



Optimization of the Response to nCOVID-19 Pandemic in Pregnant Women – An Urgent Appeal in Indian Scenario

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ABSTRACT

Corona virus Disease 2019 (nCOVID-19), the novel corona virus infection caused by SARS-CoV-2 is a global pandemic with an estimated global mortality rate of 3.4% respectively. SARS-CoV-2 is the seventh human corona virus after SARS-CoV and MERS-CoV. The disease presentation can range from no symptoms (asymptomatic) to severe pneumonia and death. As of now, the experience in Indian set-up is limited. There is even less to draw from in terms of experience in pregnant women and neonates. Pregnancy is a physiological state involving changes that predispose to respiratory complications of viral infection. Limited knowledge available on corona virus infections during pregnancy is attributable to the findings in SARS and MERS epidemics. Clinical manifestations in pregnancy were found to be similar to those of non-pregnant adults with nCOVID-19 that have been reported in the literature without increased susceptibility. Recent evidences have shown the absence of vertical transmission of the SARS-CoV-2 virus from mother to infant. In India, cost-effective and readily available drugs such as hydroxychloroquine and azithromycin are used for nCOVID-19 infection as per guidelines given by the Federation of Obstetric and Gynaecological Societies of India (FOGSI). All the patients with nCOVID-19 in labour universally delivered by caesarean section. Initiation of breastfeeding is controversial. The principle guidelines for isolation, quarantine, case definition, contact tracing, notification and testing are same as that of the general public.

Key Words: nCOVID-19, Pregnancy, SARS-CoV-2, Pandemic

INTRODUCTION

Corona virus Disease 2019 (nCOVID-19), the novel corona virus infection caused by SARS-CoV-2 is a global pandemic as declared by the WHO on March 11, 2020.¹ Since the time the first case of nCOVID-19 pneumonia was reported in Wuhan, Hubei Province, China, in December 2019, the infection has rapidly spread across the world.²⁻⁴ Currently, it has affected 208 countries and territories around the world with 32,49,022 total cases and 2,30,804 deaths (As on 1st May, 2020).⁵ The report of the World Health Organization (WHO) estimated a high R_0 (reproduction⁶ number) of 2–2.5 and an estimated global mortality rate of 3.4% respectively.⁷ India reported its first case on 30th January, 2020. There was a travel history from Wuhan, China. Since then (as on 1st May, 2020), 35,043 confirmed cases and 1075 deaths have

been reported from 27 States/ Union Territories (UTs).⁸ As of now, the Indian experience in this context is limited. There is even less to draw from in terms of experience in pregnant women and neonates.

Corona Virology

Corona viruses are enveloped, non-segmented, positive sense ribonucleic acid (RNA) viruses belonging to the family Coronaviridae, order Nidovirales with three approved genera (alpha, beta and gamma). Around the world, corona viruses are found widespread in bats with many other species including birds, cats, dogs, pigs, mice, horses, whales, and humans being the host to a lesser extent. There is a huge diversity of these viruses which can be explained by their unusually large genomes, infidelity of the RNA-dependent

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RNA polymerase and the high frequency of RNA recombination.^{9,10} This has enabled the emergence of new viruses with traits that allow them to adapt to new hosts and ecologic niches, sometimes leading to zoonotic events. In humans, four respiratory corona viruses (human corona viruses (HCoV) 229E, OC43, NL63, and HKU1) are known to be endemic.¹⁰ Other corona viruses such as Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV) and Middle East Respiratory Syndrome Corona Virus (MERS-CoV) have caused large scale epidemics in 2002 and 2012 respectively, with more than 10 000 cumulative cases in the past two decades, and mortality rates of 10% for SARS-CoV and 37% for MERS-CoV.¹¹⁻¹³

Pathogenesis

SARS-CoV-2, the seventh human corona virus belongs to β -corona virus genus and has genome similarity of about 79% and 50% with SARS-CoV and MERS-CoV respectively. It has structural similarity of the receptor-binding domains with SARS-CoV and uses ACE-2 as the receptor for host cellular binding.^{14,15} nCOVID-19 is spread by respiratory droplets and direct contact. Fecal shedding has been demonstrated from some patients. Airborne spread and fecal-oral route does not appear to be a major driver of transmission based on available evidence. The natural symptomatology of the disease can range from no symptoms (asymptomatic) to severe pneumonia and death.² Typical signs and symptoms include fever (87.9%), dry cough (67.7%), fatigue (38.1%), sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%), headache (13.6%), myalgia or arthralgia (14.8%), chills (11.4%), nausea or vomiting (5.0%), nasal congestion (4.8%), diarrhea (3.7%), hemoptysis (0.9%), and conjunctival congestion (0.8%). Approximately 80% of confirmed cases have mild to moderate disease, which includes non-pneumonia and pneumonia cases, 13.8% have severe disease (dyspnea, respiratory rate ≥ 30 /minute, blood oxygen saturation $\leq 93\%$, PaO₂/FiO₂ ratio 50% of the lung field within 24-48 hours) and 6.1% are critical (respiratory failure, septic shock, and/or multiple organ dysfunction/failure).^{1,6,16,17}

Pregnancy with nCOVID-19 Infection

On extensive review of scientific literature, it was found that out of a total of 1794 articles on the Corona virus infection; only 36 addressed the issue in pregnant women. A total of eight studies (10 case series/reports and 1 retrospective cohort study) reported outcome in 73 pregnant women with corona virus infection.¹⁹ There is a dearth of studies in this area as highlighted by the Indian obstetric and neonatology forums.^{18,19} Analysis in the Indian context is lacking. No clinical trials have compared specific care including isolation strategies in pregnant women. Due to absence of comparative group it is not possible to assess the effect of nCOVID-19 infection in pregnancy.

Pregnancy is a physiological state with changes in the immune and cardiopulmonary systems that predispose the women to respiratory complications of viral infection. During previous influenza pandemics (1918-2010), pregnant women were at higher risk for hospitalization than non-pregnant women a year before pregnancy²⁰ or those 6 months after delivery²¹ and mortality rates were also higher among antenatal women.²²⁻²⁶ Infection with SARS-CoV in pregnancy was associated with adverse pregnancy outcomes. High incidences of spontaneous miscarriage (57%), preterm delivery (80%), and intrauterine growth restriction (16.67%) were seen. There is no evidence of perinatal SARS infection among infants born to these mothers. The case fatality rate of such pregnant women is up to 25%.²⁷ MERS-CoV is known to be responsible for severe complications during pregnancy, including the need for endotracheal intubation, admission to an intensive care unit (ICU) (54%), renal failure and death (27%). All the reported cases were symptomatic with the case fatality rate of 35%. The infant death rate was 27%.²⁸ Currently, however, the impact of nCOVID-19 infection on pregnant woman is not fully elucidated. There are concerns relating to the potential effect on fetal and neonatal outcome. Therefore, pregnant women require special attention in terms of prevention, diagnosis and management of nCOVID-19 infection.

Maternal Symptomatology

The mean incubation period is 5 to 7 days with maximum infection seen by 11 days of exposure.²⁹ The evidence and the limited knowledge available on Corona virus infections during pregnancy is attributable to the findings in SARS and MERS epidemics. They are responsible for serious maternal and neonatal outcomes, both in terms of morbidity and mortality as previously mentioned. But the findings with SARS-CoV-2 follow a different milder trajectory.

Nan Yu et al³⁰ studied seven infected pregnant patients in late pregnancy (mean = 39 weeks plus 1 day) admitted at a Chinese Hospital from 1st Jan to 8th Feb, 2020. Clinical manifestations were found to be similar to those of non-pregnant adults with nCOVID-19 that have been reported in the literature which ranged from fever (86%), cough (14%), shortness of breath (14%) to diarrhoea (14%). The pregnancy and neonatal outcomes were good which was achieved with intensive and active management that might be the best practice in the absence of more robust data.

Chen H et al³¹ retrospectively studied 9 infected pregnant Chinese females admitted from January 20th to 31st, 2020. Cases presented with low-grade fever without chills (77.8%), cough (44.4%), myalgia (33.3%), sore throat (22.2%), malaise (22.2%) and obvious gastrointestinal symptoms (11.1%), shortness of breath and pre-eclampsia (11.1%). However, none of the nine patients developed severe pneumonia, requiring mechanical ventilation, or died of

nCOVID-19 pneumonia, as of Feb 4, 2020.

In a detailed report of 38 infected pregnant Chinese women, of whom 37 were confirmed cases, there were no cases of either severe pneumonia or maternal deaths. Although there were co-morbid conditions (like gestational hypertension, pre-eclampsia, hypothyroidism and influenza infection) present in some of the women, mostly obstetrical in etiology, they apparently did not result in life-threatening maternal SARS-CoV-2 disease.³²

Similarly, two case reports of a Chinese infected pregnant woman showed a two-day history of dry cough, chills without fever, or shortness of breath³³ and fever without cough or sputum³⁴ respectively.

Royal College of Obstetricians and Gynaecologists (RCOG) has also postulated that pregnant women don't appear to be more susceptible to consequences of infection of nCOVID-19 than general population.³⁵

Maternal-fetal Transmission and Neonatal Cases

Nan Yu et al³⁰ reported that 33.33% of the neonates were infected with SARS-CoV-2 36 hours after birth. Similarly, Chinese case report by Wang S et al³⁴ described a positive neonatal case at 36 hours of birth. The babies had no contact with their mothers after birth. Both cases were discharged after 12-14 days of birth following two consecutive negative nucleic acid test results. The suspected vertical transmission of the SARS-CoV-2 infection could not be confirmed because of the late collection of the neonatal oropharyngeal swab, performed 36 hours after birth.

Whereas other studies were able to prove conclusively that no vertical transmission of the infection to the neonates occurred. A retrospective study of 9 confirmed pregnant cases confirmed negative detection of the virus in amniotic fluid, umbilical cord blood and nasopharyngeal swab of newborns.³¹ Another case report showed negative vertical transmission.³³ Schwartz et al described a series of 30 neonates with no confirmed SARS-CoV-2 infection cases, despite the existence of perinatal complications in some of the infants. The virus was not identified in the amniotic fluid, placenta, breast milk of 6 mothers or in the nasal secretions of their neonates tested so far.³² Similar to the previous SARS and MERS epidemics, all these studies show no evident vertical transmission with the current SARS-CoV-2.³⁶ Thus, the evidence to support the absence of vertical transmission of the SARS-CoV-2 virus from mother to infant is continuously increasing.

Treatment Protocols followed

All the patients with nCOVID-19 in labour had caesarean section

after consultation with a multidisciplinary team within a few days of the admission to the hospital.³⁰⁻³⁴ There is no proven scientific rationale for this. It could reflect local preference and practices. Another reason could be lack of knowledge about the intrapartum course with its possible complications such as prolonged labour, or chorioamnionitis with suspected fetal jeopardy. Because nCOVID-19 is an emerging infectious disease, the optimal treatment for affected individuals has not yet been established.

In a study by Nan Yu et al³⁰ all patients received oxygen therapy, via nasal catheter in isolation. Antiviral treatment included oseltamivir (75 mg every 12 hour orally), ganciclovir (0.25 g every 12 h, intravenously), and interferon (40 µg daily, atomized inhalation) and arbidol tablets (200 mg three times daily, orally). Traditional chinese medicines, such as Jinyebaidu granules and Lianhuaqingwen capsules were also used. Antibiotic treatment (cephalosporins, quinolones, and macrolides) was given for all with 29% patients given single antibiotic and 71% patients given combination therapy. Methylprednisolone was given after caesarean section in 71% cases.

Wang S et al³⁴ in Tongji Hospital, Wuhan, China used antiviral treatment (40 µg of recombinant human interferon α_{1b} atomized inhalation and ganciclovir, 0.25 g every 12 h, intravenously), methylprednisolone (20 mg intravenously) and antibiotics (Abipenem, 0.3g every 12h, intravenously and moxifloxacin, 0.4g q.d, intravenously) for treatment for nCOVID-19 infection.

General measures for nCOVID-19 infections should include rest, oxygen supplementation, fluid management and nutritional care as needed. According to Federation of Obstetric and Gynaecological Societies of India (FOGSI), its treatment can be attempted by two approaches. The first approach involves utilizing Hydroxychloroquine and Azithromycin in combination. These are cost-effective and readily available in India. The other approach being the use of antiviral drugs, some of which are not yet available in India.¹⁹

Outcomes and Discharge

The outcomes of the pregnant women were good among the various institutions observed.³⁰⁻³⁴ There were no intensive care unit admissions for mothers throughout the study period, including before and after delivery. All patients were discharged from the hospital after adequate care. Body temperature returned to normal for more than 3 days; respiratory symptoms improved significantly; pulmonary imaging showed a significant improvement in acute exudative lesions; and nucleic acid test of respiratory specimens such as results of sputum and nasopharyngeal swabs were negative twice in a row (sampling interval ≥ 24 h).³⁰⁻³⁴ The mother's breast milk sample was negative for SARS-CoV-2.^{31,32,34} and therefore breastfeeding is not a contraindication. The main risk for infants of breastfeeding is the close contact with the mother, who is likely to share infective airborne droplets. Whether it could be allowed with

proper hygienic practices and keeping in mind the risk-benefit ratio, is still controversial.³⁷ This should be discussed with the parents before a decision is made. In accordance with RCOG and FOGSI guidelines, hand hygiene and respiratory hygiene (wearing a mask and not sneezing in front of a baby) should be strictly followed during breast feeding. Milk can be expressed with a manual or electric breast pump after adequately washing hands and according to the recommendations for proper pump cleaning after each use. This could later be fed to the baby by someone well.^{19,35}

DISCUSSION AND IMPLICATIONS

Due to the rapid outbreak and need of time for evaluation and follow-up, the long-term outcomes of neonates and whether in-utero or vertical transmission is possible has not been demonstrated so far.

Postnatal transmission from infected mother or caregivers to the neonate is definitely possible. A delay in testing can make it difficult to differentiate a mother to fetal transmission (or at birth) from postnatal (contact/droplet) transmission. Lastly, fetal effect of maternal infection during first and second trimester of pregnancy is not known.

It must be emphasized that as vaccine development is currently under progress for nCOVID-19, pregnant women should be considered for inclusion in the clinical trials as well as the eventual distribution of the vaccine unless the risks outweigh the potential benefits.³⁸

Transparent and comprehensive reporting of all cases of nCOVID-19 pregnancies is very essential to get concrete results helping in generating evidences and guiding clinical management. Government of India guidelines³⁹ should be followed for the same. The principle guidelines for isolation, quarantine, case definition, contact tracing, notification and testing are same as that of the general public.

CONCLUSION

This review article of the presentation of nCOVID-19 infection in pregnant women provides a scaffold on which further investigations and studies can be added, to its ever-evolving knowledge to equip us in fighting this global crisis better.

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