Perinatal COVID-19

Despina Briana, MD, PhD, Garyffalia Syridou, MD, and Vassiliki Papaevangelou, MD, PhD

The severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) pandemic posted unique challenges to perinatal care. Rapidly acquired population-based data on the epidemiology, pathophysiology, clinical implications and outcomes of perinatal SARS-CoV-2 infection have urged for international guidelines on the management of mothers and neonates with suspected or confirmed infection. Almost 18 months after coronavirus disease 2019 (COVID-19) pandemic has been officially proclaimed, cumulative evidence addressing the potential of perinatal transmission, the diagnosis and clinical management of perinatal COVID-19, as well as the development of prevention strategies are reviewed.

EPIDEMIOLOGY

Prevalence of COVID-19 among pregnant women is difficult to estimate given geographic/temporal variability and varying thresholds for testing pregnant women. A high rate of asymptomatic infection among pregnant women with COVID-19 has been demonstrated wherever universal perinatal screening has been implemented.[1]

Large population-based studies have conclusively demonstrated that pregnant women with SARS-CoV-2 infection are at increased risk of developing severe disease when compared with nonpregnant women.[2,3] Additionally, older age, higher body mass index and pre-existing comorbidities, mainly diabetes, hypertension and lung disease, seem to predispose to severe COVID-19 during pregnancy.[1,3]

Obstetrical and neonatal outcomes appear to be influenced by the severity of maternal disease. Pregnant women with COVID-19 are at increased risk of delivering via cesarean section and delivering preterm.[1,2] In a recently published review, cesarean delivery rates, preterm deliveries before 37 weeks and infection positivity status of the newborn varied from 48.3% to 100%, 14.3% to 61.2% and 0% to 11.5%, respectively.[4]

Adverse effects of perinatal COVID-19 are not limited to the morbidity and mortality caused directly by the disease itself. Nationwide lockdowns, disruption of health-care services and fear of attending health-care facilities might have affected the wellbeing of pregnant women and their babies, probably accounting, for instance, for the substantial increase of stillbirths observed in a few studies during the pandemic.[1,2]

VERTICAL VERSUS HORIZONTAL TRANSMISSION: WHAT IS THE EVIDENCE?

As an increasing number of pregnant women with perinatal COVID-19 are being reported globally, the potential of mother-to-infant transmission of SARS-CoV-2, either in utero, intrapartum or in the early postnatal period has received much attention. World Health Organization (WHO) proposed definitions and categorization of the timing of mother-to-child vertical transmission of SARS-CoV-2, aiming to enable comparison of data across studies.[5]

At present, the extent to which SARS-CoV-2 vertical transmission occurs is largely unknown. Significant variability is noted in infection prevention practices, timing, number of tests and sample sites of neonatal SARS-CoV-2 polymerase chain reaction (PCR) tests, which makes differentiation of vertical versus horizontal transmission extremely challenging. A systematic review and meta-analysis demonstrated a pooled proportion of 3.2% for vertical transmission using nasopharyngeal swab.[6] However, these data need to be interpreted with caution since there is an underrepresentation of asymptomatic pregnant women while many neonates were tested on the first day of life.

Data from the American Academy of Pediatrics National Perinatal COVID-19 Registry showed that the highest rate of positive neonatal tests was observed in infants born to symptomatic mothers who had first positive tests within 1 week of delivery, while

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From the Third Department of Pediatrics, National and Kapodistrian University of Athens, University General Hospital "ATTIKON", Athens, Greece.
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Address for correspondence: Vassiliki Papaevangelou, MD, PhD, Third Department of Pediatrics, National and Kapodistrian University of Athens, School of Medicine, University General Hospital ATTIKON, Rimini 1, Chaidari 12462, Athens, Greece. Address e-mail to vpapaev@gmail.com.

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the rate of positivity was not higher in infants who roomed in with their mothers.[2] Standardized testing of neonates born to mothers with COVID-19 may increase test sensitivity and allow differentiation between vertical and horizontal transmission.

Despite lack of rigorous case definitions for mother-to-child transmission, cumulative transmission of SARS-CoV-2 infection from mother to infant by transplacental, perinatal and postnatal routes appears to be low.[7] When it occurs, it seems that neonatal COVID-19 is largely horizontally acquired during postnatal period due to close contact by droplet or airborne transmission.[1,5] Vertical transmission from mother to infant does not seem common but remains possible based on available reporting.[1] Moreover, the risk of transmission via breast milk is estimated to be low to very low.[1]

DIAGNOSTIC CHALLENGES

Diagnosis of perinatal transmission is based on molecular testing and to a lesser extent on serology. Real-time reverse transcriptase-polymerase chain reaction in nasopharyngeal swabs is the gold-standard of diagnosis with highly sensitivity and specificity. The best time of testing is at 24 hours and again at 48 hours of life irrespectively of symptoms of the neonate. A positive test within 24 hours from birth must be repeated since positivity may have several interpretations, including detection of viral fragments acquired via passage through the birth canal or environmental contamination. On the other hand, a negative PCR at birth might be falsely negative in asymptomatic neonates and must be repeated. The identification of the mode of transmission based on molecular methods and serology remains tricky. Several factors such as estimated time of maternal infection as well as time of testing in mother/neonate dyad must be taken into account. According to WHO, intrauterine infection is confirmed only if there is (a) evidence of maternal infection at any time during pregnancy and (b) fetal exposure in utero with at least 1 neonatal specimen positive for SARS-CoV-2 infection by 24 hours of age and (c) viral persistence/immune response in the newborn meaning at least 1 neonatal specimen again PCR positive at 24–48 hours of age, or positive serology (IgM or IgA) at 24 hours to 7 days of life. In addition, intrapartum or postpartum infection is defined when the maternal infection is close to delivery, from 14 days before to 2 days after birth. In this case, a positive PCR from a sterile sample or from repeated non-sterile samples at 2–7 days of life or positive serology at 7–14 days of life, confirmed by a second serology 10 days after the first one verifies the diagnosis.[5]

The value of serology alone for the diagnosis of perinatal infection is still unclear. The presence of IgM at birth as well as the increasing IgG titer during follow-up may indicate in utero transmission. In a recent meta-analysis among the total number of neonates born to SARS-CoV-2–infected mothers, only 3.7% of those tested with serology were positive for anti-SARS-CoV-2 IgM antibodies. The lack of real-time reverse transcriptase-polymerase chain reaction positivity in repeated neonatal samples in such babies implies probable in utero transmission.[6] On the other hand, the rapid decline of IgM levels in some of the seropositive neonates raises a question about true vertical transmission, given the known limitation of high rates of false-positive testing at birth.

CLINICAL PRESENTATION AND MANAGEMENT

Adverse health outcomes among neonates born to SARS-CoV-2 positive mothers are mostly associated with worsening maternal COVID-19 illness and associated in-utero hypoxia, often prompting preterm delivery.[7] Conversely, health outcomes of neonates with positive SARS-CoV-2 test results are largely favorable.[7] Infants with perinatal transmission have no or mild signs of disease and rarely require readmission for clinical signs consistent with COVID-19.[2] Observed symptoms may include respiratory signs, often associated with prematurity, fever, hypotonia, gastrointestinal symptoms and cough.[2] In a recently published review, fetal distress and neonatal respiratory distress syndrome were the most frequently reported moderate to severe presentations, while the most frequent newborn complications were related to admission to neonatal intensive care units (NICUs) and prematurity.[1] However, these data need to be confirmed by future studies since most severe symptoms could be attributed to prematurity, while rates of admissions to NICUs could be misleading, as studies do not clarify whether babies were admitted to NICU for isolation purposes or because they needed intensive care for medical reasons.[1]

There are no specific laboratory markers in COVID-19 neonates. Leucopenia and lymphocytopenia, mild to moderate thrombocytopenia and increased creatine phosphokinase, transaminases and lactate dehydrogenase are reported while C-reactive protein and procalcitonin are usually within normal limits.[8] Decisions regarding additional testing including monitoring of inflammatory markers such as ferritin, D-dimers or interleukin-6 as well as high resolution computational tomography are individualized.

The management of infected neonates is mainly supportive with supplementary oxygen when needed, intravenous fluids and electrolytes and antibiotic treatment when bacterial coinfection is suspected. The experience from the use of remdesivir so far is very limited in neonates, although its use is available through an Food and Drug Administration Emergency Use Authorization for the treatment of COVID-19 in hospitalized pediatric patients weighing 3.5 to <40 kg or <12 years of age and weighing ≥3.5 kg.

According to National Institute for Health & Care Excellence guidelines, remdesivir can be considered, in consultation with a pediatric infectious disease specialist, for hospitalized children of all ages with COVID-19 who have emergent or increasing need for supplemental oxygen. Optimal neonatal dosage, duration of treatment and clear indications to start treatment have not yet been defined. Although the drug has not been tested for its safety or efficacy in terms of treating SARS-CoV-2 infections in neonates, it was used in children as young as 5 days old during the Ebola outbreak.[9] Remdesivir has been effectively used in 2 preterm neonates with severe respiratory symptoms for a 5-day course (2.5 mg/kg loading dose on day 1 followed by 1.25 mg/kg once daily on days 2–5) with no adverse events.[10] Before treatment, patients >28 days old and full-term neonates ≥7 to ≤28 days old must have an estimated glomerular filtration rate and serum creatinine determined, respectively, according to Emergency Use Authorization requirements. The risks and benefits of using dexamethasone in neonates with COVID-19 are still unknown. Dexamethasone may be administered on a case-by-case basis at a dose of 0.15 mg/kg daily, through oral, intravenous or nasogastric administration for all children including neonates with COVID-19 who require high-flow oxygen, noninvasive ventilation, invasive mechanical ventilation or extracorporeal membrane oxygenation.

PREVENTION STRATEGIES

Vaccination against COVID-19 is the most important prevention tool. Pregnant women, at any time during pregnancy, even during the first trimester, as well as all family members (cocooning strategy) should get vaccinated. Although currently data on safety among pregnant women is still limited, all scientific bodies strongly recommend vaccination of pregnant women to reduce maternal and fetal complications of COVID-19 infection. Conversely, women may elect to get vaccinated during postpartum period while lactating. Additionally, to prevent exposure, nonpharmaceutical prevention measures should be carefully reviewed by clinicians.

Pregnant women presenting to delivery room with known or suspected COVID-19 infection should be cared with precautions, while their newborns should be considered

as having suspected SARS-CoV-2 infection, should be tested irrespectively to symptoms and isolated until test results available.[11] Initial testing of neonates should be performed at 24 hours of life and repeated at 48 hours of life if negative or not done.[11] Rooming-in and breast-feeding are recommended for their well-established benefits to both mother and newborn, since risk of horizontal transmission is low once parental education on necessary safety measures is provided. Wearing face mask while breast-feeding, keeping a physical distance of 6 feet or greater between the mother and newborn and placing the neonate in a temperature-controlled isolette are recommended. Alternatively, mothers may choose to feed their babies through expressed breast milk.

However, mothers with COVID-19 may choose to separate from their newborn to reduce risk of transmission. Moreover, separation may be needed when either the mother or her infant needs higher levels of care. Home discharge for mother and newborn is preferred when asymptomatic or paucisymptomatic. Close outpatient follow-up is proposed until the end of isolation period.

CONCLUSIONS

Pregnant women and newborns constitute special vulnerable populations for COVID-19. Further prospective studies and high-quality evidence synthesis of comparative studies are needed to clarify the clinical aspects of perinatal COVID-19 and guide future clinical practice.

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