Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Infectious Diseases Now 51 (2021) 435–439

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Original article

Outcomes of newborns to mothers with COVID-19

K. Ghema*, M. Lehlimi , H. Toumi , A. Badre , M. Chemsi , A. Habzi , S. Benomar

Department of Neonatology, Institute of Maternal and Child Health, Casablanca Children's Hospital, Casablanca, Morocco

ARTICLE INFO

Article history:
Received 15 February 2021
Received in revised form 26 February 2021
Accepted 10 March 2021
Available online 17 March 2021

ABSTRACT

Introduction: Coronavirus disease 2019 (COVID-19) has spread rapidly across the world. Given the sharply increased infection rate, the number of pregnant women and children with COVID-19 is correspondingly on the rise. SARS-CoV-2 infection is transmitted through droplets; though hypothesized, other transmission routes have not been confirmed. As of now, it remains unclear whether and how SARS-CoV-2 can possibly be transmitted from the mother to the fetus.
Method: This study examines the medical records of 30 neonates born to women with COVID-19, the objective being to provide documented information on maternal-child transmission and infant outcomes.
Results: Out of the 30 newborns, 28 had negative PCR test results for SARS-CoV-2; among their mothers, fifteen had fever, nine had cough and twenty had delivered by cesarean section. The median birth term was 37wk2dy, and twenty of the neonates were male. Most of them were asymptomatic, except for the three who presented with shortness of breath. Two of them were intubated and both died, the first because of severe sepsis and the second due to severe hyaline membrane disease. As regards the two infected neonates, the first represents a probable case of congenital SARS-CoV-2 infection, which appears unlikely in the second case. The outcome for both of them was good, without any complications.
Conclusion: Maternal-fetal transmission of the SARS- CoV-2 virus was not detected in the majority of the reported cases, although two of 30 neonates had positive qRT-PCR test results. Our study supports the hypothesis that though it seldom actually occurs, in utero SARS-CoV-2 vertical transmission is possible.

1. Introduction

The coronavirus disease 2019 (COVID-19) has spread rapidly across the world. Given the sharply increased infection rate, the number of pregnant women and children with COVID-19 is correspondingly on the rise.

The possibility of mother-to-fetus transmission of SARS-CoV-2 is currently a highly debated concept in perinatal medicine. 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. At present, the evidence for intrauterine transmission from mother to fetus or intrapartum transmission from mother to neonate is sparse. There are limitations associated with the sensitivity and specificity of the diagnostic tests used, and the classification of patients based on test results has also been questioned.

2. Method

This is a descriptive study on the clinical characteristics and neonatal outcomes of pregnant women infected with COVID-19.

In this study, all neonates born to mothers with COVID-19 were recruited from the neonatal ICU of Harouchi Mother and Child Hospital in Casablanca, Morocco. The diagnosis and management of newborns with or at risk of COVID-19 were in accordance with the guidelines provided by the National Health Commission.

Data regarding demographic, epidemiologic, and clinical features were obtained from the medical records system and collected from January 2020 to December 2020.

3. Result

Out of the 30 newborns, 28 had negative PCR test results for SARS-CoV-2; among the mothers, fifteen were symptomatic; fifteen had fever, nine had cough, five had anosmia, one had pneumonia on the CT, and two were hospitalized in the ICU, where one died after 72 hours (her newborn died as well, due to severe sepsis) and one was intubated and extubated after 7 days with good outcome. The other fifteen mothers were asymptomatic. Twenty had delivery by cesarean. Median birth term was 37wk2dy, and 20 of the neonates were male. Most of them were asymptomatic, with the

* Corresponding author.
E-mail addresses: Karima.ghema91@gmail.com (K. Ghema), lehlimimouna@gmail.com (M. Lehlimi), hanane.toumi@gmail.com (H. Toumi), badreamal@gmail.com (A. Badre), mounirchemsi@yahoo.fr (M. Chemsi), Abdohabzi@gmail.com (A. Habzi), S.benomar2@yahoo.fr (S. Benomar).

https://doi.org/10.1016/j.idnow.2021.03.003
2666-9919/© 2021 Elsevier Masson SAS. All rights reserved.

Table 1
General information and clinical features of 30 newborns with mothers with COVID-19.

	Neonates with SARS-COV2 negative	Patients with SARS-COV 19	
		Patient 1	Patient 2
Variable	28		
Maternal features			
Fever on admission	15	Yes	Yes
Cough	9	Yes	Yes
ICU admission	2	No	No
Pneumonia per CT	1	No	No
Nasopharyngeal swab	27	Yes	Yes
Delivered by cesarean	22	No	Yes
Premature rupture of membranes	6	Yes	No
Neonate features			
Male	20	No	Yes
Term	37 wk 2dy	GA: 38 W4 dy	GA: 41w1dy
Asphyxia	6	No	No
Fever	0	No	Yes
Respiratory distress syndrome	3	No	No
Cyanosis	2	No	No
White blood cell count,cells/μL	11200 (6800–23,730)	7240	5780
Neutropenia[a]	No	No	No
Lymphopenia[b]	No	No	No
Thrombocytopenia[c]	No	No	No
C-reactive protein	7,34	2.7	1.2
Treatment	7	Yes	Yes
Mechanical ventilation	2	No	No
Antibiotic	14	Yes	Yes
Duration of neonatal intensive care unit, median	6.8	6	7
Death	2	No	No

[a] Neutropenia: neutrophil count ≤ 1500 cells/μL.
[b] Lymphopenia: Lymphocyte count ≤ 2000 cells/μL.
[c] Thrombocytopenia: Platelets ≤ 150 × 103/μL.

exception of three, who presented with shortness of breath. Two of them were intubated and both died, the first because of severe sepsis and the second due to severe hyaline membrane disease. More details are given in Table 1.

SARS-CoV-2 in one mother was diagnosed by thoracic computed tomography, which showed a pathognomonic SARS-CoV-2 lesion, despite the negative nasopharyngeal swab.

Among the 30 neonates there was no sign of inflammatory syndrome, and in all cases, c-reactive protein was negative.

Here are the details regarding the two infected neonates.

3.1. Case 1

The mother was 37 years old (gravida 3, para 3), and she had presented with myalgia, fatigue, dry cough and temperature of 39 °C over the preceding 24 hours. No other member of the family had been reported positive for COVID 19. Data from laboratory tests showed a normal leucocyte count, and while lymphocytes were below the normal range, platelets were normal. Concentrations of C-reactive protein were abnormally high at 49.3 mg/L. She was diagnosed with SARS-CoV-2 infection through a nasopharyngeal swab, and she gave birth spontaneously by vaginal delivery at 38 + 4 weeks. Four hours after rupture of membranes, the amniotic fluid was clear.

A female baby was born, weighing 3800 g, with an Apgar score of 8 and 10 at 1 and 5 min. She was immediately removed from the operative field, in sterile fashion, and taken to the neonatal intensive care unit (there was neither skin-to-skin mother-child contact nor breast feeding). On examination, the baby girl was conscious, with normal skin color, normal temperature at 36.6°, normal respiratory frequency at 48 cycles/min, and normal oxygen saturation at 96%. There was no abnormal manifestation in digestion, urination or defecation.

Two days later she repeatedly presented with a fever at 38.2C° and 39C°. Data from laboratory tests showed a normal leucocyte (7240 cells/μL) and neutrophil counts (4800 cells/μL), and the platelets were normal (301 × 103/μL). As for infection-related biomarkers, C-reactive protein concentrations were normal at 2.7 mg/L. At day 2 of life, D-dimer were normal, as was thoracic computed tomography.

Through nasopharyngeal swab at 32 hours, the newborn was diagnosed with SARS-CoV-2 infection.

Treatment with ceftriaxone and aminoglycoside was started empirically (beginning because of the fever) and discontinued 48 hours later, after negative blood culture and after COVID-19 was diagnosed. It was replaced by azithromycin, and the neonate's temperature was maintained in an incubator.

With a good outcome, the baby was discharged at 6 days of hospitalization.

3.2. Case 2

Patient 2, a boy, was born by cesarean at 41 weeks of gestation and remained with his mother before being admitted to neonatal ICU for fever at day 3 of life. On examination, it was shown that in the preceding 72 hours, his mother had dry cough and a temperature of 39 °C. Immediately performed, nasopharyngeal swab confirmed that she was positive to COVID-19, and the father likewise tested positive.

On examination we found a baby boy, conscious, with normal skin color, with high temperature at 37.9°, normal respiratory frequency at 52 cycle/min, and normal oxygen saturation at 98%. There was no abnormal manifestation in digestion, urination or defecation.

Data from laboratory tests showed normal leucocyte (5780 cells/μL) and neutrophil counts (3200 cells/μL), and the platelets were likewise normal (189 × 103/μL). As for infection-related biomarkers, the concentrations of C-reactive protein were normal at 1.2 mg/L, as was chest radiographic image.

Table 2
Summary of findings in studies of newborns infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).

Study	Country	Terme	Delivery	Apgar score	Clinical assessment	Nasopharyngeal swab	C-reactive protein	Treatment	Evolution
Vivanti, Alexandre J	France	35 wk 2dy	Cesarean section	4/10	Irritability, poor feeding, axial hypertonia at day 2 after birth	Positive 4 hours after birth	≤ 5	No	Gradually recovered and discharged from hospital after 18 days
Andrea Carosso	Italy	37 wk	Vaginal delivery	9/9	Asymptomatic	Positive immediately after birth and negative 36 h later	–	No	Good outcome
Lingkong Zeng	China	40 wk	Cesarean	Normal	Lethargy and fever at day 2	Positive on day 2 of life	–	No	Good outcome Discharged after 2 dy
		40 wk 2d	Cesarean	Normal	Lethargy, vomiting, and fever	Positive on day 2 of life	–	No	Good outcome Discharged after4 dy
		31 wk 2d	Cesarean	4/10	Respiratory distress syndrome, asphyxia pneumonia and bacteremia	Positive on day 2 of life	–	Antibiotic mechanical ventilation	Good outcome Discharged after 11 dy
Wang, Shaoshuai	China	40 wk	Cesarean	8/10	Asymptomatic	Positive 36 hours after birth	–	No	Discharged after 17 dy
Dong, Lan	China	34 wk 2d	Cesarean	9/10	Asymptomatic	Negative 2 hours after birth (elevated IgM antibody 2 hours after birth)	≤ 5	No	Good outcome discharged after 26 days
Lowe B	Australia	40 wk	Vaginal delivery	9/10	Asymptomatic	Negative 24 h after birth	–	No	Good outcome

Through nasopharyngeal swab at day 3 of life, the newborn was diagnosed with SARS-CoV-2 infection.

Treatment with azithromycin was started immediately and with a good outcome. Apyrexia was obtained 24 hours after admission, and the baby was discharged after 7 days.

4. Discussion

Human coronaviruses are among the most common pathogens that cause respiratory infection. SARS-CoV-2 is characterized by enveloped virions that measure about 50–200 nm in diameter with a single positive-sense RNA genome [1].

SARS-CoV-2 infection causes the new coronavirus disease (COVID-19) and while it is mainly transmitted through droplets, other transmission routes have been hypothesized. Some cases of perinatal transmission have been reported, but it is unclear if these occurred via the transplacental or the transcervical route or through environmental exposure [2].

Our first case represents a probable case of congenital SARS-CoV-2 infection in a liveborn neonate. Congenital infection is supported by the following findings: (a) there was no skin-to-skin contact with the mother before collection of the first neonatal nasopharyngeal swab and (b) the baby was in full isolation immediately after delivery. Given a lack of detection of SARS-CoV-2 gene targets in the umbilical cord tissue and a lack of availability of cord blood for SARS-CoV-2 testing, we consider this to have been a probable rather than a confirmed https://www.cmaj.ca/content/192/24/E647 – ref-6 case of congenital SARS-CoV-2 infection.

However, vaginal delivery may entail a risk of vertical transmission, as was recently reported in a COVID-19 positive pregnant woman with rectal and stool maternal positive swabs for SARS-CoV-2, suggesting that the virus can enter the neonatal nasopharynx during vaginal delivery, potentially triggering neonatal infection [3].

In the second case, congenital SARS-CoV-2 is not impossible because of the initial contact of the neonate with his mother (risk of transmission through droplets), but three days is a short period for virus incubation and clinical manifestation. Transmission may have been vertical or airborne.

The clinical presentation of the neonates was not highly revelatory; two of them had fever for one day, but notwithstanding the full clinical of their mothers, their inflammation biomarkers were very low; it would consequently seem that the clinical presentation of the newborns was independent of the clinical severity of the mothers.

In a previous study, while Zeng and colleagues identified SARS-CoV-2 RNA in nasopharyngeal swabs in 3 out of 33 cases, the clinical symptoms from the 33 neonates with (or at risk of) COVID-19 were mild and their outcomes were favorable. Concerning the 3 neonates with symptomatic COVID-19, the most seriously ill may have been symptomatic from prematurity, asphyxia or sepsis, rather than SARS-CoV-2 infection [4]. Wang and colleagues identified one neonate in Wuhan who was born under emergent cesarean delivery to a mother with COVID-19 pneumonia and tested positive for SARS-CoV-2 at 36 hours after birth. The clinical manifestations of the mother and the baby were both mild, and the baby's prognosis was favorable [5].

Symptomatic and supportive treatment consisting in oxygen supply, water-electrolyte maintenance, and acid-base balance is the mainstay of therapy for patients with SARS-CoV-2 infection. The water and electrolyte supplement should be appropriate, the objective being to avoid aggravating the pulmonary edema and reduced oxygenation. Respiratory support for neonates with suspected/proven COVID-19 infection is guided by the usual principles of lung-protective strategy, including supplemental low flow O2, CPAP, noninvasive positive pressure ventilation (NIPPV), and invasive ventilation as per existing policy for respiratory support with customized infection prevention strategy [6].

Antivirals or chloroquine/hydroxychloroquine are not recommended for symptomatic neonate with suspected/confirmed COVID-19 infection:

- use of adjunctive therapy such as systemic corticosteroids and intravenous immunoglobulin (IVIG) is not recommended in symptomatic infants with confirmed/suspected case of COVID-19;
- use of oseltamivir may be considered in selective cases

Antivirals or chloroquine/hydroxychloroquine are not recommended for symptomatic neonates with suspected/confirmed COVID-19 infection, nor is adjunctive therapy such as systemic corticosteroids or intravenous immunoglobulin (IVIG). Oseltamivir may be considered in selective cases, as may micronutrients such as zinc and vitamin A, C and D with immunomodulation effect and given in recommended dietary allowance (RDA): Vitamin C (40 mg OD); vitamin D3 drops (1 mL = 400 IU) 1 mL OD; vitamins A to Z drops (0.5 mL BD); Omega3 fatty acids (500 mg) [7].

The determination of whether or not to separate a mother with known or suspected COVID-19 from her infant should be made on a case-by-case basis through shared decision-making involving the mother and the clinical team. Some reports in this review show that isolation and non-promotion of breastfeeding have been implemented, in accordance with the recommendations of Chinese experts. On the other hand, routine separation of mother and baby has not been endorsed by the Royal College of Obstetricians & Gynecologists, which provides guidance on individualized care based on a systematic review of COVID-19 in pregnancy and delivery. In one case included in this review, which was characterized by implementation of strict prevention measures and support from the health system, no infection of a newborn by a COVID-19-positive mother occurred, despite unrestricted attachment and breastfeeding [8,9] (cf. Table 2).

5. Conclusion

Maternal-fetal transmission of the SARS- CoV-2 virus was not detected in the majority of the reported cases, although two of 30 neonates presented positive qRT-PCR. Our results support the hypothesis that in utero SARS-CoV-2 vertical transmission, while low, is possible. These findings might help to orient obstetric management of COVID-19 pregnant women, for example in putative indications for mode and timing of delivery. And given the pronouncedly limited number of clinical presentations of positive neonates with low inflammation markers, we suggest not to separate the newborn baby from his or her mother, and even to allow breast-feeding in compliance with infection prevention and control measures involving close monitoring of neonates at risk of COVID-19.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments.

Disclosure of interest

The authors declare that they have no competing interest.

Authors' contributions

Karima Ghema: main author.
Lehlimi Mouna: secondary author and supervisor.
Hanane Toumi: data analysis.
Badre Amal: supervisor.
Chemsi Mounir: supervisor.
Habzi Abderrahim: supervisor.
Said Benomar: supervisor.

References

[1] Pal M, Berhanu G, Desalegn C, et al. Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2): An Update. Cureus 2020;12(3):e7423, http://dx.doi.org/10.7759/cureus.7423.
[2] Vivanti AJ, Vauloup-Fellous C, Prevot S, Zupan V, Suffee C, Do Cao J, et al. Transplacental transmission of SARS-CoV-2 infection. Nat Commun 2020;11(1):3572, http://dx.doi.org/10.1038/s41467-020-17436-6.
[3] Carosso A, Cosma S, Borella F, Marozio L, Coscia A, Ghisetti V. Prelabor anorectal swab for SARS-CoV-2 in COVID-19 patients: is it time to think about it? Eur J Obstet Gynecol Reprod Biol 2020;249:98–9, http://dx.doi.org/10.1016/j.ejogrb.2020.04.023 [2020.04.023].
[4] Zeng L, Xia S, Yuan W, Yan K, Xiao F, Shao J, et al. Neonatal early-onset infection with SARS-CoV-2 in 33 neonates born to mothers with COVID-19 in Wuhan, China. JAMA Pediatr 2020;174(7):722–5, http://dx.doi.org/10.1001/jamapediatrics.2020.0878.
[5] Dong L, et al. Possible vertical transmission of SARS-CoV-2 from an infected mother to her newborn. JAMA 2020;323:1846–8.
[6] Shalish W, Lakshminrusimha S, Manzoni P. COVID-19 and neonatal respiratory care: current evidence and practical approach. Am J Perinatol 2020;37:780–91.
[7] WHO. Clinical management of severe acute respiratory infection when COVID-19 is suspected. Available online at: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected (accessed Mar 13, 2020) COVID-19 and newborn health: systematic review.
[8] Duran P, et al. COVID-19 and newborn health: systematic review. Rev Panam Salud Publica 2020;44:e54, http://dx.doi.org/10.26633/RPSP.2020.54.
[9] Lowe B, Bopp B. COVID-19 vaginal delivery – a case report. Aust N Z J Obstet Gynaecol 2020;60(3):465–6, http://dx.doi.org/10.1111/ajo.13173.