Classification system and case definition for SARS-CoV-2 infection in pregnant women, fetuses, and neonates

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The possibility of mother-to-fetus transmission of SARS-CoV-2, the cause of coronavirus disease 2019 (COVID-19), is currently a highly debated concept in perinatal medicine.[1] It has implications for the mother, fetus, and neonate, as well as for healthcare providers present at the time of birth and caring for the child during the neonatal period, including obstetricians, midwives, family doctors, anesthetists, pediatricians, neonatologists, nurses, and respiratory therapists. At present the evidence for intrauterine transmission from mother to fetus or intrapartum transmission from mother to the neonate is sparse. There are limitations associated with sensitivity and specificity of diagnostic tests used and classification of patients based on test results has also been questioned.[2-7] As a result, differing recommendations have emerged regarding which samples should be collected and when, and how to distinguish infection from contamination,[8-11] making it difficult for clinicians "on the ground" to know which recommendations to follow.[12] Additionally, a woman could be infected at any time during pregnancy and the impact on the fetus when maternal infection occurs earlier in pregnancy may be different than when it occurs in the two weeks prior to delivery. Infection during the first or second trimester has the potential to cause miscarriage, preterm birth, birth defects or possibly other features of congenital infection. In late gestation maternal infection, we need to consider the possibility that the newborn could have active infection and consequently at risk of adverse outcomes and also that the infant could pose a risk to healthcare workers. Therefore, in this paper, we focus solely on newborn infants whose mothers have documented or suspected COVID-19 at the time of onset of labor and delivery. Fortunately, the majority of neonates born to mothers with SARS-CoV-2 infection either do not become infected or exhibit mild symptoms at birth. However, the fact that a significant proportion of maternal and neonatal infections can be asymptomatic creates difficulty in ascertaining the disease burden on neonates and the possibility of transmission to healthcare providers during resuscitation or admission to a unit.

Unequivocal diagnosis of most fetal or neonatal infections is typically made by detection of the organism in culture or by nucleic acid amplification tests that identify the presence of the pathogen's RNA or DNA in amniotic fluid prior to onset of labor or in properly collected fetal/neonatal blood or body fluid samples, or by histopathological demonstration of the organism in fetal/neonatal tissues. Serology plays an important role in diagnosis for certain congenital infections such as cytomegalovirus, toxoplasmosis and syphilis. The role of serology in the diagnosis of active

SARS-CoV-2 infection is still uncertain and consequently it is difficult to envision how serology may contribute to newborn diagnosis – especially when maternal infection occurs late in pregnancy and there may not have been sufficient time for antibodies to be generated. Until there is a clear understanding of appropriate diagnostic methods and interpretation of results for newborn infants, a detailed classification system is likely to be helpful. Such a system could aid healthcare practitioners in evaluating patients, determining appropriate infection control measures, planning appropriate follow-up for neonates and infants, allowing large epidemiological studies and helping collaboration between international efforts to learn about potential effects of maternal infections. In this paper, we present such a classification.

In developing this system, we adopted an approach similar to Lebech et al[13] in creating five mutually exclusive categories of the likelihood of infection: (a) confirmed, (b) probable, (c) possible, (d) unlikely, and (e) not infected. The first and last categories (*confirmed* and *not infected*) are to be considered absolute and confirmatory. The *probable* category denotes strong evidence of infection but a lack of absolute proof. The *possible* category denotes evidence that is suggestive of infection but is incomplete. The *unlikely* category applies when there is little support for a diagnosis, but infection cannot be completely ruled out. Notably, a case may be initially assigned to one category and later moved to another category as more information is available. All five categories will not be applicable to all types of infections. We have avoided terminology such as 'vertical' or 'horizontal transmission' and rather developed a system that classifies transmission as *congenital infection in intrauterine death/ stillbirth*, *congenital infection in live born*, *neonatal infection acquired intrapartum*, or *neonatal infection acquired postnatally*,[14] which aligns with the actual pathological process as opposed to unknown directions of transmission.[15] Our classification system is presented in **Table 1**. Currently, the classification system takes into account the results of maternal testing, clinical status of the neonate at birth, and results of neonatal testing. The criteria suggested are based on current evidence. For the perinatal infection categories, it assumes that maternal status is either definitive or probable and is in the vicinity of childbirth. These categories may need to be modified as a clearer picture of the effects of SARS-CoV-2 infection on developing fetus emerges.

We believe that this rapid, easy, and accessible system will also facilitate the development of good clinical practice parameters and guidelines for managing neonates and ensuring safety of

families and healthcare providers. This classification system is dependent on the availability of reliable diagnostic tests and emerging methods may lead to its modification. We have not included testing of breast milk, maternal skin swabs, or rectal swabs in the proposed classification as their roles in diagnosing maternal-fetal-neonatal SARS-CoV-2 infections are unclear at this time. We expect refinements to this classification system as additional data become available and further experience is gained.

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Table 1. Classification System for Maternal-Fetal-Neonatal SARS-CoV-2 Infections

Patient	Category	Case Definition
Maternal infection during pregnancy		
Symptomatic mother	Confirmed	Detection of the virus by PCR in a respiratory sample (nasopharyngeal/ nasal/ broncho-alveolar lavage)
	Possible	No testing done
	Unlikely[a]	No detection of the virus by PCR in a respiratory sample and no other cause identified
	Not infected[a]	No detection of the virus by PCR in a respiratory sample and other cause identified
Asymptomatic mother who has positive contact history	Confirmed	Detection of the virus by PCR in a respiratory sample
	Unlikely[a]	No detection of the virus by PCR in a single respiratory sample
	Not infected	No detection of the virus by PCR in two respiratory samples taken at different time points
Congenital infection with intrauterine fetal death /stillbirth		
Fetal tissues or autopsy material	Confirmed	Detection of the virus by PCR from fetal or placental tissue or electron microscopic detection of viral particle in tissue or viral growth in culture from fetal or placental tissue
	Possible	Detection of the virus by PCR in surface swab from fetus or placental swab on fetal side
	Unlikely	Detection of the virus by PCR in surface swab from maternal side of placenta only and no testing done or no detection of the virus by PCR from fetal or placental tissue
	Not infected	No detection of the virus by PCR or by electron microscopy in fetal tissue(s) on autopsy
Congenital infection in live born neonate		
Clinical features of infection in newborn and mother with	Confirmed	Detection of the virus by PCR in umbilical cord blood[b] or neonatal blood collected within first 12 hours of birth or amniotic fluid collected prior to rupture of membrane[c]
	Probable	Detection of the virus by PCR in nasopharyngeal swab at birth

SARS-CoV-2 infection		(collected after cleaning baby) AND placental swab from fetal side of placenta in a neonate born via cesarean section before rupture of membrane or placental tissue
	Possible[a]	No detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) BUT presence of anti-SARS-CoV-2 IgM antibodies in umbilical cord blood or neonatal blood collected within first 12 hours of birth or placental tissue
	Unlikely	No detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) or umbilical cord blood, or neonatal blood collected within first 12 hours of birth or amniotic fluid AND antibody testing not done
	Not infected	No detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) or umbilical cord blood, or neonatal blood collected within first 12 hours of birth or amniotic fluid AND no anti-SARS-CoV-2 IgM in umbilical cord blood or neonatal blood collected within first 12 hours of birth
No clinical features of infection in newborn and mother with SARS-CoV-2 infection	Confirmed	Detection of the virus by PCR in cord blood[b] or neonatal blood collected within first 12 hours of birth
	Probable	Detection of the virus by PCR in amniotic fluid collected prior to rupture of membrane but no detection in umbilical cord blood or neonatal blood collected within first 12 hours of birth
	Possible	Presence of anti-SARS-CoV-2 IgM in umbilical cord blood or detection of the virus by PCR in placental tissue but no detection of the virus by PCR in umbilical cord blood or neonatal blood collected within first 12 hours of birth or amniotic fluid
	Unlikely	No detection of the virus by PCR in cord blood or neonatal blood collected within first 12 hours of birth or amniotic fluid collected prior to rupture of membrane[c] AND serology not done
	Not infected	No detection of the virus by PCR in cord blood or neonatal blood collected within first 12 hours of birth or amniotic fluid collected prior to rupture of membrane[c] AND no anti-SARS-CoV-2 IgM in

		cord blood
Neonatal infection acquired intrapartum		
Clinical features of infection in newborn and mother with SARS-CoV-2 infection	Confirmed	Detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning the baby) AND at 24-48 hours of age AND alternate explanation for clinical features excluded
	Probable	Detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) but not at 24-48 hours of age AND alternate explanation for clinical features excluded
	Possible	No detection of the virus by PCR in nasopharyngeal swab at birth AND detection of the virus by PCR in any of maternal vaginal / placental / cord / skin swab at birth AND alternate explanation for clinical features excluded
	Unlikely	No detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) OR in any of maternal vaginal / placental / cord / neonatal nasopharyngeal / skin swab at birth AND alternate explanation for clinical features not identified
	Not infected	No detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning baby) OR in any of maternal vaginal / placental / cord / neonatal nasopharyngeal / skin swab at birth AND alternate explanation for clinical features identified
No clinical features of infection in newborn and mother with SARS-CoV-2 infection	Confirmed	Detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning the baby) AND at 24-48 hours of age
	Possible	Detection of the virus by PCR in nasopharyngeal swab at birth (collected after cleaning the baby) AND not at 24-48 hours
	Not infected	No detection of the virus by PCR in nasopharyngeal swab at birth AND no detection of the virus by PCR in any of vaginal swab in mother / placental swab / skin / cord swab at birth
Neonatal infection acquired postpartum		
Clinical features of infection in newborn at ≥48	Confirmed	Detection of the virus by PCR in nasopharyngeal / rectal swab at ≥48 hours of birth in a neonate whose respiratory sample tested negative by PCR at birth

hours age (parent or caregiver may or may not have SARS-CoV-2 infection or were not tested)	Probable	Detection of the virus by PCR in nasopharyngeal / rectal swab at ≥48 hours of birth in a neonate who was not tested at birth
	Not infected[a]	No detection of the virus by PCR in nasopharyngeal / rectal swab at ≥48 hours of birth and other cause identified

This system is for maternal SARS-CoV-2 infection diagnosed prenatally or within 2-3 weeks of birth.

[a]In highly suspicious cases, repeat sample may be needed due to test limitations.

[b] Collected using sterile precaution and thorough cleaning of cord.

[c] Includes sample taken at cesarean section performed before rupture of membranes.

Category definitions: Confirmed, Strong evidence of infection with confirmatory microbiology; **Probable**, Strong evidence of infection but confirmatory microbiology lacking; **Possible**, Evidence suggestive of infection but incomplete; **Unlikely**, Little support for diagnosis but infection cannot be ruled out; **Not infected**, No evidence of infection.

Abbreviations: IgM, immunoglobulin M; PCR, polymerase chain reaction.