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SUPPLEMENT ARTICLE

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SARS-CoV-2 infection and neonates: Evidence-based data after 18 months of the pandemic

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Abstract

After 18 months of the COVID-19 pandemic, data concerning SARS-CoV-2 infection in pregnant women and their neonates are progressively taking the place of complete uncertainty. Here, we summarize updated evidence regarding several critical aspects of perinatal SARS-CoV-2 infection, including 1) vertical transmission of the virus *in utero*, which is possible but seems rare according to current epidemiological data; 2) how COVID-19 during pregnancy can shape maternal and neonatal outcomes, either directly or indirectly; 3) how recommendations regarding the management of infected dyads have been progressively modified in light of new scientific evidence; and 4) how maternal infection or vaccination can induce the passive protection of fetuses and neonates against the infection, through the transfer of specific antibodies before and after birth.

KEYWORDS
antibodies, breastmilk, COVID-19, neonate, newborn, pregnancy, prematurity, SARS-CoV-2, vaccine, vertical transmission

1 | INTRODUCTION

At the time of submitting the present manuscript, roughly 18 months have passed since the first cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection were declared to the world from Wuhan, China, in December 2019. During the first pandemic year, unanswered questions about the virus-host interaction vastly exceeded evidence-based data, especially in those groups of patients with fewer cases of severe coronavirus disease 2019 (COVID-19), such as neonates and pregnant women. Approximately one year ago, we recapitulated the most relevant unanswered questions regarding perinatal COVID-19. Now, we provide a summary of the evidence-based data that support a rational answer to several critical questions regarding SARS-CoV-2 infection in the prenatal and neonatal period.

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

Based on common practice on adult patients, the diagnosis of SARS-CoV-2 vertical transmission in neonates born to mothers with SARS-CoV-2 infection was initially based on the results of RT-PCR for viral RNA on nasopharyngeal swab only, with an overall mother-to-infant transmission rate ranging between 1.9% and 3.2%.[1] However, the positivity of neonatal nasopharyngeal swab may also indicate contamination rather than a true *in utero* infection or infection acquired intrapartum/early after birth mistaken for *in utero* infection. Thus, in February 2021, the WHO enacted the precise criteria to define *in utero*, *intrapartum*, and postnatal transmission of SARS-CoV-2 from infected mothers to their neonates.[2] The definition of confirmed *in utero* transmission requires the presence of maternal infection during pregnancy together with a positive (RT-PCR or microscopy-based

technique) neonatal/placental sample during the first 24 h of life (or neonatal IgM/IgA positivity) and a second positive neonatal sample from sterile site obtained between 24 and 48 h of life, to avoid the possible contamination of samples acquired peripartum. Reports following this methodology are still scarce, but Fenizia and coll.[3] Described one neonate with confirmed *in utero* acquisition of SARS-CoV-2 in a cohort of 31 infected mothers (vertical transmission rate of 3.2%), and Raschetti and coll.[4] report a prevalence of congenital infection among infected neonates of 5.7%. A relatively higher transmission rate is conceivable but still needs to be robustly demonstrated in most severe cases of maternal COVID-19, where a high viral load, the hematogenous spread in the mother, and the placental vascular damage induced by SARS-CoV-2 (or other causes) can all contribute to the breakdown of fetal protection.

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

A meta-analysis[1] and two large cohort studies[5,6] on pregnant women with SARS-CoV-2 infection clearly showed that infected pregnant women with COVID-19 are more likely to suffer from pregnancy and infection-related complications compared to non-infected or non-pregnant women. Being pregnant at the time of infection increased the probability of admission to intensive care unit (ICU, odds ratio [OR] 2.13, 1.53 to 2.95), invasive ventilation (OR 2.59, 2.28 to 2.94), and the need for extracorporeal membrane oxygenation (OR 2.02, 1.22 to 3.34) compared to non-pregnant women. At the same time, SARS-CoV-2 infection during pregnancy raised the probability of maternal death (OR 2.85, 1.08 to 7.52), ICU admission (by approximately 18 times), and preterm birth (OR 1.47, 1.14 to 1.91) compared to non-infected pregnant women. In particular, the rate of preterm birth increased from 10.6% (average WHO rate) to 12–17% in SARS-CoV-2-infected mothers, but it seemed to be globally decreased in non-infected women in 2020-early 2021. This possibly represents a beneficial effect of the behavioral, social, and environmental changes caused by the pandemic. The cesarean section rate seems inconsistently affected by SARS-CoV-2 infection, but pregnant women with SARS-CoV-2 infection are clearly at higher risk for preeclampsia/eclampsia (relative risk [RR], 1.76, 1.27 to 2.43) and thromboembolic disease (RR 2.7, 1.7 to 4.4). Vascular malperfusion, micro-thrombosis, and fibrin deposition in the syncytiotrophoblast have been consistently reported in the placenta of COVID-19 patients, even in the absence of vertical viral transmission, and can be interpreted as pregnancy-specific manifestations of the pro-thrombotic phenotype and endothelial end-organ dysfunction well described in non-pregnant COVID-19 patients. Finally, most reports on the consequences of COVID-19 during pregnancy are still related to the third trimester/peripartum infection. With the progression of the pandemic, more data should be gathered to separately analyze the effect of COVID-19 in different trimesters of pregnancy.

Key message

SARS-CoV-2 infection in pregnancy concerns maternal and neonatal outcomes, despite vertical transmission, and seems rare; passive protection after maternal infection or vaccination can be transferred to the neonate.

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

SARS-CoV-2 has rarely been detected in the vaginal swab, but shedding is frequent in the feces of infected individuals. The presence of SARS-CoV-2 in the maternal perineal area, thus, could potentially allow perinatal infection of the newborn. Nonetheless, a recent systematic review,[7] including 1035 neonates born to infected mothers, showed a lower perinatal infection rate in neonates born by vaginal delivery (9/417, 2.16%) than neonates born by cesarean section (25/618, 4.05%). These data support the practice of individualizing the mode of birth based exclusively on the disease severity and obstetric indications. As most scientific societies now recommend, COVID-19 should not be considered an indication for cesarean section.

Early in the pandemic, the initial recommendations about rooming-in practice and breastfeeding varied worldwide. Ronchi and coll.[8] and Salvatore and coll.[9] provided evidence-based data on the management of mother-infant pairs. Both studies showed that postnatal mother-to-infant transmission of SARS-CoV-2 in the context of both rooming-in and breastfeeding is rare (0–1.6%), provided that the mothers take correct contact and droplet precautions. As with other infections, milk produced by infected mothers is a beneficial source of specific immunoglobulins, and, to date, no replication-competent virus has been detected in breast milk. Therefore, updated evidence sets aside the initial conservative recommendations, leaving room for an encouraging attitude toward "protected" rooming-in and breastfeeding in the context of asymptomatic-paucisymptomatic maternal COVID-19.

5 | QUESTION 4: ARE MATERNAL ANTIBODIES TRANSFERRED FROM AN INFECTED OR VACCINATED MOTHER TO HER NEONATE? ARE THEY PROTECTIVE?

The transplacental transfer of antibodies from a previously SARS-CoV-2-infected pregnant mother to her fetus has been repeatedly demonstrated. Both anti-SARS-CoV-2 Spike protein (anti-S)

anti-receptor-binding domain (anti-RBD) IgGs have been detected in the cord blood (CB) of 87–90% of neonates born to a previously infected mother with positive serology at the time of delivery.[10] The presence and titer of CB antibodies are affected by maternal titer and maternal infection timing. Low or absent IgGs in the CB despite maternal seropositivity were demonstrated in cases of peripartum maternal infection (mother seropositive for IgM but not for IgG) or cases of very low maternal antibody titers. This, in turn, may be due to a long span between maternal infection and delivery or to individual weaker antibody production.

Conversely, IgM positivity of neonatal blood is considered a fingerprint of neonatal infection, while positivity of CB should be carefully investigated to discern between neonatal infection and contamination by maternal blood.[11] The persistence of maternal anti-SARS-CoV-2 IgGs in neonatal blood is positively correlated with the CB titer and has been demonstrated up to 27 weeks after birth.[11] For what concerns breastmilk, the presence of specific anti-SARS-CoV-2 IgG and/or IgA has been demonstrated in 76–100% of samples from previously infected mothers,[12] starting 10–15 days after the first maternal positivity. Therefore, passive protection of breastfed infants is at least conceivable.

Since late 2020, analog albeit limited data has been obtained from vaccinated mothers, pregnant, or lactating. Antibody titers after vaccination of pregnant or lactating women seem equivalent to those generated by non-pregnant or non-lactating women and, interestingly, higher than those induced by natural infection during pregnancy.[13] Both mRNA- and adenovirus-based vaccines seem to induce adequate antibody response, and these antibodies are transferred to the fetus and the neonate through the placenta or breastmilk.[14] Large cohort studies will be needed to clarify whether maternally derived antibodies can effectively protect neonates from SARS-CoV-2 infection.

CONFLICT OF INTEREST

All authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTION

Carlo Pietrasanta: Conceptualization (equal); Writing-original draft (equal). **Giacomo Artieri**: Conceptualization (equal); Writing-original draft (equal). **Andrea Ronchi**: Conceptualization (equal); Writing-original draft (equal). **Beatrice Crippa**: Methodology (equal); Writing-review & editing (equal). **Claudia Ballerini**: Methodology (equal); Writing-review & editing (equal). **Riccardo Crimi**: 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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