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SUPPLEMENT ARTICLE

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SARS-CoV-2 infection and neonates: a review of evidence and unresolved questions

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Abstract

SARS-CoV-2 infection in the neonatal period poses previously unmet challenges to obstetricians and neonatologists, but several key questions are yet to be answered. Few cases of presumed *in utero* vertical transmission of the virus from infected mothers to fetuses have been reported, but stronger evidence is needed, from larger datasets with multiple biospecimens rigorously analyzed. Whether acquired before or after birth, SARS-CoV-2 infection in neonates can be symptomatic, but our comprehension of neonatal immune response and the subsequent clinical characteristics of COVID-19 in early life are incomplete. Finally, the pandemic challenged several dogmas regarding the management of mother-infant dyads, and again more robust data are needed to support the formulation of evidence-based guidelines. Here, we briefly summarize existing evidence and key unresolved questions about SARS-CoV-2 infection and COVID-19 in the neonatal period.

KEYWORDS

2019-nCoV, COVID-19, neonate, newborn, pregnancy, prematurity, SARS-CoV-2

1 | INTRODUCTION

Until mid-May 2020, more than 4 million cases of coronavirus disease 2019 (COVID-19), caused by "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) infection, have been recorded worldwide, with almost 300.000 confirmed deaths.[1] More than 95% of COVID-19 patients are above 20 years of age, with significantly higher mortality rates in elderly males.[1] Nonetheless, a limited but growing number of SARS-CoV-2–infected neonates have been described. Infection in the first 28 days of life can be acquired horizontally, akin to several respiratory viruses including other coronaviruses, or possibly vertically, during pregnancy, parturition, or through breastmilk.[2] Due to the novelty of SARS-CoV-2 infection and to the paucity of reported cases, several questions with important health care and social implications regarding COVID-19 in early life are currently unresolved.

2 | QUESTION 1: CAN SARS-COV-2 BE TRANSMITTED TO FETUS *IN UTERO*?

Even though more than 100 cases of neonates born to mothers with COVID-19 have been described, and many more are unreported, the possibility of intrauterine transmission of the virus has not been

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undoubtedly confirmed nor ruled out so far. In most described cases, RT-PCR for SARS-CoV-2 tested negative on neonatal (nasal-pharyngeal swab, anal swab, or cord blood) and maternal biospecimens (amniotic fluid, rectal swab, or vaginal swab). In the few cases of reportedly vertical transmission, a definitive diagnosis was hindered by either (a) the lag between birth and testing time, that could not rule out a droplet- or contact-mediated transmission from nursing mothers, (b) a negative re-testing soon later, or 3) no confirmation on neonatal biospecimens other than nasal-pharyngeal swab.[2] Nonetheless, 3 cases of neonates with circulating anti-SARS-CoV-2 IgM antibodies soon after birth were reported, suggesting the possibility of intrauterine acquisition of the virus despite negative RT-PCR testing after birth. Finally, a preliminary report confirmed (by RT-PCR, immunohistochemistry, and electron microscopy) the presence of SARS-CoV-2 in the placental tissue of a COVID-19 mother concomitantly affected by severe preeclampsia.[3] Given these areas of uncertainty, future research will have to focus on the analysis of multiple maternal and neonatal biospecimens simultaneously, to clarify whether and in which situations an intrauterine transmission of SARS-CoV-2 is possible.

3 | QUESTION 2: DOES MATERNAL SARS-COV-2 INFECTION INCREASE THE RISK OF PRETERM DELIVERY?

The majority of SARS-CoV-2–positive pregnant women give birth at term or near term. In a few reported cases of preterm delivery, the exact role of SARS-CoV-2 infection is not clear. COVID-19 can lead to maternal acute respiratory distress syndrome (ARDS), with subsequent fetal hypoxia, fetal distress, and induction of preterm labor.[4] Alternatively, COVID-19 maternal complications can be sufficient per se to prompt a medically indicated preterm delivery in the absence of spontaneous labor. Two reports described interesting cases of very preterm operative delivery, at 22 and 26 weeks of gestational age, in SARS-CoV-2–positive women simultaneously affected by preeclampsia and hemolysis-elevated liver enzyme-low platelets (HELLP) syndrome, respectively.[3,4] Considered the role of vascular endothelial damage in COVID-19 pathogenesis, direct involvement of SARS-CoV-2 in placental vascular abnormalities is conceivable, prompting further investigation.

4 | QUESTION 3: ARE VAGINAL DELIVERY, ROOMING-IN PRACTICE, AND BREASTFEEDING HARMFUL FOR THE NEONATE?

At present, most scientific societies agree that the mode of delivery should not be influenced by maternal COVID-19, provided the mother is in good clinical conditions. Indeed, SARS-CoV-2 has not been identified in vaginal secretions so far.[5] Rooming-in practice and breastfeeding are beneficial for mother-infant dyads, and, to date, SARS-CoV-2 transmission through breastmilk has not been demonstrated. Thus, several current recommendations encourage rooming-in practice and breastfeeding with contact and droplet precautions, but are not based on robust data yet to be acquired.[5] Studies on large populations are urged to clarify whether active SARS-CoV-2 can be transmitted through breastmilk, whether the risk of mother-to-neonate transmission is through respiratory droplets or contact, and, more importantly, whether breastfeeding may exert a protective role against neonatal infection, through specific anti-SARS-CoV-2 IgA or indirect mechanisms.

Key message

COVID-19 in early life is a reality, but evidence on SARS-CoV-2 infection in neonates is still limited, and several key questions are yet to be answered.

5 | QUESTION 4: WHAT IS THE PATHOGENESIS OF COVID-19 IN NEONATES?

Evidence regarding the infectivity and pathogenicity of SARS-CoV-2 in infancy is progressively accumulating, as well as few speculations and little data about the age-specific virus-host interaction. A recent report on 731 children affected by COVID-19 highlighted that 10% of patients below 1 year of age presented severe or critical symptoms, although specific data on neonates were lacking.[6] Based on smaller reports, neonates usually present fever, hyporeactivity, mild respiratory distress, and feeding difficulty.[7] Severe symptoms have been described in few neonates. However, they could not be unambiguously attributed to SARS-CoV-2 infection due to the presence of comorbidities, in particular prematurity.[8] The overall lower susceptibility to COVID-19 of children and neonates has given rise to multiple speculations about the underlying biologic reasons. It is known that SARS-CoV-2 accesses host cells through angiotensin-converting enzyme 2 (ACE-2), and that several human cell types express the viral receptor.[9]

During COVID-19, immune cells triggered by viral antigens frequently fuel a potent systemic inflammatory response, and vascular endothelium physiology is greatly deranged, either because of direct damage induced by the virus or due to the systemic inflammatory response itself. In light of this evidence, some unique biologic and immune characteristics of neonates may contribute to explain the lower pathogenicity of SARS-CoV-2 in early life. First, neonates are known to mount a differently shaped systemic inflammatory response as compared to adults, with less T-helper (Th)-1 polarization of innate and adaptive immune responses, a lower production of pro-inflammatory mediators (TNFα, IFNγ, IL-8 among others) and prevalence of regulatory responses. A precise characterization of predominant soluble mediators in neonatal COVID-19–related cytokine storm is still lacking and might shed light on the age-specific pathogenicity of

SARS-CoV-2. Second, the susceptibility of neonatal vascular endothelium to systemic inflammation or to the virus itself, possibly through an age-specific expression of ACE-2, is not clear and deserves future investigation. Finally, germinal centers (GCs) respond quicker to viral pathogens in early life, under the continuous stimulation of multiple new antigens, and the level of circulating broad-reactivity, low-specificity natural antibodies is higher. This may limit the viral pathogenicity at the early stages of infection, avoiding the insurgence of the aforementioned systemic inflammatory response.[10] Whether and how the synergy between all these mechanisms can reduce the pathogenicity of SARS-CoV-2 in neonates is still to be elucidated.

6 | QUESTION 5: ARE ANTIBODIES INHERITED FROM AN INFECTED MOTHER PROTECTIVE FOR THE NEONATE?

Transplacental passage of maternal IgG to the fetus during the 3rd trimester of pregnancy protects neonates against several infectious diseases, and represents the rationale for maternal vaccination during pregnancy. Furthermore, breastmilk IgA contributes to the protection of neonates against gastrointestinal and upper respiratory tract infections. Whether this holds also for maternal SARS-CoV-2 infection has not been established. Among neonates reportedly infected early after birth, in one case IgG and IgM levels over time were described.[11] Interestingly, and provided the reliability of serological tests, both IgG and IgM titers significantly drop between birth and 14 days of life, which may suggest a short persistence of antibodies in neonates. This single report needs further confirmation. However, and even more important, the immunologic correlate of protection to SARS-CoV-2 is still to be established, in neonates as well as in adults.

In conclusion, scientific evidence regarding SARS-CoV-2 infection in neonates after the first six months of the pandemic is limited. Further investigations are imperative to understand the possibility of intrauterine fetal infection and vertical transmission through breastmilk, as well as immunologic mechanisms underlying the lower pathogenicity of SARS-CoV-2 in early life.

CONFLICT OF INTEREST

The authors declare no commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTION

Carlo Pietrasanta: Conceptualization (equal); Writing-original draft (equal). **Andrea Ronchi:** Conceptualization (equal); Writing-original draft (equal). **Federico Schena:** Conceptualization (equal); Methodology (equal); Writing-review & editing (equal). **Claudia Ballerini:** Methodology (equal); Writing-review & editing (equal). **Lea Testa:** Methodology (equal); Writing-review & editing (equal). **Giacomo Artieri:** Methodology (equal); Writing-review & editing (equal). **Domenica Mercadante:** Conceptualization (equal); Methodology (equal); Writing-review & editing (equal). **Fabio Mosca:** Conceptualization (equal); Supervision (equal); Writing-review & editing (equal). **Lorenza Pugni:** Conceptualization (equal); Supervision (equal); Writing-review & editing (equal).

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