-19 infection was associated with higher rate of preterm birth, preeclampsia, cesarean, and perinatal death [23]. Similar findings were reported in a meta-analysis of 13 publications, adding that the most common complications were neonatal pneumonia and respiratory distress syndrome in infants born to COVID-19-positive mothers [24].

In general, it appears that pregnant women who experienced a mild to moderate COVID-19 infection did not have an increased risk for adverse pregnancy outcomes. A study by Metz., *et al.* found that mothers with a critical COVID-19 infection were at increased risk of perinatal complications. Women who were seriously ill (12%) were more likely to be of older age, obese, or have a higher BMI and were more likely to have comorbidities, such as diabetes or hypertension [25].

There is limited data describing the effects of COVID-19 maternal infection during early pregnancy, that and data detailing the occurrence of spontaneous abortion. More studies are needed to assess this impact, especially that there is hypothetical concern that fever occurring in the first trimester may increase the risk of miscarriage and genetic abnormalities. We would like to caution the readers of reports of abortions occurring in the first trimester that these were terminations of pregnancy and not miscarriages, due to the worry of carrying a fetus infected with SARS-CoV-2 and the fear of the unknown outcome of COVID-19 on pregnancy in its early days.

### Premature labor or delivery (PTL)

Rates of PTL were relatively heightened by SARS-CoV-2 infections in mothers, with estimated rates ranging from 12% to 26%. These rates could be exaggerated however since studies mostly assessed severely ill mothers, while others attributed them to different obstetrical practice patterns in different countries [26,27]. The symptoms accompanying COVID-19 infection, such as fever and hypoxemia may increase the threat of PTL or force unnecessary intervention. Other factors include untimely rupture of membranes and irregular fetal heart rates. However, it appears that pregnant women who were infected but asymptomatic also showed more preterm delivery than non-infected pregnant women.

A national cohort from the UK Obstetric Surveillance System (UKOSS), of pregnant women admitted to hospital with confirmed COVID-19 infection, reported that of 262 women who gave birth during the study period, 66 (25%) women delivered prematurely, and maternal COVID-19 infection was ascertained to be the cause in almost half of them (48%) [28]. Death was reported among women and neonates. Three women died as a direct result of complications of COVID-19 and two from other causes [28]. Others reported that in

critically ill women, 60% underwent a cesarean delivery, 50% of babies were admitted to the NICU, 42% had preterm births, and 40% developed high blood pressure during pregnancy. Four women (0.3%) died due to COVID-19 - a rate much higher than that for uninfected pregnant women in the US [25].

The pandemic related psychological distress, which is discussed in a separate section in this review, poses a great threat on the fetus in terms of premature birth and its untoward consequences. In general, stressful events during pregnancy are associated with a 1.76-fold increase in the incidence of PTL [29]. The pathway starts with an exposure to stress that causes the release of corticotropin-releasing hormone (CRH) from the hypothalamus, which then stimulates the release of adreno-corticotropin hormone (ACTH) from the pituitary gland resulting in the release of cortisol from the adrenal cortex. In pregnancy, cortisol stimulates placental CRH (p-CRH) sparking a positive feedback loop between the fetal adrenal gland and p-CRH that causes an exponential rise in estrogen hormone, thus triggering premature labor [30].

### Cesarean section (C-section)

It also appears that rates of delivery via cesarean section (c-section) are higher among pregnant women infected with SARS-CoV-2. A multinational retrospective cohort study from 22 different countries revealed that the most common delivery mode in infected women was c-section, at a rate of 54% [26]. Almost similar rates were reported in a systematic review by Metz., *et al.* and the UKOSS study [25,28].

This increased rate of c-sections might be explained by the concerns of vertical transmission in some hospitals at the beginning of the pandemic. Others were also concerned about possible transmission through vaginal delivery [31]. Moreover, studies have reported infected mothers choosing elective c-section to terminate pregnancy [32,33]. Additional explanations could be the increased fetal distress and abnormal heart rate which could lead to an emergency c-section to relieve distress [34]. This explains why a review of the first 13 articles published between January and March 2020 reflecting the maternal and perinatal outcome of COVID-19 infection reported a remarkably high c-section rate of 84.7% [27].

### Stillbirth and neonatal death

An increase in stillbirth rate has been observed during the COVID-19 pandemic, however none were associated with COVID-19 [35,36]. As per the World Association of Perinatal Medicine (WAPM) paper, of 266 infected women who gave birth, there were 11 cases of perinatal death. Six (2.3%) of the neonates were stillbirths. There were 5/251 (2.0%) cases of neonatal death, of which three were born preterm and the other two died after developing late-onset sepsis [26]. Anand and colleagues reported a stillbirth rate of 57 per 1000 total births (4/69); and none could be classified as congenital infection due to COVID-19 as no autopsy or examination of placental or fetal tissue was performed [37]. Knight., *et al.* also reported five cases of neonatal death; three deaths were unrelated to SARS-CoV-2 infection, and two stillbirths of undetermined cause of death [28].

Most recently, a case of fetal death associated with vertical transmission of COVID-19 was reported [38]. The mother had an uneventful pregnancy until 25 weeks gestation, and at 27 weeks she presented with severe COVID-19 infection and intrauterine fetal death. Following her cesarean delivery, consented autopsy was carried out on the stillborn. The placenta and blood collected from the umbilical cord tested positive for the virus, but all fetal tissue samples tested negative for the RNA of SARS-CoV-2. However, the presence of oligohydramnios along with low weight placenta that was showing severe decidual vasculopathy on maternal surface and focal thrombosis of fetal placental vessels were confirmatory of placental insufficiency that led to fetal demise.

There are speculations that maternal infection during the early months of pregnancy could lead to more drastic consequences on the fetus. Baud., *et al.* reported a second-trimester miscarriage in a mother infected with COVID-19. The miscarriage could be related to placental infection as confirmed by virological findings in the placenta [39].

It is unclear so far if there is a causative effect for COVID-19 infection when it comes to stillbirths, therefore further studies to evaluate this outcome are needed.

### **Pandemic lifestyle and effect on fetus**

The state of alarm that has driven the world to impose lockdowns and confinement at home in addition to social distancing and isolation, lead to drastic modifications in the lifestyle of the human population, including pregnant women.

What is interesting is that a number of institutions around the world have reported anecdotal observations that during the peak of COVID-19 pandemic, there actually was a reduction in preterm birth, and hence admissions to neonatal care units. Hedermann, *et al.* revealed that in Denmark, a significantly lower rate of extremely premature children was reported during the lockdown compared with the corresponding mean rate for the same dates in previous years [40]. A similar study in Ireland by Philip, *et al.* reported unprecedented reduction in birth of very low birth weight (VLBW) and extremely low birth weight (ELBW) infants [41]. A recent retrospective cohort by Lemon, *et al.* sought to explore the potential causes behind the decrease in preterm birth and found a decreased incidence of PTL in the full population studied. Stratification of finding however indicated that the decreased incidence of PTL was only observed in white, advantaged populations receiving care from non-outpatient care providers [42].

We believe that reduced social contact and strict hygiene during the pandemic may have reduced maternal infections, which is a common cause of PTL. Additionally, the lockdown reduced iatrogenic interventions by health care professionals (HCPs) that might have caused some early deliveries. It also could have had some positive impact on pregnant women. Working-from-home in less stressful environments and without the need for commuting may have played a role in reducing stress.

### **Pandemic psychology and effect on fetus**

Maternal stress levels, anxiety and depressive symptoms have increased during the pandemic. It appears that food scarcity and lockdown has led pregnant women to consume inadequate diets [43] with excessive amounts of sugar which would predispose them to overweight and obesity. Additionally, confinement has rendered mothers less active, and restricted their engagement in regular physical activity such as walking. These could potentially lead to various pregnancy complications and maternal-fetal pathologies.

Many women have also shown high levels of stress during the COVID-19 pandemic, their major concerns being contracting the virus alongside financial difficulties, psychological distress, and domestic conflict [44]. Several studies have consistently linked maternal stress in the prenatal period with deleterious effects on the fetus. In utero exposure to maternal grief for example was associated with an increased likelihood of an individual taking medication for attention-deficit/hyperactivity disorder (25%) in childhood and taking medication to treat anxiety (13%) or depression (8%) in adulthood [45]. Elevated maternal glucocorticoids due to stress during fetal development are associated with a higher likelihood of preterm birth and intrauterine growth restriction and predisposition to obesity and other late-onset diseases [46].

It is quite difficult to follow-up on the impact of prenatal maternal stress through the childhood years. Some studies have been able to confirm the impact on brain development, however. The first prospective study to show that a pattern of pregnancy anxiety is related to specific changes in fetal brain morphology, revealed altered gray matter volume in brain regions of children aged 6 to 9 years, thus making them more vulnerable to neurodevelopmental and psychiatric disorders as well as cognitive and intellectual impairment [47].

### **Fetal interventions during the pandemic**

This pandemic has had quite an impact on health care provision for both the mother and the fetus. On one hand, HCPs who have been at the frontline, have either been affected by the infection themselves, or have practiced self-isolation and shielding [44]. On the other

hand, women are reluctant to attend clinics and hospitals out of fear of contracting the virus. This could therefore lead to delay in seeking treatment and aggravating pregnancy outcomes [44].

Given the challenges for HCPs to balance risks and benefits of providing care in the pandemic setting, the North American Fetal Therapy Network (NAFTN) has suggested guidelines (Table 1) to follow when caring for the fetus during the COVID-19 pandemic [48]. It is of utmost importance to remember that maternal health always takes priority over fetal status, and that the evidence for risk of vertical transmission of the infection through fetal intervention is still limited.

	NAFTN recommendations
HCPs	<ul style="list-style-type: none"> <li>• Use of appropriate personal protective equipment (PPE).</li> <li>• Allow participation of essential HCPs only.</li> <li>• Adequate cleansing of equipment following stringent protocols as per ISUOG.</li> <li>• Limit direct patient contact especially for all non-essential staff.</li> <li>• Suspend all interventional research protocols during the pandemic.</li> <li>• Conduct preoperative SARS-CoV-2 testing for patients undergoing fetal interventions. In patients with positive test results or who are symptomatic, procedures should be delayed for 14 days or until patients meet local standards for recovery.</li> </ul>
Fetal procedures	<ul style="list-style-type: none"> <li>• Conduct fetal procedures arising from life-threatening conditions and that are of life-threatening nature as they are not elective. These include but are not limited to fetal blood transfusions, fetoscopic placental laser surgery or selective reduction, shunting procedures, myelomeningocele repair and ex-utero intrapartum therapy.</li> <li>• Avoid transplacental passage of the needle or fetoscope or shunt trocar. An exception might be fetal transfusion into an anterior placental cord insertion, or procedures requiring open fetal surgeries.</li> <li>• Avoid general anesthesia as procedures that violate the aerodigestive mucosa and/or result in body fluid aerosolization are associated with SARS-CoV-2 transmission. Instead, most fetal procedures can be performed under conscious sedation or local anesthesia.</li> </ul>

**Table 1:** NAFTN guidelines for fetal care during the COVID-19 pandemic.

Be aware of a potential aggravation of SARS-CoV-2 infection with any intervention; this could result in increased morbidity or mortality for both fetus and mother. Decisions for any intervention should be made based on local healthcare practices and patients made aware of adjustments to adapt to evolving pandemic.

It is also worth noting that women’s basic human rights during labor have been inadvertently violated worldwide, as per the Board of Human Rights in Childbirth. These rights include women being denied the right to a companion during birth, women being subjected to forced inductions and c-sections without medical indications, and mothers being separated from their infants and discouraged from breastfeeding [44].

### Fetal outcome post covid infection

Data describing the effect of SARS-CoV-2 in the neonatal population is scarce. A prospective population-based cohort study in the United Kingdom by Gale, *et al.* confirmed that neonatal infection following birth to a mother with perinatal SARS-CoV-2 infection is generally mild and asymptomatic and the possibility of vertically acquired infection is rare. Of 66 neonates with confirmed infection, of whom 42% had severe cases, 17 (26%) babies were born to perinatally infected mothers; two (3%) were considered to have possible vertically transmitted infection within 12 hours of birth, and eight (12%) had suspected nosocomial acquired infection [49].

Gao, *et al.* reported on 24 infants born to women with COVID-19, results of nucleic acid tests from throat and anal swab specimens and results of antibody assays were negative and none had complications related to pneumonia. A total of 15 (62.5%) had detectable IgG and 6 (25.0%) had detectable IgM. These findings are not sufficient to confirm SARS-CoV-2 vertical transmission without positive nucleic acid testing [50].

Preterm neonates may be at an increased risk for perinatal COVID-19 infection. The fetus is prepared towards immunologic tolerance in the semi-allogeneic environment of the uterus and may not mount efficient inflammatory reactions to infection [51]. Additionally, maternal immunoglobulins which have a protective effect, do not reach their maximum levels until term; they reach about 50% level at 28 - 30-weeks of gestation [52]. To top it all off, the skin integrity of preterm neonates is still immature and may also be a risk factor for perinatal transmission [53].

Even though the impact of infection in the neonate has been reported to be mild and none worrying, the aftermath may not be apparent at birth and long-term follow-up of neonates born during this period, whether infected or not, remains a necessity.

### COVID-19 and risk of birth defects in the fetus

Viruses can have a detrimental impact on the fetus. The inflammation that arises in response to a maternal viral infection can affect numerous aspects of fetal brain development and thus lead to a vast range of neurological consequences [13]. Data from a large Swedish cohort study found that a mother's exposure to any viral infection during pregnancy increased the offspring's diagnosis of autism (Hazard Ratio (HR) 1.79; 95% confidence interval (CI), 1.34 - 2.40) and depression (HR, 1.24; 95% CI, 1.08 - 1.42) [54]. Infection with influenza has also been associated with congenital deformities, such as cleft palate and neuronal tube defects to name a few.

As for COVID-19, a reported case of a neonate born to a mother infected in the third trimester not only demonstrated vertical transmission but also described neurological compromise in the neonate [7]. Neuroimaging consistently indicated white matter injury, which can be caused by the vascular infection induced by SARS-CoV-2 virus [7].

The risk of defects however does not depend on exposure to virus alone, but also to the medical treatment that the mother might receive to attenuate COVID-19. Antiviral drugs, used in the treatment of COVID-19, may play a role in development of neural tube defects (NTDs) in the fetus in early pregnancy. Not only that, but the use of these drugs could also lead to other adverse outcomes such as miscarriage, fetal growth restriction, and structural abnormalities [55].

### Fetal programming

Away from genetic and epigenetic reasons, the maternal environment encompassing the fetus during its developmental stages is considered an influential mechanism for the development of late onset diseases in adulthood through prenatal or fetal programming.

During the winter of 1944 - 1945, and near the end of World War II, heavily inhabited cities in the German occupied western Netherlands faced a vicious famine. The effect of malnutrition on children born during that Dutch Famine, as it has been dubbed, was reported in

several studies. Affected children were found to be at risk of obesity, diabetes, cardiovascular diseases, among other diseases throughout their developmental and adult years [56]. This has been explained by the phenomenon of fetal programming which was reproduced in experimental animals [57] and proved that the programming of adult obesity can be initiated by intrauterine food restriction. Fetal programming can create permanent alterations of one or more relevant pathways during early development. These pathways may include appetite regulation and altered energy expenditure in the fetus or the adult later in life.

Mothers during the current lockdown are not malnourished, but they consume junk food and have an unbalanced diet that can be rich in fat coupled with lack of exercise. Research has revealed that the fetal offspring from both lean and obese mothers who are chronically consuming a high-fat diet has a 3-fold increase in liver triglycerides and a 2-fold increase in percent body fat. A developing fetus is highly vulnerable to excess lipids, independent of maternal diabetes and/or obesity [58].

In addition, altered expression of adipocytes has already been reported in response to maternal undernutrition [59]. Studies have confirmed that both overeating and undereating during pregnancy can increase an infant's risk of obesity and heart disease later in life, but for different reasons. The drastic consequences of lockdown on fetuses conceived during this period may include obesity and other health issues that the future can only tell.

### Conclusion

To sum up, it appears that the fetus is being attacked by 3 weapons during this pandemic: the virus itself through vertical transmission, severe maternal illness that jeopardizes fetal health, and antiviral medication which may prove to be teratogenic. Understanding how these weapons impact the fetus is of concern as they could particularly cause neurodevelopmental malformation.

The short-term impact of COVID-19 infection on the fetus is manifesting itself as we speak. The impact of this virus down-the-line however remains to be explored, with emphasis on long-term surveillance of infants who are SARS-CoV-2-positive at birth or have been exposed to the virus in utero.

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