



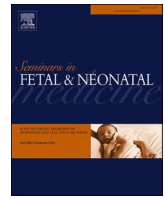
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Transmission of SARS-CoV-2 from mother to fetus or neonate: What to know and what to do?

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ABSTRACT

SARS-CoV-2 can be vertically transmitted from the mother to the fetus and the neonate. This transmission route is rare compared to the environmental or horizontal spread and therefore, the risk can be deemed inconsequential by some medical providers. However, severe, although just as rare, fetoneonatal consequences are possible: fetal demise, severe/critical neonatal COVID-19 and multi-inflammatory syndrome (MIS-N) have been described. Therefore, it is important for the clinicians to know the mechanism of vertical transmission, how to recognize this, and how to deal with neonatal COVID-19 and MIS-N. Our knowledge about this field has significantly increased in the last three years. This is a summary of the pathophysiology, diagnostics, and therapeutics of vertical SARS-CoV-2 transmission that clinicians apply in their clinical practice.

1. Background

Although initially denied when the worldwide attention was concentrated on the effect of pandemics in the general population, the vertical transmission of SARS-CoV-2 (i.e.: from the mother to the fetus or the neonate) eventually became evident. In 2020, two separate teams in Germany and United States detected SARS-CoV-2 in placental tissues at the maternal-fetal interface using electron microscopy [1,2]. This was not totally surprising as the placenta similar to the lung is an organ of gas exchange. In July of the same year, our team was able to demonstrate, for the first time, the transplacental passage of SARS-CoV-2 in a woman affected by COVID-19 who gave birth to a critically ill baby requiring neonatal intensive care unit (NICU) admission [3]. This case had worldwide media coverage but was published several months after its occurrence, to allow completing multiple virological, immunological and pathological tests needed to confirm the transplacental transmission. In 2021, the World Health Organization (WHO) added SARS-CoV-2 to the list of vertically transmittable infectious agents, whose last example was the Zika virus [4]. We offer here a comprehensive update of the SARS-CoV-2 vertical transmission with focus on pathophysiology and clinical management.

2. Where and when does it happen? Defining the transmission routes

The term "vertical transmission" encompasses different types of transmission that may happen: **1) "In-utero"** transmission during pregnancy through the placenta, infecting the amniotic fluid and subsequently entering the airways or the gastro-intestinal tract or the ear canal, **2) "Intrapartum"** transmission at the moment of delivery, through the contact with the maternal genital mucosa and its secretions or with another maternal biological fluid (i.e., blood, fecal matter, urine etc.) and, **3) "Ascending"** infection - during the pregnancy or the delivery as vaginal ascending infection with the virus passing from the vagina into the uterine cavity via the cervical mucosa. The first two ways have been described [4], while the third has not been demonstrated for SARS-CoV-2 as of this writing. It is a more complex scenario implying that SARS-CoV-2 would gain upstream access into the uterine cavity and then into the amniotic sac which may become compromised and ruptured [5,6]. Once the amniotic fluid is infected, the fetus would become infected as described above. The ascending infection is the most common route by which bacteria may invade the uterine cavity [5,6], but the relatively low prevalence of SARS-CoV-2 positivity in cervico-vaginal mucosa [7–10] may prevent its occurrence. Patients with vaginal secretions positive for SARS CoV-2 are likely to present

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with a higher circulating viral load and may facilitate the transplacental infection [7,11–14]. But even in presence of a mucosal infection, to create an ascending transmission, it should locally spread, trespass the mucosal immune defenses and gain access to the uterine cavity which is uncommon for viruses [15].

The first two scenarios have been defined as *in utero* and *intrapartum* transmission by the WHO [4]. The possibility of SARS-CoV-2 transmission via human milk has been essentially excluded as the virus has been inconsistently found in milk, and when present, a very low viral load was detected, although the capability to replicate has not been confirmed [10,16]. Conversely, antibodies have been detected in human milk, particularly after maternal immunization using mRNA vaccines [17]. Theoretically, the mother-to-child transmission through droplets or aerosol occurring in the first 72 h after delivery might also be considered “vertical”, but this has the same biological features of common environmental “horizontal” transmission, therefore, it will not be discussed here.

3. How often does it happen? The epidemiology

In the last 3 years, relevant data has been accumulated for both *in utero* and *intrapartum* transmissions. According to a meta-analysis published right after the first pandemic wave, these seem to represent approximately 40% and 60% of all vertical infections, respectively, which in their turn account for approximately 30% of all neonatal infections (i.e.: ~70% of neonates are infected environmentally through the common route based on droplets and aerosol) [18]. In the beginning of pandemics the prevalence of vertical SARS-CoV-2 infection was estimated around 5% of positive pregnant women [19]. Recent data accumulated from a living meta-analysis had reduced the estimated prevalence at around 2% [20]. This clearly indicates that the vertical SARS-CoV-2 transmission does not represent a public health problem. Nonetheless a potential publication bias can be hypothesized so the prevalence may be relatively underestimated. Moreover, fetal and neonatal SARS-CoV-2 infections are classified with a variable level of likelihood using a dedicated clinical definition [21] or the WHO criteria [4] and this is needed because of the biological complexity of SARS-CoV-2 perinatal infection: the exact classification can only be obtained performing several tests on various matrices, which are not always available in all clinical laboratories [22]. In some, cases may go undiagnosed and, as an additional consequence, it is difficult to know the relative exact proportion of *in utero* and *intrapartum* transmissions, since not all tests that are needed to classify a case are systematically performed. Along these lines, COVID-19 is much less common in neonates than adults, although severe and life-threatening cases have been described. It is then important for obstetricians, pediatricians, and particularly for neonatologists, to be aware of this and to know how to recognize these cases and strategize management. Vertical SARS-CoV-2 transmission is significantly more likely when maternal COVID-19 is severe (OR: 2.4 (1.3–4.4), when mothers need critical care (OR: 3.5 (1.7–6.9) or die (OR: 14 (4.1–48) [20]. It is also known that some viral strains could theoretically influence the risk of vertical transmission by increasing the maternal disease severity, as this has been demonstrated for the alpha (α), gamma (γ) and delta (δ) variants [23–26], while omicron (\omicron) strain causes less placental damage and might be associated with a reduced clinical severity and likelihood of vertical transmission [27]. These data were accumulated mainly in the pre-vaccination era such that immunization has changed the maternal disease severity and the risk of vertical transmission [28]. Further, it is unknown if the currently available antivirals may reduce this risk by reducing the circulating viral load and the maternal clinical severity. Some additional factors suggesting an increased risk of transplacental infection might be identified by the fetal monitoring close to delivery and will be discussed further. No link between vertical transmission and any other maternal characteristics has been demonstrated.

Table 1

Summary table of the principle to distinguish the two main SARS-CoV-2 vertical transmission routes, according to the WHO definition [4].

	Maternal Infection	Evidence of <i>in utero</i> exposure	Viral persistence or immune response*
<i>In utero</i>	Yes	Yes	Yes
<i>Intrapartum</i>	Yes*	No	Yes

Note:

1. Maternal infection must be diagnosed according to standard WHO criteria. Maternal infection is intended to have occurred anytime during the pregnancy for *in utero* and in the time window from 30 days before to 2 days after the delivery, for *intra partum* transmission.
2. Evidence of *in utero* exposure is granted with several possible (virological, pathological or immunological) tests performed on placenta, amniotic fluid or cord blood. Viral persistence or immune response in the neonate is demonstrated with RT-PCR performed on several possible sites or with serology assay at different timepoints.
3. Both types of infection are classified in three level of likelihood (confirmed, possible and unlikely) according to the type of specimen and test used. The policy we suggest in the main text is compliant with this WHO guidance.
4. *For the diagnosis of *in utero* transmission with fetal demise, the viral persistence or immune response is replaced by the fetal tissue positivity (that might be associated with placenta or amniotic fluid positivity) obtained with RT-PCR or several possible pathology/immunology techniques.
5. More details regarding sampling, tests and their timing are freely available in the WHO definition for perinatal SARS-CoV-2 infections [4].

4. How does it happen? The mechanisms

Mechanisms of SARS-CoV-2 vertical transmission are different if it occurs *in utero* or *intrapartum*. A complete molecular review of biological mechanisms is out of the scope of this manuscript, but we will focus on the main principles of the pathophysiological aspects. It is important to remember that, because of the complex biology of perinatal SARS-CoV-2 infections, the distinction between the two transmission routes can only be achieved with multiple tests on different samples, as described by WHO guidance [3]: these are schematically summarized in Table 1. The data summarized below have been accumulated mainly in the early phase of the pandemic. As the immunization progressed worldwide, the cases of COVID-19 during pregnancy decreased and so were the vertical infections [28,29], as anti-Spike-IgG can easily pass the placenta in vaccinated pregnant women [17]. Therefore, it might be more difficult to further improve our knowledge on these mechanisms.

4.1. *In utero* transmission

For SARS-CoV-2 to be transmitted transplacentally, a few things must occur (Fig. 1): 1) there should be a relevant circulating maternal viral load, although transiently; 2) at the same moment, viral receptors must be expressed on cellular membranes in placental and fetal tissues; 3) the placental barrier must be disrupted, and its defensive mechanisms must be overcome to allow the viral passage. All these conditions must occur at the same time and in a significant way to produce an active fetoneonatal infection, thus the need for this coincidence helps explaining the relative rarity of transplacental transmission. Maternal viremia has been reported during SARS-CoV-2 infection, but inconstantly and in relation with the clinical severity [30–32]. Angiotensin-converting enzyme-2 (ACE2) receptors are expressed in placental tissues throughout the pregnancy [33]. This expression is, however, variable depending on interindividual genetic variability, gestational age and comorbidities, such as pre-eclampsia [34–37]. The presence of ACE2 receptors in fetal tissues was already known before the pandemics [38] and it has been confirmed thereafter, although it is not constant in all fetal tissues [39,40]. For the virus to invade the cells, these receptors are not sufficient though, since the Spike protein must be cleaved by transmembrane protease serine-2 (TMPRSS2) [41]. In fact, this is needed to expose a fusogenic peptide that promotes the fusion of the

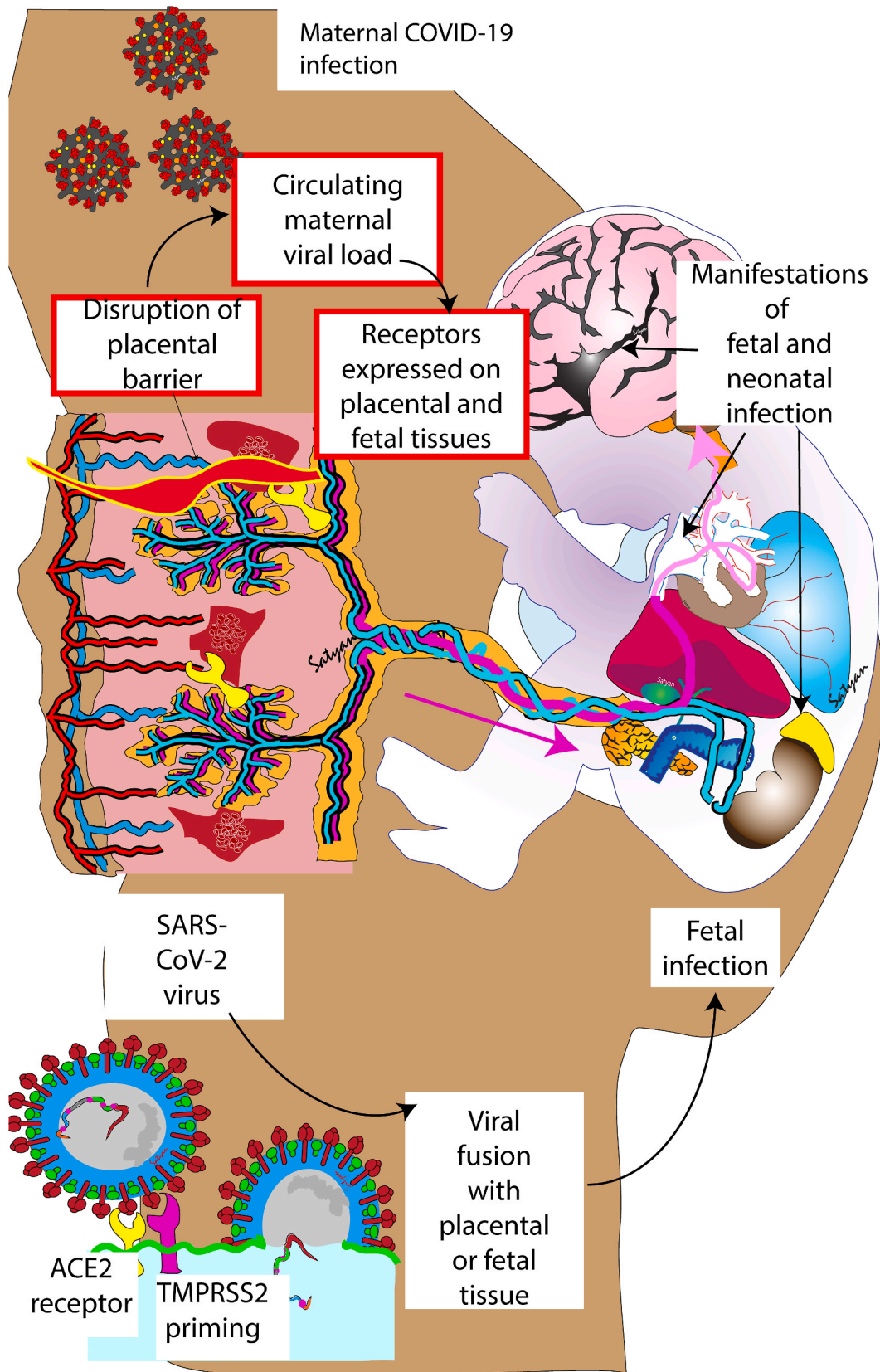


Fig. 1. Potential mechanisms factors influencing SARS-CoV-2 in utero (transplacental) transmission. Maternal viremia, disruption of placental barrier and presence of receptors in fetal and placental tissue (red boxes) should occur simultaneously for in-utero transmission to occur. The presence of angiotensin converting enzyme 2 (ACE2) receptors in fetal tissue and co-existence of transmembrane serine protease 2 (TMPRSS2) receptor that can prime the spike protein in the fetal tissue is necessary to enable viral fusion with fetal tissues. Copyright Satyan Lakshminrusimha.

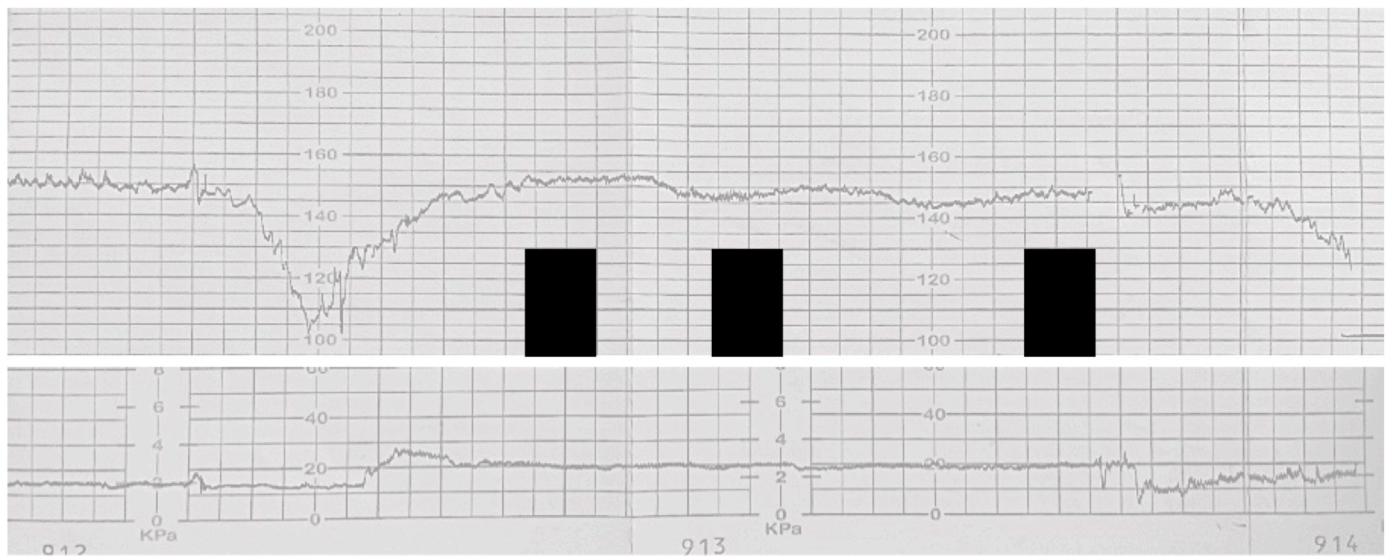


Fig. 2. Cardiotocogram (CTG) from an illustrative case of *in utero* (transplacental) transmission. Category III-CTG (absent baseline fetal heart rate variability and recurrent decelerations outside labor) recorded at 33 weeks' gestation (black boxes mask personal informations). Maternal history was marked by biochemical abnormalities during moderate COVID-19 (prolonged APTT, lymphocytopenia, transaminitis). A cesarean delivery was performed, and the neonate suffered mild perinatal asphyxia (5' Apgar score = 5, cord pH = 7.25). The case fulfilled the WHO definition for confirmed *in utero* infection [4]: RT-PCR was positive on nasopharyngeal aspirate both at the birth and DOL4; RT-PCR was also positive on non-bronchoscopic bronchoalveolar lavage (DOL1) and in the placental tissue. Placenta showed the typical signature of SARS-CoV-2 placentitis (perivillous fibrin deposition, chronic histiocytic intervillitis and trophoblastic necrosis).

viral envelope with the host cell membrane [42]. Nonetheless, the factors controlling TMPRSS2 expression (beside fetal sex [43]) are not well known and may not coincide with those influencing ACE2 receptor, thus this complicates the situation. Finally, the existence of other pathways and viral receptors have been hypothesized: placental macrophages (Hofbauer's cells) and circulating fetal monocytes could carry the virus [44], but this mechanism is present, if at all, only in a minority of cases [45]; other receptors might be used by some viral strains and particularly by the omicron variant, but little is known about their placental presence and their possible role in the transplacental transmission [37, 46,47].

The presence of viremia and viral receptors may be less important than the third requirement, that is the disruption of the placental barrier. In fact, the histological or virological evidence of SARS-CoV-2 placental infection is more common than the fetoneonatal infection, thus local defenses must play a relevant role in preventing the contamination [48]. Recently we demonstrated, in a controlled study [49], that the placental viral load and the levels of ACE2 and TMPRSS2 placental expression do not significantly influence the transplacental transmission. Conversely, a strong placental inflammatory reaction is known to prevent the passage of many infectious agents to the fetus [50] and this reaction has been observed in many COVID-19 pregnant patients [51,52]. Following placental inflammation, post-entry pathways and autophagy can be activated to eliminate the virus from the already infected placental cells [53,54]. All these obstacles must be overcome in order to produce an active transplacental infection.

An excessive or dysregulated host inflammatory reaction can also play the opposite role and facilitate viral spread, as it happens for acute respiratory distress syndrome and multi-organ failure observed in patients with critical COVID-19 [55]. A strong inflammatory reaction (typically characterized by diffuse chronic intervillitis, necrosis and massive fibrin perivillous deposits (>50% of the placenta)) has been seen in almost all cases of transplacental transmission and is now considered a typical "SARS-CoV-2 placentitis" [49]. This causes vascular fetal malperfusion and creates suitable anatomical environments for the passage of virions to the fetus. It is unclear if these anomalies may increase the risk of fetal growth restriction [56,57] (see below), however they are certainly associated with fetal distress (recognizable at the

cardiotocogram, Fig. 2), stillbirths, birth acidosis and need for NICU admission [49,58]. The factors facilitating or preventing *in utero* SARS-CoV-2 transmission are summarized in Fig. 2.

4.2. Intra partum transmission

Intrapartum transmission is a common way of contamination for several infectious agents during vaginal delivery and it can happen for SARS-CoV-2 as well. This transmission route is obviously possible only for assisted or unassisted vaginal deliveries. ACE2 receptors are upregulated in vaginal epithelium during the pregnancy, making the contamination theoretically possible [59], although we do not have any data about the vaginal TMPRSS2 expression and the prevalence of SARS-CoV-2 vaginal infection is relatively low [7–9]. The virus can reach the vaginal mucosa through systemic circulation and seminal or fecal contamination [7,60]. Personal hygiene measures may therefore be important, since the viral shedding in the stools is longer than in other bodily fluids [61]. *Intrapartum* might be more common than *in utero* contamination [18], but available data on this point are conflicting [62]. The actual proportion of *intrapartum* and *in utero* transmissions is difficult to clarify since there is a relevant degree of publication bias and many data come from the first pandemic waves when, at least in some settings, perinatal care might have been suboptimal and some tests may have been lacking. Furthermore, both *in utero* and *intrapartum* transmission requires several pre-existing factors (such vaginal delivery or disruption of placental defenses as discussed above) to occur and this complicates the estimation of their relative incidence.

Interestingly, *intrapartum* infections have been described irrespective of the elimination of SARS-CoV-2 from maternal airways and despite the presence of circulating antibodies [63]. This is likely due to the persistent viral presence that may last longer in vaginal or rectal tissue than in upper airways [61]. To reduce the transmission risk, particular care should be provided during vaginal birth assistance by reducing fecal contamination [64]. Performing recto-vaginal swabs to all pregnant women affected by COVID-19 or infected by SARS-CoV-2 in the proximity of delivery is useful to classify an eventual vertical transmission [4] and is a common practice for other perinatal infections [65]. The positive results from these tests should not be used to decide about the



Fig. 3. Factors increasing (green) and decreasing (red) the likelihood of SARS-CoV-2 *in utero* transmission. Factors have been listed according to the current available translational and clinical knowledge; see references in the text. The relative weight of each factor cannot be estimated.

delivery route. The delivery route choice should be based on common principles of obstetric care and case-by-case evaluation of multiple factors (see below). The factors facilitating or preventing *intra partum* SARS-CoV-2 transmission are summarized in Fig. 3.

5. What can we do to prevent and detect vertical SARS-COV-2 transmission?

There is not much to do to prevent the vertical transmission, beside promoting vaccination which has decreased the incidence by virtue of the reduction of maternal infection and its severity [28,29]. Strict hygiene measures should be adopted in the delivery room to prevent contamination from maternal biological fluids and the multidisciplinary team should be adequately trained to assist these deliveries [66].

During the first pandemic waves, approximately 10–22% of COVID-19 pregnant patients delivered vaginally [67,68] and this percentage is likely to be higher now. It is unclear if and how the vaginal delivery protects against the vertical transmission although some data suggest so [62,69,70]. It must be taken into account that cesarean section may be needed for reasons unrelated to COVID-19 and that the SARS-CoV-2 placentitis, which is strongly associated with the transplacental transmission, can present with fetal heart rate abnormalities, which may justify emergency cesarean delivery outside of labor [71]. Since many factors interplay on the occurrence of vertical transmission [72] and the choice of the delivery, a generalized recommendation cannot be provided.

When the risk of vertical transmission is relevant (i.e.: in case of higher maternal clinical severity, high viral load, maternal viremia or cardiotocogram abnormalities suggesting fetal hypoxia, Fig. 2), we advise to send the placenta for virological and pathological analysis. Cord plasma and sterile amniotic fluid collection should also be taken and frozen: they can be used for later testing to provide a correct classification of the vertical transmission [4]. Placenta, amniotic fluid and plasma are therefore considered 2nd level tests, while the first (and often unique) test to be done is the real time-polymerase chain reaction (RT-PCR) on a neonatal nasopharyngeal sample, after having cleansed and dried the baby. It is advised to perform a nasopharyngeal lavage, rather than a swab, because it is easier due to the small size of newborn nostrils and because it ensures a higher sensitivity [73]. In our practice, we perform the test in every neonate born from a mother affected by COVID-19 in the last month before delivery: results are available with a quick turnaround time (approximately 1 hour). If the result is negative, there is no need for any further test, otherwise the aforementioned 2nd level tests will help to classify the case and nasopharyngeal lavage will

have to be repeated after 24–48 h to rule out an exposure without active infection; readers are referred to the WHO definition for more details [4]. In sick neonates admitted to the NICU, other RT-PCR might eventually be done on different samples (i.e.: broncho-alveolar lavage, cerebro-spinal fluid etc ...), depending on their conditions. The neonates should otherwise be assisted according to currently recommended practices and should be cleansed and dried as usual. This policy is compliant with the WHO definition and may provide the needed information to classify perinatal SARS-CoV-2 infections [4].

6. What can happen next? The fetoneonatal consequences

Vertically transmitted SARS-CoV-2 infections can have various consequences both for the fetus and the neonate. They are rare and generally mild, although life-threatening cases and deaths have been reported. The effects on neonates are globally better known than those on fetuses. We summarize here both focusing on practical clinical aspects.

6.1. Fetal consequences of vertical SARS-CoV-2 infection

SARS-CoV-2 does not cause malformations but fetal demises have been described both early [74,75] and late during the pregnancy [76,77]. Owing to its rarity, we are not yet able to identify a critical period when fetal SARS-CoV-2 infection would be more dangerous. Cases of fetal demise have been described only in small case series and we cannot exclude the existence of a publication bias. In fact, by meta-analyzing the published reports, we recently demonstrated that there is no clear relationship between the severity of maternal COVID-19 and fetal demise, while a relevant proportion (34%) of fetuses died without sufficient evidence of an actual fetal infection [76]. This suggests that at least some cases of fetal demise could be due to SARS-CoV-2 placentitis causing fetal hypoxia and hypoperfusion, without the transplacental viral passage. A relevant number (66%) of fetuses, however, presented a certain evidence of viral infection in various organs and tissues and this may be an additional mortality cause [76]. Consistently, we found that stillbirths/late miscarriages occurred approximately 6–13 days after the confirmation of SARS-CoV-2 infection or the beginning of maternal symptoms [76].

This problem may have been underestimated for the same reasons described above (lack of complete virological and pathological investigations). To address this, we performed an analysis of our internal database at Paris Saclay University, and the incidence of miscarriages (between 14- and 24-weeks' gestation) since the beginning of pandemic

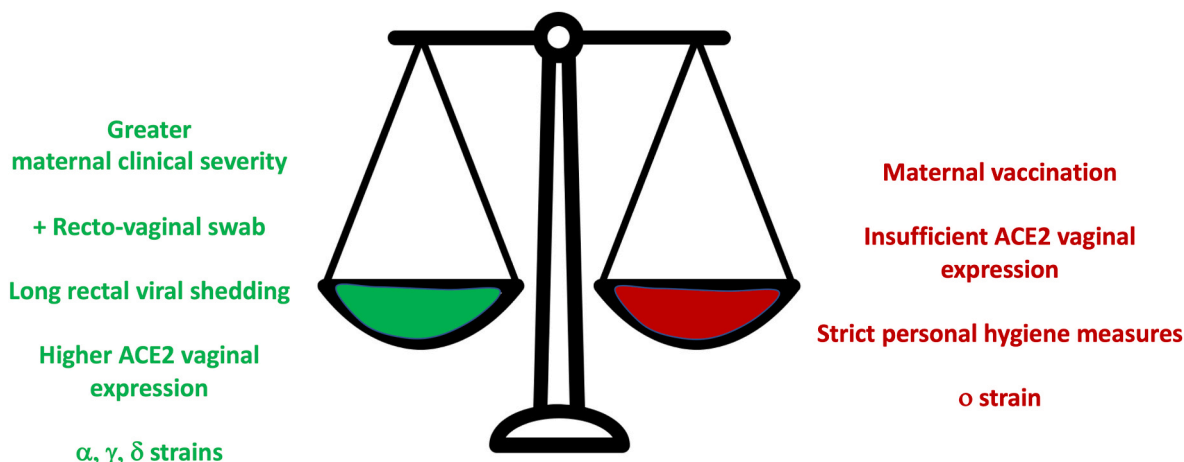


Fig. 4. Factors increasing (green) and decreasing (red) the likelihood of SARS-CoV-2 *intra partum* transmission. Factors have been listed according to the current available translational and clinical knowledge; see references in the text. The relative weight of each factor cannot be estimated.

(that is, from March to October 2020, 3.4%) was like that observed between March and October in 2019 (3.8%) and 2018 (3.7%, $p = 0.862$, χ^2 -test). This suggests that fetal demises induced by SARS-CoV-2 infection might need other still unknown cofactors. With the diffusion of maternal vaccination, these events are likely to become even more uncommon [29] (of note, amongst the meta-analyzed cases, none of the mothers experiencing fetal demise was vaccinated [76]).

The transplacental transmission of SARS-CoV-2 is associated with

fetal distress, acidosis with need for neonatal resuscitation and NICU admission: this seems to be caused by the placental insufficiency induced by the SARS-CoV-2 placentitis [49]. The placental damage might theoretically cause intrauterine growth restriction as observed for other viral placental infections [78]. However, solid data coming from several studies negate an association between SARS-CoV-2 infection and fetal growth restriction at a population level. Intra-uterine growth restriction following SARS-CoV-2 placentitis may however occur in some

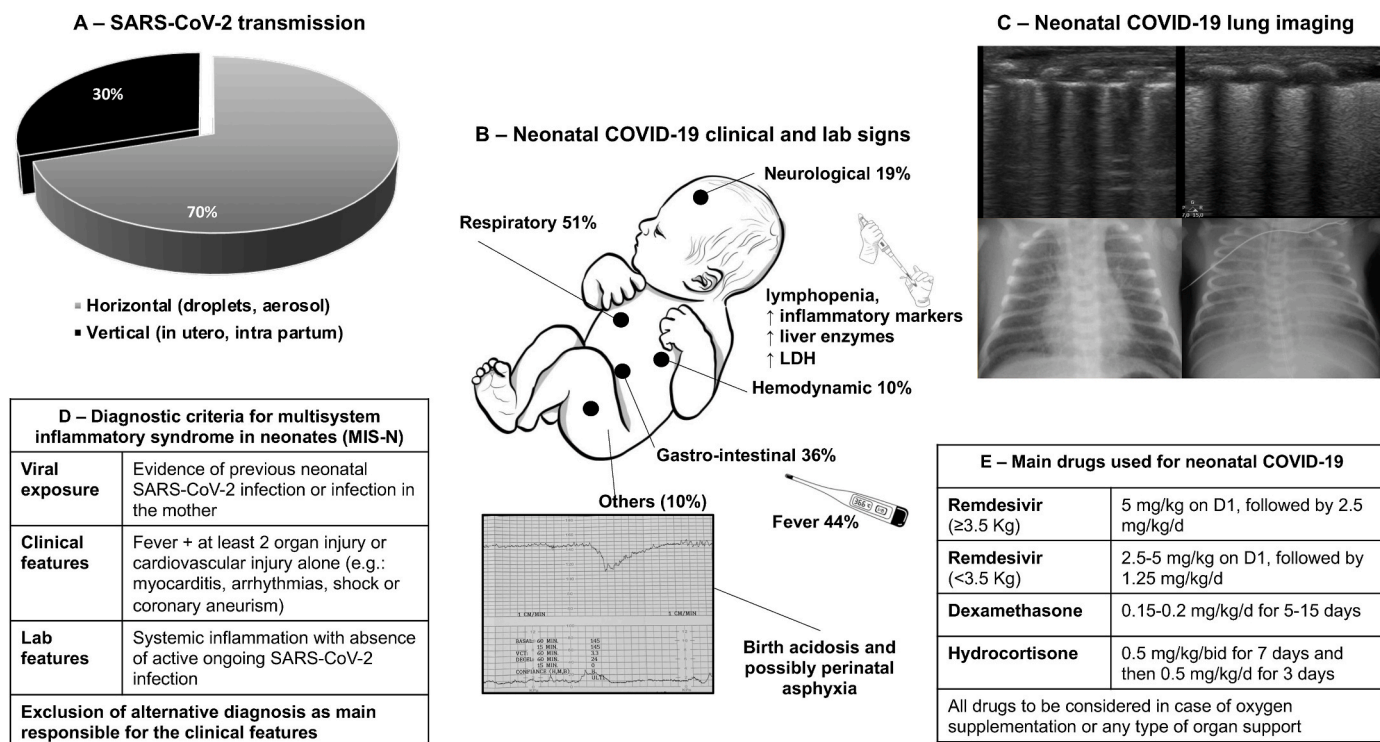


Fig. 5. Main clinical features, laboratory and imaging abnormalities of neonatal COVID-19, as well as diagnostic criteria for MIS-N (adapted from Ref. [96]). **Panel A** shows the distribution of SARS-CoV-2 transmission routes: black and grey areas indicate vertical and horizontal transmission, respectively. **Panel B** reports the clinical and laboratory signs observed in neonates with clinically evident SARS-CoV-2 infection (at least one clinical sign develops in approximately 50% of neonatal infections; multiple signs are possible in a patient), as reported by Ref. [18]. **Panel C** illustrates lung ultrasound and conventional radiology findings in neonates with respiratory involvement: images on the left- and on the right-side show a typical interstitial and alveolar pattern, respectively: the interstitial is more common, but it may evolve in alveolar pattern; neonatal ARDS [106] has been diagnosed in the rare severest cases. **Panel D** reports the diagnostic criteria for multisystem inflammatory syndrome in neonates (MIS-N), as proposed by Ref. [94]. **Panel E** summarizes drug doses for severe/critical neonatal COVID-19 and MIS-N treatment. Remdesivir (VEKLURY®, Gilead, Foster City-CA, USA) has been approved by FDA and EMA for the treatment of neonates weighing at least 3 Kg; same case reports have described its use, at lower doses, also for smaller neonates [96]. Dexamethasone and hydrocortisone are the two steroids used in case series of neonatal COVID-19 and MIS-N have also been used together with intravenous immunoglobulins-G with classical dosing.

Practice points

- Vertical transmission of SARS-CoV-2 happens in 2% of infected pregnant women and consist in either *in utero* or *intrapartum* transmission.
- Specific WHO criteria should be followed for the diagnosis of SARS-CoV-2 vertical transmission, and these requires multiple tests.
- Vertical acquired transmission represent 30% of all neonatal SARS-CoV-2 infections and most of the time they are silent or mild although severe consequences have been described.
- Severe disease may result in fetal demise, neonatal COVID-19 and MIS-N. Neonates infected by SARS-CoV-2 require critical care in approximately 2% and the case fatality rate is approximately 0.1%.
- Intravenous remdesivir and steroids can be used to treat severe/critical neonatal COVID-19 and MIS-N.

particular circumstances, as some cases have been anecdotally reported [79,80]: these might have occurred because of the co-existence of other factors, such as the timing of viral infection in relation to the delivery or the pre-existing placental function.

6.2. Neonatal consequences of vertical infection

SARS-CoV-2 vertical infection can cause neonatal COVID-19. Neonates infected by SARS-CoV-2 are asymptomatic in approximately half of cases and those with clinical manifestations are usually not very ill: this might be due to the lower alveolar expression of viral receptors in neonates compared to adults, while they seem to be preferentially expressed in the upper airways [81–83]. Despite their clinical mildness, neonates can be important virus spreaders, since they still represent a significant proportion of the unvaccinated population [84]. Severe and critical cases of neonatal COVID-19 were also anecdotally reported with clinical features similar to those of adult patients [18,85,86]. The risk for NICU care remains low and difficult to be quantified but it has been estimated at 2% of all neonatal infections [87]; the case fatality rate has been estimated at 0.1% [88]. This creates logistic and epidemiological consequences, since these patients must be isolated to protect the NICU population, and particularly the preterm infants. Isolation should be done in negative pressure rooms (of which not all NICUs are provided), whereas, it is important not to use NICU beds to isolate SARS-CoV-2 positive-neonates not needing critical care [89]. As these infants are more likely doing well, isolation would cause more harm than benefit and is important to avoid it since neonatal emergencies may always happen and catching COVID-19 during the pregnancy increases the odds of prematurity and the general need for NICU admission [90,91]. As NICU beds are a valuable and often insufficient resource, it is pivotal to keep them for those who really need them [89].

We do not know yet if neonatal COVID-19 is more severe following *in utero* or *intrapartum* infection and if clinical severity is different between vertical- and environmental-acquired neonatal infections. The EPI-CENTRE registry will soon provide data on this matter [92]. As we know, the viral strain may influence the severity of neonatal COVID-19 as seen in neonatal infections by omicron variant which, although less frequent [27], were more severe, as their rate of hospitalization is equal in infants aged less than 6 months and in adults beyond 65 years [93].

The distribution of neonatal COVID-19 signs is similar to that observed in adults, with a predominance of respiratory involvement but also neurological, cardiovascular and gastro-intestinal signs [18]. Beside neonatal COVID-19, neonatal inflammatory multi-system syndrome

(MIS-N) can also occur after several weeks from SARS-CoV-2 infection, or in absence of neonatal infection, after a maternal one [94]. MIS-N is characterized by widespread inflammation leading to multiorgan injury and failure possibly linked to the presence of circulating anti-SARS-CoV-2 antibodies and autoantibodies against several antigens induced by the previous viral infection (in the neonate or the mother), while an active SARS-CoV-2 infection is lacking [95,96]. In some genetically susceptible patients, these antibodies would bind to several receptors causing hyperinflammatory state, macrophage activation and organ injury [97]. Neonatal COVID-19 and MIS-N can significantly share the clinical appearance and their difference is essentially represented by the presence or absence of an active SARS-CoV-2 infection. Fig. 5 summarizes the main clinical features of neonatal COVID-19, its laboratory and imaging abnormalities as well as the diagnostic criteria for MIS-N (see Fig. 5).

Some evidence suggests that prenatal exposure to SARS-CoV-2 may be associated with long-term neurodevelopmental sequelae in infants up to 12 months of age [98,99]. This does not seem related to the vertical transmission as the incidence of these sequelae is higher than that of fetoneonatal infection. As worrisome as it can be, this finding requires further studies to understand the cause-effect link and exclude any confounding effect. An in-depth discussion of long-term consequences of neonatal COVID-19 is presented in a different manuscript in this issue.

There are no dedicated criteria to classify the severity of neonatal COVID-19. By modifying the WHO criteria for the adult population, we advise to classify neonatal cases as follows [100].

- **Mild:** only minor clinical signs (e.g.: conjunctivitis, runny nose, rash)
- **Moderate:** fever, mild feeding difficulties, mild diarrhea
- **Severe:** signs requiring hospitalization (e.g.: need for oxygen therapy, dehydration needing intravenous line, neurological signs needing monitoring)
- **Critical:** respiratory, hemodynamic, kidney or liver failure needing vital support; seizure or coma.

Treatment of neonatal COVID-19 shall be based on supportive care, including temperature control with paracetamol (acetaminophen), upper airway cleansing and humidification, attentive hydration, and nutrition for mild-to-moderate cases. Breastfeeding should be encouraged whenever possible according to maternal and infant conditions. Moderate cases may require hospitalization for clinical observation, while severe-to-critical cases require vital function monitoring in NICU. This should be provided according to usual protocols and the best

Research directions

- The role of the type of transmission on clinical severity and outcomes.
- Pathobiological mechanisms of MIS-N.
- The effect of delivery route on the risk of viral transmission.
- The long-term effect of maternal and neonatal SARS-CoV-2 infections.

available evidence [101–103]. We advise to use negative pressure rooms and place a high-capacity HEPA filter on the expiratory limb of ventilatory circuits and other common measures to reduce nosocomial infections [104]. Clear protocols for personnel protection, isolation/deisolation and resource optimization should be available in each center [105].

Drugs that have been used to treat severe/critical neonatal COVID-19 are essentially remdesivir (VEKLURY®, Gilead, Foster City-CA, USA), which is FDA- and EMA-approved for neonates weighing at least 3 Kg, and steroids (Fig. 4). Remdesivir has also been anecdotally used, at lower dose, in smaller neonates [96]. It is strongly recommended to consult with an expert neonatal/pediatric intensivist and/or a pediatric infectious disease specialist to treat these cases, as this may require expertise in both advanced critical care and COVID-19.

Declaration of competing interest

None.

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