**SARS-CoV-2 infection in neonate - What do we know so far?**

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**SARS-CoV-2 infection in neonate - What do we know so far?**

Dear editor,

Since the emergence of coronavirus disease 2019 (COVID-19) in Wuhan, China in December 2019, caused by a novel coronavirus called SARS-CoV-2, there has been an exponential increase in the number of new cases worldwide, so we are currently facing a challenging pandemic.

There is still scarce data about COVID-19 during the neonatal period due to the low number of cases reported. Hence, available studies have small samples and guidelines are non-consensual, which makes this issue not yet well understood in this special population.

To clarify SARS-CoV-2 infection in the neonatal period, we searched in MEDLINE and PubMed databases, published in the last four months (since December 2019 until March 2020) about COVID-19 in pregnancy and neonate.1-4 We resume the main findings and controversies in figure 1.

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

So far, all the reported cases have been managed individually, according to the newborn’s clinical status and local guidelines.Regarding symptoms, most cases of COVID-19 in neonates had mild symptomatic infection. However, there is still insufficient data to determine the prognosis of COVID-19 in newborns in both short and long-term. Fortunately, there have been no severe cases of COVID-19 or mortality reported in the neonatal period up until now.

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

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| **Figure 1 –** Major topics about SARS-CoV-2 in neonate born from mother with SARS-CoV-2 infection |
| **Delivery Room Management** | **Articles and guidelines** |
| **Umbilical cord clamping**(early *vs* delayed cord clamping) | Given a lack of evidence to the contrary, **delayed cord clamping is still recommended**, provided there are no other contraindications.  | WHO guidelines1Obsterician and Gynaecologists UK guidelines2Pregnancy and Labourportuguese guidelines3 |
| The baby can be **cleaned** and **dried** as normal, while the cord is still intact. | Obsterician and Gynaecologists UK guidelines2 |
| **Early umbilical cord** **clamping** is recommended with the aim of reducing the possibility of infection. | Neonatal Portuguese guidelines4 |
| If mother has suspected SARS-CoV-2 infection and mother and newborn’s isolation is adequate, late cord clamping **could be done**, although pros and cons should be analyzed individually. | Neonatal Spanish guidelines5 |
| **Skin-to-skin contact** | If the mother has suspected or confirmed SARS-CoV-2 and if the baby is well and doesn’t require care in the neonatal unit, skin-to-skin contact **can be done**, although pros and cons should be analyzed individually. | Obsterician and Gynaecologists UK guidelines2  Neonatal Spanish guidelines5 |
| Skin-to-skin contact is **not recommended**. | Pregnancy and Labour and Neonatalportuguese guidelines3, 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 Portuguese4,Spanish5 and UK6 guidelines |
| **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 assuring contact and droplet isolation measures.Mechanical extraction of breast milk and administration to the newborn by an healthy caregiver can be an alternative, ensuring preventive isolation measures. | Neonatal Portuguese4,Neonatal Spanish5,Pediatrics UK6 andItalian7 guidelines |
| **Treatment** |  |
| Until now there is no specific treatment for neonatal SARS-CoV-2 infection. Main goal of treatment should be support measures.Inappropriate use of antibiotics should be avoided. | Neonatal Spanish5, Pediatrics UK6 and Neonatal Portuguese4 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 guidelines8, Pediatrics Spanish guidelines9, FDA10 |
| Consider using **Oseltamivir** until Influenza Virus infection is excluded. | Pediatrics Portuguese guidelines8 |
| Some guidelines suggest the use of **Chloroquine and Hydroxychloroquine** to treat SARS-CoV-2 infection in children but there is no sufficient information about doses and toxicity in the neonatal period. | Pediatrics Portuguese guidelines8, Pediatrics Spanish guidelines9 |
| 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 no sufficient information about doses and toxicity in the neonatal period. | Pediatrics Portuguese guidelines8, Pediatrics Spanish guidelines9 |
| **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.* 11 |
| 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.* 12 |
| 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.*13 |
| Feeding intolerance – *total 1 newborn*. | Wang S, *et al*.14 |
| **SARS-CoV-2 PCR screening in neonates born from mothers with SARS-CoV-2 infection** |  |
| Samples collected from amniotic fluid, cord blood and neonatal swab throat were **negative** (n=6) – *total 9 newborns.* | Chen HJ, *et al.* 11 |
| All sample from neonatal swab throat were **negative** (n=9) – *total 10 newborns.* | Zhu H, *et al.* 12 |
| 3 samples from nasopharyngeal and anal swabs were **positive** on days 2 and 4 – *total 33 newborns.* | Zeng L, *et al.*13 |
| **Positive** pharyngeal swab at 36 hours after birth. Negative cord blood, placenta and breastmilk specimens – *1 newborn.* | Wang S, *et al.14* |
| **Other laboratory findings in neonates** |  |
| Positive IgM antibodies to SARS-CoV-2 (2 hours after birth) – *1 newborn.*  | Dong L, *et al.*15 |
| Mild increase in myocardial enzymes (n= 1) – *total 9 newborns.*  | Chen HJ, *et al.* 11 |
| Thrombocytopenia complicated with abnormal liver function (n=2) – *total 10 newborns.*  | Zhu H, *et al.* 12 |
| Leukocytosis, lymphocytopenia and elevated creatine kinase–MB fraction (n=1), increased procalcitonin without other alterations (n=1), suspected sepsis, with an *Enterobacter* positive blood culture, leukocytosis, thrombocytopenia and coagulopathy (n=1), normal laboratory tests (n=30) – *total 33 newborns.* | Zeng L, *et al.*13 |
| Lymphopenia, increased aminotransferase, increased total bilirubin and elevated creatine kinase – *total 1 newborn.* | Wang S, *et al.14* |
| **Chest radiographic image** |  |
| Infections (n=4), neonatal respiratory distress (n=2), pneumothorax (n=1), normal (n=3) – *total 10 newborns* | Zhu H, *et al.* 12 |
| Nonspecific findings (n=30), pneumonia (n=2), neonatal respiratory distress and pneumonia (n=1) – *total 33 newborns*. | Zeng L, *et al.*13 |
| Thickened lung texture (n=1) – *total 1 newborn.* | Wang S, *et al.14* |
| 1. Guideline: Delayed umbilical cord clamping for improved maternal and infant health and nutrition outcomes. World Health Organization (WHO). 2013
2. RCOG. Coronavirus (COVID-19) Infection in Pregnancy. Royal College of Obsterician & Gynaecologists. 2020
3. DGS. Orientação nº 018/2020 de 30/03/2020. Access: https://www.dgs.pt/directrizes-da-dgs/orientacoes-e-circulares-informativas/orientacao-n-0182020-de-30032020-pdf.aspx
4. Recomendações para a abordagem do recém-nascido em contacto com a infeção por SARS-CoV-2 (COVID-19), Sociedade Portuguesa de Neonatologia (SPN). 2020
5. Seneo. Recomendaciones para el manejo del recién nacido en relacion con la infeccion por SARS-CoV-2. Sociedad Española de Neonatología. Versión 5.0. Fecha 23/03/2020
6. RCPCH. COVID-19 guidance for paediatric services. Royal College of Paediatrics and Child Health. 2020
7. Davanzo R, Mosca F. Breastfeeding and SARS-CoV-2 Infection. Societá Italiana di Neonatologia. Feb 2020
8. SPCIP-SPP. Orientações para a abordagem e tratamento do doente pediátrico com COVID-19. Sociedade Portuguesa de Cuidados Intensivos Pediátricos-SPP. Março de 2020.
9. AEP. Documento de manejo clinico del paciente pediátrico com infeccion por SARS-CoV-2 -Extracto del Documento de Manejo Clínico del Ministerio de Sanidad. Associacion Española de Pediatria. Actualización: 29 de marzo de 2020
10. www.accessdata.fda.gov (homepage). USA: FOOD&DRUG Administration. Access: https://www.accessdata.fda.gov/drugsatfda\_docs/label/2016/021251s052\_021906s046lbl.pdf
11. Chen HJ, Guo J, Wang C, Luo F, Yu XC, Xhang W, et al. Clinical characteristics and intrauterine cervical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *The Lancet* 2020
12. Zhu Huaping, Wang Lin, Fang Chengzhi, Peng Sicong, Zhang Lianhong, Chang Guiping, Xia Shiwen, Zhou Wenhao. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr.* 2020
13. Zeng Lingkong, Xia Shiwen, Yuan Wenhao, Yan Kai, Xiao Feifan, Shao Jianbo, Zhou Wenhao. Neonatal Early-Onset Infection with SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Whuan, China. *JAMA Pediatrics.* March 26, 2020
14. Wang Shaoshuai, Guo L, Chen L, Liu W, Cao Y, Zhang J, Feng l. A case report of neonatal COVID-19 infection in China. Infectious Disease Society of America. 2020
15. Dong Lan, Tian Jinhua, He Songming, Zhu Chuchao, Wang Jian, Liu Chen, Yang Jing. Possible vertical transmission of SARS-CoV-2 from as infected mother to her newborn. *JAMA.* March 26, 2020.
 |

**References:**

1. Zeng Lingkong, Xia Shiwen, Yuan Wenhao, Yan Kai, Xiao Feifan, Shao Jianbo, Zhou Wenhao. Neonatal Early-Onset Infection with SARS-CoV-2 in 33 Neonates Born to Mothers With COVID-19 in Whuan, China. *JAMA Pediatrics.* Mar 26, 2020.
2. Chen HJ, Guo J, Wang C, Luo F, Yu XC, Xhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *The Lancet.* Feb 12, 2020.
3. Zhu Huaping, Wang Lin, Fang Chengzhi, Peng Sicong, Zhang Lianhong, Chang Guiping, Xia Shiwen, Zhou Wenhao. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Transl Pediatr.* Feb 6, 2020.
4. Wang Shaoshuai, Guo L, Chen L, Liu W, Cao Y, Zhang J, Feng l. A case report of neonatal COVID-19 infection in China. *Clin Infect Dis*. Mar 12, 2020.