

COVID - 19

NEONATAL COVID-19

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Abstract: *Novel coronavirus infection is a disease caused by severe acute respiratory syndrome coronavirus 2 and named as coronavirus disease 2019. First confirmed case in adult was reported in December 2019 in China. Since then, research is being conducted in multiple sites in order to better define the epidemiology, clinical characteristics, prevention and treatment of severe acute respiratory syndrome-coronavirus-2 infection in adults. Few cases have been observed in children and newborn infants who seem to have a milder form of clinical disease than other age groups. The purpose of this review is to summarize the available evidence on severe acute respiratory syndrome-coronavirus-2 transmission, the associated clinical presentation, outcomes and treatment in newborn infants with the aim to provide adequate information to neonatologists, pediatricians and obstetricians for managing such patients.*

Keywords: *COVID-19, Perinatal COVID, Neonatal COVID, Corona virus, Vertical transmission.*

Since the first case in December 2019, the coronavirus disease 2019 (COVID-19) has spread rapidly across the world. As of May 20, 2020, the World Health Organization (WHO) had reported just over 5 million people infected with COVID-19 worldwide.¹ At the same time, 1.1 Lakh people were infected in India according to Ministry of Health and Family Welfare Department (MOHFW).² During the earlier stage of the pandemic, older adults were reported to be more likely infected.^{3,4} However, with the sharp increase in the number of infections, the number of pregnant women, newborn infants and children with COVID-19 is also on the rise.

The general information from the literature so far indicates that neonatal COVID-19 infection may be uncommon. Besides, it is generally acquired through postnatal transmission rather than vertical transmission. Newborn infants with COVID-19 infection exhibit either no symptoms or mild respiratory illness.⁵ Some researchers postulate that milder disease in newborn infants and young children is due to the relative immaturity of angiotensin-converting enzyme 2 (ACE2) protein, which usually acts as a receptor for SARS-CoV-2 in adults.⁶ Furthermore, the higher percentage of fetal hemoglobin in newborn infants may be protective over SARS-CoV-2.⁷

With the current pandemic, there is an urgent need to address certain pertinent issues- whether pregnant women who have confirmed COVID-19 infection are more likely to spread the virus vertically to endanger the fetus, clinical features and management of newborns born to those affected mothers. A comprehensive review of the available evidence regarding all such issues is presented.

Vertical transmission

Initial reports suggested that while severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection could result in adverse pregnancy outcomes, newborn infants did not show any clinical signs of illness and had negative viral testing.^{8,9} However, new evidence for this is being published often that contest the information from the earlier reports. A recent review found 27 publications describing 217 newborns born to mothers with COVID-19.¹⁰ They showed that 7 out of 217 newborns (3%) had evidence of SARS-CoV-2 infection. Three had positive serum levels of IgG and IgM antibodies with negative PCR tests, and four had positive PCR tests. All positive infants had favorable neonatal outcomes with no major morbidities. Thirty (14%) newborns were born through vaginal delivery and all were negative for SARS CoV- 2 PCR. Vertical transmission during pregnancy is thought to be unlikely in these cases as PCR testing on placenta, umbilical cord, amniotic fluid, vaginal secretions and breast milk samples has been uniformly negative. Likely explanation for this is the postnatal infection through horizontal transmission. Another systematic review by Elshafeey et al., also presented similar findings from their

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review of 33 studies and 385 pregnant women with COVID -19 infection.¹¹

More recently, there are case reports indicating the possibility of vertical transmission.^{12, 13} Sinelli et al., reported that the mother and newborn tested positive for PCR from nasopharyngeal swab on day 2 of age.¹² The newborn required non-invasive ventilation with 30 % FiO₂ for few days, but recovered well. In the second report, the nasopharyngeal swab of the newborn, taken at 16 hours after delivery, was positive for SARS-CoV- 2 PCR, and immunoglobulin IgM and IgG were negative.¹³ This newborn was ventilated for 12 hours in the beginning, but recovered well soon. Both authors discussed the possibility of vertical transmission in these babies.

Among the small number of pregnancies described until now, there is no strong evidence of vertical transmission to the neonate; however, women were infected in the third trimester. The effects of the virus earlier in pregnancy (first and second trimester) are yet to be known.

Clinical features

The extent of the disease severity in newborn infants is difficult to describe with available limited data. The incubation period may vary from 2-14 days with a median of 5 days. Newborn infants tend to get diseases that are milder and associated with better outcomes compared to adults.⁵ They can be asymptomatic most of the times or can present with mild symptoms like minimal respiratory distress. The review by Elshafeey et al, discussed the clinical outcomes of newborn infants who were born to 252 COVID positive mothers.¹¹ Among the 256 newborns (248 singleton and eight babies as four twins), the reported outcomes were, respiratory distress syndrome (4.7%), neonatal pneumonia (1.2%) and disseminated intravascular coagulation (1.2%). Majority of newborns were asymptomatic. Three newborns died. Two stillbirths were reported for two critical women

(one maternal mortality and one woman on ECMO). One early neonatal death occurred due to complications of prematurity following cesarean delivery at 34 weeks for antepartum hemorrhage. All these three infants who died were PCR negative. Four (1.6%) newborns, delivered by cesarean, had a positive RT-PCR test result and were classified as mild. They recovered well and were discharged. Another three (1.4%) were positive for IgM antibodies and were asymptomatic or mildly symptomatic. All three infants again recovered well and were discharged. Two recent reports indicated that one newborn required ventilatory support for brief period, but recovered well and another newborn with mild febrile illness with hypoxia who required non-invasive ventilation, also recovered well.^{12, 13}

Laboratory features in the newborn infants may include lymphopenia, elevated liver enzymes, coagulation abnormalities and X-ray chest showing bilateral infiltrates in the lungs suggestive of pneumonia.⁷ All clinical features and laboratory features of newborns with PCR positive for SARS-CoV-2 are summarized in Table I.

Diagnosis

Diagnosis of a newborn infant born to a suspected or COVID positive mother is imperative, but can be challenging at times as the sensitivity of the test depends on the timing and sample. RT-PCR testing of nose and throat swab for detection of SARS-CoV-2 nucleic acid has been recommended as the confirmatory test for COVID-19. Other alternative sample could be endotracheal aspirate. FOGSI, NNF and IAP, have teamed up together recently and published the criteria for testing newborns as follows.¹⁴

Whom to test: All newborn infants who have any one of the following:

- 1) History of exposure to COVID-19 positive adult (irrespective of symptoms), mother had COVID-19 infection within 14 days before birth, history of contact

Table I. Clinical and laboratory features of all neonates who tested positive for COVID-19, reported so far in the literature.

Clinical characteristics	Laboratory characteristics
Asymptomatic	Lymphopenia
Respiratory distress - mild to moderate	Leukocytosis
Cough – sporadic	Elevated transaminases
Mild fever	Elevated cytokine levels (IL-6 and IL -10)
Cyanosis (without respiratory distress)	X-ray Chest – normal or bilateral infiltrates
Feed intolerance	

with COVID-19 positive persons (including mother, family members in the same household or direct healthcare provider) in the postnatal period.

- 2) Irrespective of history of exposure: Presenting with pneumonia or severe acute respiratory infection (SARI) that require hospitalization, with onset at more than 48-72 hours of age, unless there is another underlying illness that completely explains the respiratory signs and symptoms.

When to do the test

- a) At birth (if mother had COVID-19) or at detection of the history of contact with COVID-19 positive person (postnatal exposure)
- b) If a sample is not obtained at birth due to logistic reasons, it should be obtained as soon as possible.

When to do repeat test?

If the first test is negative, a repeat test should be done after 5-14 days of birth/exposure. However, the test should be done immediately, if new symptoms such as respiratory distress, lethargy, seizures, apnea, refusal to feed, diarrhoea appear.

Management

Management of newborn infants includes team work involving obstetricians, neonatologists, staff nurses and hospital management. Management flow chart is depicted in Fig.1.

Personal protective equipment (PPE)

SARS-CoV-2 is a respiratory virus transmitted from person-to-person primarily by respiratory droplets. Precautions have to be taken and personal protective equipments have to be worn while taking care of newborn infants with COVID-19 positive mother. Following definitions for precautions were given by AAP.¹⁵

Droplet and contact precautions: Gown, gloves, standard procedural mask and eye protection (either face shield or goggles) should be used for most encounters with infants born to mothers with COVID-19.

Airborne, contact and droplet precautions: Gown, gloves, N95 respiratory mask with eye protection should be used when patients require bag-mask ventilation, intubation, tracheal suctioning, nasal cannula oxygen at a flow greater than 2 liters per minute/kilogram, continuous positive airway pressure and/or positive pressure ventilation of any type, given the potential for these supports to generate aerosols.

Antenatal management

Pregnant women should follow the same recommendations as nonpregnant adults for avoiding exposure to the virus like social distancing, hand hygiene, disinfecting surfaces and wearing a mask in public. Pregnancy is a partially immunocompromised state, however despite the fact that COVID-19 is known to cause severe life-threatening respiratory complications in adults, especially the immunocompromised, there are no comparative data to determine whether pregnancy is a risk factor for severe COVID-19. Pregnant women should be monitored and clinical manifestations are similar to those in nonpregnant individuals.¹¹ Pregnant women with confirmed COVID-19 should be managed with supportive care recommended for non-pregnant adults. Currently recommended management includes: oxygen therapy/respiratory support for treatment of hypoxemic respiratory failure, fluid therapy, antibiotics and management of shock.¹⁴ All COVID-19 positive pregnant women should be referred to designated COVID care facility. In such COVID care facilities, three demarcated zones (clean, potentially contaminated, contaminated), each housing all the needed equipment and services for women and newborns are required for management of non-COVID, suspected and confirmed COVID-19 mothers. The standards and facilities required for infection control in these areas should be same as that for other adults with suspected or confirmed COVID-19. Every pregnant woman should be triaged at entry and then allotted into one of the zones. If a pregnant woman, who delivers in a non-COVID facility, turns out to be COVID-19 positive, actions should be taken as per the Ministry of Health and Family Welfare and referred to COVID facility, and take steps to disinfect the non-COVID facility.¹⁴

Antenatal steroids have proven benefits in neonatal mortality and morbidity. American College of Obstetricians and Gynecologists (ACOG) continues to recommend its use in pregnant women between 24+0 and 33+6 weeks of gestation with suspected or confirmed COVID-19.¹⁶ For pregnant women between 34+0 and 36+6 weeks of gestation, these decisions may need to be individualized, weighing the neonatal benefits with the risks of potential harm to the pregnant woman.¹⁶ The use of magnesium sulfate for maternal seizure prophylaxis and/or neonatal neuroprotection should be decided on a case-by-case basis.¹⁶

Delivery room management

The mode of delivery and anesthesia is best decided as per maternal and fetal indications by the obstetric and

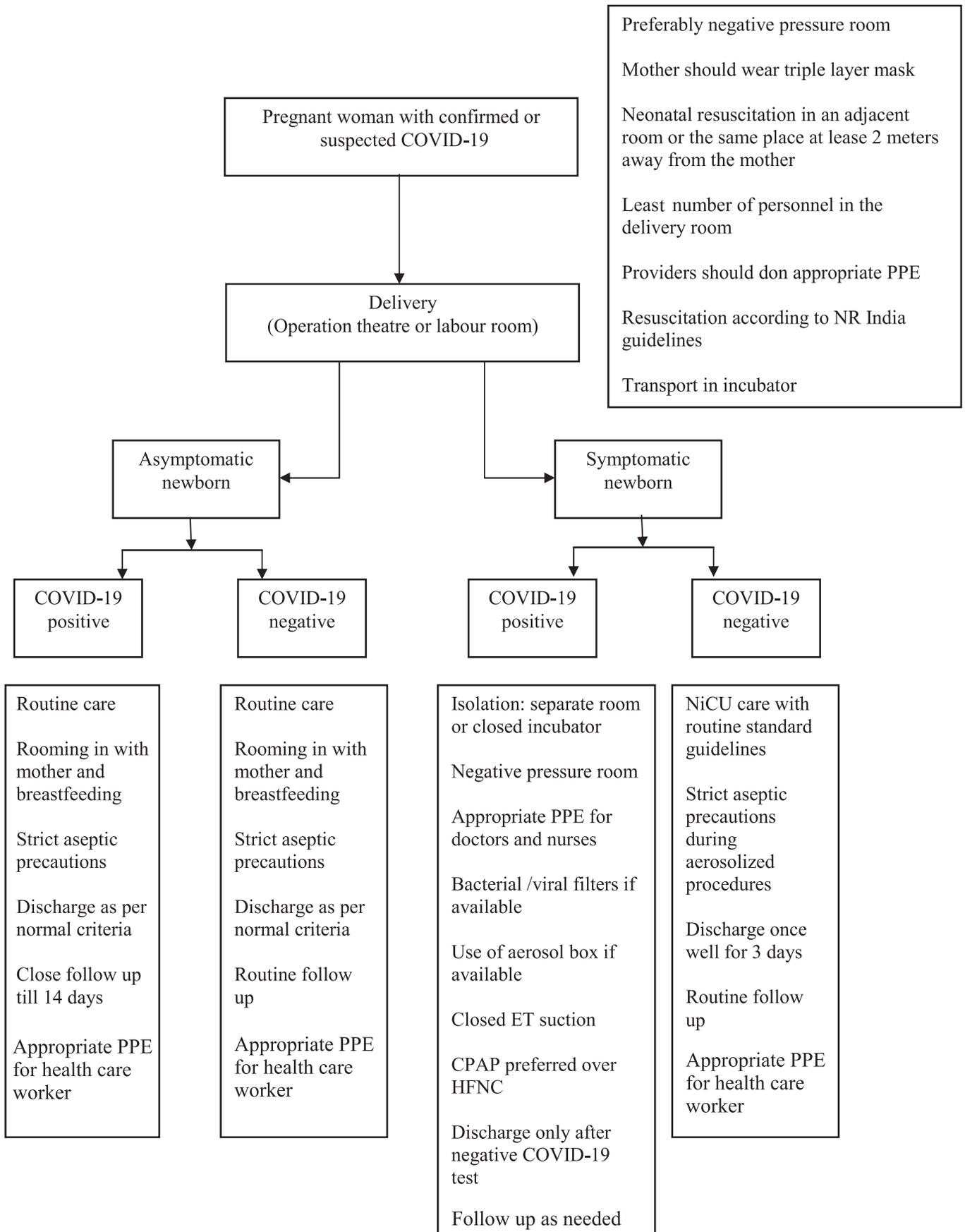


Fig.1. Management of newborn infants born to the suspected or confirmed COVID-19

anesthesia teams regardless of the COVID-19 status. There is no evidence to suggest one mode of delivery is preferred over the other.¹⁰ Delivery of a suspected or confirmed COVID-19 patient should rather take place in a center with the capacity to care for critically ill adults and newborns and in a negative pressure room if available. The optimal location for neonatal stabilization and resuscitation could be in an adjacent room or the same place at least 6 feet or 2 meters away from the mother with a physical barrier. To minimize exposure, the least number of personnel should enter the delivery room. Providers should don appropriate PPE as mentioned above. Mother should perform hand hygiene and wear triple layer mask.

Neonatal resuscitation should be performed according to the Neonatal Resuscitation India, 3rd edition, published by National Neonatology Forum, India.¹⁷ Delayed cord clamping and skin-to-skin contact can be practiced. Following key aspects must be kept in mind during resuscitation:

- During initial steps: Routine neonatal care and the initial steps of neonatal resuscitation are unlikely to be aerosol generating, however, suction of the airways is an aerosol generating procedure and should not be performed routinely for clear or meconium-stained amniotic fluid.
- During endotracheal intubation and medications (Endotracheal intubation and instillation of medications, such as surfactant or epinephrine, are aerosol generating procedures): Intravenous administration of medicines via umbilical venous catheterization is rather preferred.
- Transport to NICU: Closed incubator transfer should be used to transfer newborns to neonatal intensive care when available.

Management in NICU

In the NICU, the baby should be cared for in an incubator in a single room preferably with the potential for negative room pressure. If this is not available or not possible, newborns should be maintained in a closed incubator at least 6 feet apart. These areas should not be a part of the central air-conditioning. If room is air-conditioned, ensure 12 air changes/ hour and filtering of exhaust air.¹⁴ In NICU, doctors and nurses have to wear PPE as mentioned above.

In the NICU, following aspects must be kept in mind while providing respiratory care to newborns:

- During manual ventilation, bacterial/viral filters could

be used to reduce viral dispersion if available.¹⁸ Addition of a filter can reduce efficiency by increasing mask leaks and so it is vital to understand and provide pressure accordingly while using the filter. It is better to avoid filters in ELBW infants (birth weight <1000 grams) to avoid possible iatrogenic hypercapnia with subsequent intraventricular hemorrhage.

- Consider use of aerosol box during intubation if available.
- The area providing respiratory support should be a negative air pressure area.
- Closed ET suction circuit should be used, and a hydrophobic filter placed at the exhalation port.
- CPAP should be preferred over high flow nasal cannulas (HFNC). Limited data from adults suggest that there is possibly a significant dispersion of exhaled air with HFNC.¹⁹

Location of care and breastfeeding

There is some ambiguity around neonatal infection risk during postnatal period and care practices vary for newborns born to mothers with COVID-19. The possibility of the vertical transmission of SARS-CoV-2 through breast milk could not be categorically confirmed. Presently, only limited data on SARS-CoV-2 excretion in breast milk are available. Chen et al., reported that all breast milk samples from 9 mothers with COVID-19 pneumonia were negative.⁸

Recommendations on these areas from several national and international organizations are summarized in Table II. WHO supports skin-to-skin care, rooming-in and breastfeeding for infants born to mothers with COVID-19.²⁰ The Royal College of Paediatrics and Child Health from United Kingdom supports rooming-in and breastfeeding with appropriate infection prevention measures for these infants, unless mothers are too ill.²¹ The American Academy of Pediatrics (AAP) suggests separation of the COVID-19 positive mother and her infant when possible and use of expressed breast milk.¹⁵ The Centers for Disease Control and Prevention (CDC) suggest shared-decision making between family and clinical team with regards to location of care as well as breastfeeding.²² The Indian team (FOGSI, NNF and IAP) recommends rooming in and breastfeeding with strict precautionary measures.¹⁴

There are problems with separation approach, as separation limits opportunities for parent teaching, disrupts breastfeeding and may have negative impacts on mother-

Table II. National and international organizations guidance - Newborn care location and breastfeeding with COVID-19¹⁵

Organization	Location of newborn care	Breastfeeding
WHO ²⁰	Rooming-in with mother	Breastfeeding
AAP ¹⁵	Separation	Expressed Breast milk
CDC ²²	Case to case decision	Case to case decision
RCPCH, UK ²¹	Rooming-in with mother	Breastfeeding
FOGSI/NNF/IAP, India ¹⁴	Rooming-in with mother	Breastfeeding

newborn bonding. Rooming-in during hospitalization helps mother and family to learn infection prevention practices. Finally, with the available current evidence, benefits of breastfeeding outweigh the risks of passing infection from mother to infant. Nevertheless, specific precautions have to be taken, such as wearing a mask during breastfeeding and observing meticulous hand hygiene.

Specific treatment

Specific anti-COVID-19 treatment like antivirals or chloroquine/hydroxychloroquine is not recommended in symptomatic newborns. Use of adjunctive therapy such as systemic corticosteroids, intravenous immunoglobulin and convalescent plasma is also not recommended in symptomatic newborns with suspected or confirmed COVID-19.¹⁴ Only supportive care is needed, as per the problem identified.

Discharge

Stable newborns, tested negative for COVID-19, can be discharged based on the center's normal criteria with mother or care taker. Asymptomatic newborns tested positive for COVID-19, may also be discharged home with mother or care taker (if mother is unwell) with appropriate precautions and plans for frequent outpatient follow-up contacts till 14 days after birth. Specific guidance regarding use of masks, gloves and hand hygiene should be provided to all caretakers. In mild to moderate respiratory illness, they can be discharged as soon as they are well for 3 days, without waiting for a negative COVID-19 test. However, in severe illness, it is prudent to wait for a single negative COVID-19 test after resolution of symptoms, prior to discharge.

Conclusion

The proportion of newborns with the COVID-19 is extremely low when compared to adults. Besides, neonatal COVID-19 appears to be acquired postnatally rather than through vertical transmission and associated with good

outcomes. For well newborns, rooming in with mother and breastfeeding are advocated with adequate safety precautions. For unwell newborns, those who require intubation and ventilation, it is critical to consistently implement safe respiratory practices including proper isolation, ideal PPE and the use of viral filters to the expiratory limbs of any respiratory device if available. Finally, current recommendations on the management of COVID-19 positive mothers and their newborn infants are based on limited data, demanding continuous and comprehensive updates.

Points to Remember

- *Current evidence is inconclusive about vertical transmission of SARS-CoV-2 from mothers with COVID-19 to their newborns.*
- *Majority of newborns tested positive for SARS-CoV-2, are asymptomatic or have mild disease. However, their immature immune system makes them vulnerable to serious respiratory viral infections.*
- *Airborne, droplet and contact precautions should be followed when attending deliveries and in all aerosol-generating procedures like suction and endotracheal intubation.*
- *Mothers with COVID-19 can breastfeed their newborn baby, as SARS-CoV-2 has not been detected in breast milk to date.*
- *Infants born to mothers with COVID-19 should be tested for SARS-CoV-2 at birth or as soon as detection of contact with COVID-19 positive person.– Repeat testing may be needed, if the baby develops symptoms within 14 days of contact or after delivery.*

References

1. WHO. Situation Report. <https://http://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports>. 2020 accessed on 16th May, 2020.

2. Guidelines on preventive measures to contain spread of COVID-19 in workplace settings. CjPMOHFW. <https://http://www.mohfw.gov.in>. 2020. Epub. 16th May, 2020. Accessed 17th May, 2020.
3. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020 Feb 15;395(10223):507-513. PubMed PMID: 32007143. Pubmed Central PMCID: 7135076.
4. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020 Feb 15;395(10223):497-506. PubMed PMID: 31986264. Pubmed Central PMCID: 7159299.
5. Yang P, Wang X, Liu P, Wei C, He B, Zheng J, et al. Clinical characteristics and risk assessment of newborns born to mothers with COVID-19. *Journal of clinical virology: the official publication of the Pan American Society for Clinical Virology*. 2020 Apr 10;127:104356. PubMed PMID: 32302955. Pubmed Central PMCID: 7194834.
6. Fang F, Luo XP. [Facing the pandemic of 2019 novel coronavirus infections: the pediatric perspectives]. *Zhonghuaerkezazhi = CJP*. 2020 Feb 2;58(2):81-85. PubMed PMID: 32102140.
7. Rawat M, Chandrasekharan P, Hicar MD, Lakshminrusimha S. COVID-19 in Newborns and Infants-Low Risk of Severe Disease: Silver Lining or Dark Cloud? *American journal of perinatology*. 7th May, 2020. PubMed PMID: 32380565.
8. Chen H, Guo J, Wang C, Luo F, Yu X, Zhang W, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet*. 2020 Mar 7;395(10226):809-815. PubMed PMID: 32151335. Pubmed Central PMCID: 7159281.
9. Zhu H, Wang L, Fang C, Peng S, Zhang L, Chang G, et al. Clinical analysis of 10 neonates born to mothers with 2019-nCoV pneumonia. *Translational pediatrics*. 2020 Feb;9(1):51-60. PubMed PMID: 32154135. Pubmed Central PMCID: 7036645.
10. Shalish W, Lakshminrusimha S, Manzoni P, Keszler M, Sant'Anna GM. COVID-19 and Neonatal Respiratory Care: Current Evidence and Practical Approach. *American journal of perinatology*. 2020 May 2. PubMed PMID: 32359226.
11. Elshafeey F, Magdi R, Hindi N, Elshebiny M, Farrag N, Mahdy S, et al. A systematic scoping review of COVID-19 during pregnancy and childbirth. *Int J Gynaecol Obstet*. 24th Apr 2020. PubMed PMID: 32330287.
12. Sinelli MT, Paterlini G, Citterio M, Di Marco A, Fedeli T, Ventura ML. Early Neonatal SARS-CoV-2 infection manifesting with hypoxemia requiring respiratory support. *Pediatrics*. 4th May, 2020. PubMed PMID: 32366612.
13. Alzamora MC, Paredes T, Caceres D, Webb CM, Valdez LM, La Rosa M. Severe COVID-19 during pregnancy and possible vertical transmission. *American journal of perinatology*. 18th Apr, 2020. PubMed PMID: 32305046.
14. Chawla D, Chirla D, Dalwai S, Deorari AK, Ganatra A, Gandhi A, et al. Perinatal-Neonatal Management of COVID-19 Infection - Guidelines of the Federation of Obstetric and Gynecological Societies of India (FOGSI), National Neonatology Forum of India (NNF) and Indian Academy of Pediatrics (IAP). *Indian pediatrics*. 1st Apr, 2020. PubMed PMID: 32238615.
15. AAP. <https://downloads.aap.org/AAP/PDF/COVID%2019%20Initial%20Newborn%20Guidance.pdf>. 2020. 2nd Apr, 2020. Epub Accessed on 18th May 2020.
16. ACOG. <https://http://www.acog.org/clinical-information/physician-faqs/covid-19-faqs-for-ob-gyns-obstetrics>. ACOG. 2020 Published 29th April 2020. Epub Accessed 17th May 2020.
17. Ramji S, Bhat S, Chellani H, Dutta S, Thakre R, Bhatia B D et al. Neonatal Resuscitation: India, Text Book 3rd Edition 2018.
18. Chan MTV, Chow BK, Lo T, Ko FW, Ng SS, Gin T, et al. Exhaled air dispersion during bag-mask ventilation and sputum suctioning - Implications for infection control. *Scientific reports*. 2018 Jan 9;8(1):198. PubMed PMID: 29317750. Pubmed Central PMCID: 5760517.
19. Hui DS, Chow B K, Chu L, Ng S S, Sik-To Lai, Gin T, et al. Exhaled air dispersion and removal is influenced by isolation room size and ventilation settings during oxygen delivery via nasal cannula. *Respirology*. 2011;06(16):1005-1013.
20. WHO. <https://http://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-on-covid-19-and-breastfeeding>. 2020. 7th May 2020. Epub Accessed May 18th 2020.
21. RCPCH. <https://http://www.rcpch.ac.uk/resources/covid-19-guidance-neonatal-settings-breastfeeding-by-covid-19-suspected-or-confirmed-mothers>. 2020 12th May 2020. Epub accessed on 18th May 2020.
22. CDC. Care for breast feeding woman. <https://http://www.cdc.gov/coronavirus/2019-ncov/hcp/care-for-breastfeeding-women.html>. 2020 May 5 2020. Epub accessed 18th May 2020.