The Public Health and Clinical Importance of Accurate Neonatal Testing for COVID-19

David A. Schwartz, MD, MS Hyg, FCAP,[a] Daniele De Luca, MD, PhD[b]

The coronavirus disease 2019 (COVID-19) pandemic has infected large numbers of pregnant women, consequently highlighting the importance for newborns to be comprehensively evaluated for infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There is much that remains to be learned about SARS-CoV-2 infection of the fetus and newborn, including delineating the mechanisms and cofactors for vertical and environmental transmission and the best methods for neonatal testing and diagnosis. In this issue of *Pediatrics*, Sánchez-Luna et al[1] present the results of their prospective analysis of neonates delivered to 497 pregnant women with COVID-19 in 79 hospitals throughout Spain. The data obtained from this national registry are of immense importance in adding to our understanding of the effects of maternal COVID-19 infection on neonatal outcomes, including potential vertical transmission of SARS-CoV-2. Sánchez-Luna et al found that 14 of 469 (3%) neonates tested by nasopharyngeal swabs at a median period of 3 hours after delivery were positive for SARS-CoV-2; this appears consistent with recent findings from a meta-analysis.[2] After a repeat test performed 24 to 48 hours later, however, 12 of these 14 neonates tested negative for the coronavirus, and all were asymptomatic. We must be cautious in trying to interpret these results.

Accurate neonatal testing for COVID-19 is not only a public health imperative but also the cornerstone of clinical diagnosis and treatment of infection with SARS-CoV-2. After hundreds of cases of neonatal SARS-CoV-2 infections and some cases of severe COVID-19 in neonates, it is clear that this disease, although rare, does exist in newborn infants.[3] Thus, neonatologists and other pediatricians should maintain their awareness for this emerging coronaviral illness, and testing of newborn infants at risk for infection should be viewed as a clinical responsibility.

The standard diagnostic confirmatory method for COVID-19 is molecular testing of specimens by reverse transcriptase polymerase chain reaction. Although a good test, it is not without potential faults and can be subject to contamination resulting in false-positives among other issues.[4] The source of specimens for testing of children and adults is the upper respiratory tract, typically by a nasopharyngeal swab, which is the long-accepted method used for respiratory infections as the nasopharynx is the most common anatomic location for entry of viruses transmitted by aerosol and airborne mechanisms.

However, there have been some reports of variability in the timing and patterns of positive neonatal testing for the virus by using this method,[5,6] as in the current article by Sánchez-Luna et al.[1] Many things are unclear regarding the optimum sampling technique to be performed in neonates: the classic

[a]*Medical College of Georgia, Augusta, Georgia; and* [b]*Hôpital Antoine Béclère, Université Paris Saclay, Paris, France*

DOI: https://doi.org/10.1542/peds.2020-036871

Accepted for publication Nov 18, 2020

Address correspondence to David A. Schwartz, MD, MS Hyg, FCAP, 1950 Grace Arbor Court, Atlanta, GA 30329. E-mail: davidalanschwartz@gmail.com

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

COMPANION PAPER: A companion to this article can be found online at www.pediatrics.org/cgi/doi/10.1542/2020.015065.

To cite: Schwartz DA and De Luca D. The Public Health and Clinical Importance of Accurate Neonatal Testing for COVID-19. *Pediatrics*. 2021; 147(2):e2020036871

swabs can rarely reach the nasopharynx because of the small anatomic dimensions and they may retrieve other biological fluids (such as amniotic fluid or vernix caseosa); some have used pharyngeal lavage and aspiration into sterile traps, but the reliability of this sampling technique remains to be verified. Because scant data are available for neonates regarding the biological basis for the variability of test results for SARS-CoV-2 or the accuracy of upper respiratory tract specimens for diagnosis of COVID-19 in newborns, it can be difficult to distinguish true- from false-positive tests, especially in asymptomatic infants.

To further complicate matters, in many studies of neonatal SARS-CoV-2 infection, the investigators analyze nasopharyngeal specimens but unfortunately fail to test other important fetal and neonatal tissues and fluids (such as placenta, amniotic fluid, newborn peripheral or umbilical cord blood), which are necessary to make a comprehensive perinatal diagnosis. Without these data, it can be challenging or even impossible to determine if an infant is truly infected. In fact, several combinations of these tests are recommended in the 2 major international classification criteria for the diagnosis of fetal and neonatal SARS-CoV-2 infections.[7,8]

There are now increasing numbers of cases of intrauterine maternal–fetal transmission of SARS-CoV-2 being described.[9–13] These cases of transplacental transmission in maternal–neonatal dyads with COVID-19 are consistent with the proposed diagnostic criteria by Schwartz et al[7] in which SARS-CoV-2 is identified within such fetal-derived cells of the placenta as syncytiotrophoblast by using the molecular pathology techniques of immunohistochemistry to demonstrate viral antigens, or RNA in situ hybridization to demonstrate viral nucleic acid. This mechanism of transmission and its frequency appear to differ significantly from previous infections of pregnant women with respiratory RNA virus infections, including other coronavirus infections, in which intrauterine transmission was rare or nonexistent.[14,15] A recent meta-analysis of 176 published cases of neonatal SARS-CoV-2 infections estimated that ~30% of neonates acquire their infection before birth.[3]

It is assumed that SARS-CoV-2, similar to such other respiratory viruses as respiratory syncytial virus and influenza, most frequently enters the host through the nasopharynx. However, fetuses do not breathe air and are not exposed to virus-laden respiratory droplets or aerosol from the environment before delivery. As a result, how effectively can a neonate who has acquired SARS-CoV-2 infection before birth via the transplacental hematogenous route be diagnosed by sampling the nasopharyngeal or oropharyngeal mucosa after delivery?

Current attempts to increase our epidemiological and clinical knowledge of neonatal COVID-19 are hampered by several factors in addition to those mentioned above: lack of data regarding the sensitivity of reverse transcriptase polymerase chain reaction testing as well as nasopharyngeal and oropharyngeal sampling for diagnosis of SARS-CoV-2 in neonates, ignorance of the effects of intrauterine fetal infection on results of current methods for neonatal testing, unfamiliarity with the patterns of fetal and neonatal shedding of the virus into body secretions and fluids, almost no understanding of the patterns of test positivity for the coronavirus in upper respiratory specimens in neonates, and an ascertainment bias in publishing selected cases of neonatal infection. Developing and implementing reliable, sensitive, and specific neonatal testing policy is of paramount importance in answering these and other questions. Neonatal SARS-CoV-2 infections exist, and the neonatologist should always remember to test those infants who are at risk. How and when to best accomplish that remains to be clarified.

ABBREVIATIONS

COVID-19: coronavirus disease 2019

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

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Pediatrics originally published online January 21, 2021;

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