SARS-CoV-2 Infection in Neonate: What do We Know So Far?

Infecção por SARS-CoV2 no Recém-Nascido: O Que Sabemos Até Agora?

Keywords: Coronavirus Infections; COVID-19; Infant, Newborn
Palavras-chave: COVID-19; Infecção por Coronavírus; Recém-Nascido

Dear editor,

Since the emergence of coronavirus disease 2019 (COVID-19) in Wuhan, China, in December 2019, caused by a novel coronavirus SARS-CoV-2, there has been an exponential increase in the number of cases worldwide, which has led to a challenging pandemic.

Given the low number of reported cases, there are still scarce data about COVID-19 in the neonatal period.

Available studies are based in small samples and guidelines are non-consensual, which makes this issue not yet well understood in this specific population.

In order to gain a better understanding of SARS-CoV-2 infection in the neonatal period, we carefully reviewed all-publications about COVID-19 in pregnancy and neonates in the MEDLINE and PubMed databases between December 2019 and March 2020.[1-4]

The main findings and controversies are presented in Appendix 1 (see Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/13825/Appendix_01.pdf).

Although neonatal early-onset infection has been described, no evidence of vertical transmission has been demonstrated to date (Mar 2020).[1,4] The existence of positive IgM antibodies to SARS-CoV-2 in a newborn from a positive SARS-CoV-2 mother has also been reported.[5] Additionally, reported cases included neonates born from pregnant women infected during the 3rd trimester, so vertical transmission during the first two trimesters is yet to be clarified.[1-4] Assuming there is the possibility of vertical transmission, the ideal biological sample used to test newborns might not be the same used in adults. In order to exclude SARS-CoV-2 infection neonatologists might perform a throat swab and consider testing other samples such as blood, amniotic fluid, placenta, breast milk or rectal swab. However, it is important to consider horizontal transmission through respiratory secretions of the infected mother with SARS-CoV-2. Therefore, newborn separation from the mother must be considered a preventive measure.

So far, all the reported cases have been managed individually according to the newborns´ clinical status and local guidelines.[1-4]

Regarding symptoms, most cases of COVID-19 in neonates had mild symptomatic infection.[1-4] However, data are not enough to establish both short and long-term prognosis in these newborns. Fortunately, there have been no reported severe cases or related mortality in the neonatal period until now.[1-4]

More data are needed to clarify our questions and doubts. Time and systematic monitoring of clinical and laboratory test findings will provide us with a better understanding and knowledge of this disease. Until then, in the absence of evidence-based medicine, we advocate a conservative and cautious management of this immature and special population.

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Appendix 1 – Major issues concerning SARS-CoV-2 in the neonate born from mother with SARS-CoV-2 infection

Delivery Room Management		**Articles and guidelines**
Umbilical cord clamping (early *versus* delayed cord clamping)	Given a lack of evidence to the contrary, **delayed cord clamping is still recommended**, provided there are no other contraindications.	WHO guidelines[1] Obstetrician and Gynaecologists UK guidelines[2] Pregnancy and Labour Portuguese guidelines[3]
	The baby can be **cleaned** and **dried** as normal, while the cord is still intact.	Obstetrician and Gynaecologists UK guidelines[2]
	Early umbilical cord clamping is recommended with the aim of reducing the possibility of infection.	Neonatal Portuguese guidelines[4]
	If the mother has suspected SARS-CoV-2 infection and the isolation of both the mother and the newborn is adequate, late cord clamping **could be done**, although pros and cons should be analysed individually.	Neonatal Spanish guidelines[5]
Skin-to-skin contact	If the mother has suspected or confirmed SARS-CoV-2 and if the baby is well and does not require care in the neonatal unit, skin-to-skin contact can be done, although the pros and cons should be analysed individually. If the mother also requests skin-to-skin contact with her infant she should comply with strict preventive precautions.	Obstetrician and Gynaecologists UK guidelines[2], Neonatal Spanish guidelines[5], American neonatal guidelines[6]
	Skin-to-skin contact is **not recommended**.	Pregnancy and Labour and Neonatal Portuguese guidelines[3,4]
Neonatal management		
Guidelines are consensual in **implementing contact and droplet isolation measures**, limiting contacts and clinical and laboratory monitoring of newborns of SARS-CoV-2 suspected or infected mothers.		Neonatal Portuguese[4], Spanish[5], American neonatal guidelines[6] and UK guidelines[7]
Breastfeeding		
It is not yet clear whether SARS-CoV-2 can be transmitted via breast milk. Current guidelines recommend breastfeeding in asymptomatic or mild symptomatic infected mothers while ensuring contact and droplet isolation measures. Mechanical extraction of breast milk and administration to the newborn by a healthy caregiver can be an alternative, ensuring preventive isolation measures.		Neonatal Portuguese[4], Neonatal Spanish[5], American neonatal guidelines[6], Pediatrics UK[7] and Italian[8] guidelines
Treatment		
Until now there is no specific treatment for neonatal SARS-CoV-2 infection. The main goal of treatment should be support measures. Inappropriate use of antibiotics should be avoided.		Neonatal Spanish[5], Pediatrics UK[7] and Neonatal Portuguese[4] guidelines
Antiviral drugs	**Lopinavir/Ritonavir** is only recommended in neonates with ≥ 14 days and after 42 weeks gestational age. Appropriate dosage in preterm infants and neonates < 14 days of age are not known and toxicity in premature infants can be severe. FDA strongly recommends that this drug should be avoided in this age group.	Pediatrics Portuguese guidelines[9], Pediatrics Spanish guidelines[10], FDA[11]

	Consider using **oseltamivir** until influenza virus infection is excluded.	Pediatrics Portuguese guidelines[9]
	Some guidelines suggest the use of **chloroquine and hydroxychloroquine** to treat SARS-CoV-2 infection in children but there is insufficient information about dosages and toxicity in the neonatal period.	Pediatrics Portuguese guidelines[9], Pediatrics Spanish guidelines[10]
	Some guidelines suggest the use of **remdesivir** to treat SARS-CoV-2 infection in children, especially in critically ill patients with mechanical ventilation, but there is insufficient information about dosages and toxicity in the neonatal period.	Pediatrics Portuguese guidelines[9], Pediatrics Spanish guidelines[10]
Clinical signs in neonates born from mothers with SARS-CoV-2 infection		
No clinical symptoms (n = 9), prematurity (n = 4), low birthweight (n = 1) – total 9 newborns.		Chen HJ, *et al.*[12]
Shortness of breath (n = 6), fever (n = 2), increased heart rate (n = 1), vomiting/ feeding intolerance (n = 1), refusing milk (n = 1) and gastric bleeding (n = 2), prematurity (n = 6), disseminated intravascular coagulation (n = 2), refractory shock, multiple organ failure and death (n = 1) – total 10 newborns.		Zhu H, *et al.*[13]
Pneumonia (n = 3, all newborns with SARS-CoV-2 identified), lethargy and fever (n = 1 newborn with SARS-CoV-2 identified), lethargy, vomiting, and fever (n = 1 other newborn with SARS-CoV-2 identified), respiratory distress syndrome, shortness of breath, cyanosis and feeding intolerance (n = 1 the third newborn with SARS-CoV-2 identified) – total 33 newborns.		Zeng L, *et al.*[14]
Feeding intolerance – total 1 newborn.		Wang S, *et al*.[15]
SARS-CoV-2 PCR screening in neonates born from mothers with SARS-CoV-2 infection		
Samples collected from amniotic fluid, cord blood and neonatal throat swab were **negative** (n = 6) – total 9 newborns.		Chen HJ, *et al.*[12]
All samples from neonatal throat swab were **negative** (n = 9) – total 10 newborns.		Zhu H, et al.[13]
3 samples from nasopharyngeal and anal swabs were **positive** on days 2 and 4 – total 33 newborns.		Zeng L, et al.[14]
Positive pharyngeal swab at 36 hours after birth. Negative cord blood, placenta and breastmilk specimens – 1 newborn.		Wang S, et al.[15]
Other laboratory test findings in neonates		
Positive IgM antibodies to SARS-CoV-2 (2 hours after birth) – 1 newborn.		Dong L, et al.[16]
Mild increase in myocardial enzymes (n = 1) – total 9 newborns.		Chen HJ, et al.[12]
Thrombocytopenia complicated with abnormal liver function (n = 2) – total 10 newborns.		Zhu H, et al.[13]
Leukocytosis, lymphocytopenia and elevated creatine kinase–MB fraction (n = 1), increased procalcitonin without other changes (n = 1), suspected sepsis, with an Enterobacter positive blood culture, leukocytosis, thrombocytopenia and coagulopathy (n = 1), normal laboratory test results (n = 30) – total 33 newborns.		Zeng L, et al.[14]
Lymphopenia, increased aminotransferase, increased total bilirubin and elevated creatine kinase – total 1 newborn.		Wang S, et al.[15]
Chest radiographic image		
Infections (n = 4), neonatal respiratory distress (n = 2), pneumothorax (n = 1), normal (n = 3) – total 10 newborns		Zhu H, et al.[13]
Nonspecific findings (n = 30), pneumonia (n = 2), neonatal respiratory distress and pneumonia (n = 1) – total 33 newborns.		Zeng L, et al.[14]
Thickened lung texture (n = 1) – total 1 newborn.		Wang S, et al.[15]

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