

Pregnancy with Covid-19 Infection and Fetomaternal Outcomes

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ABSTRACT

BACKGROUND

The emergence of the novel coronavirus infection (SARS CoV-2) across the world is one of the most significant public health threats in current times. Due to the severity of this outbreak and the potential of international spread, the World Health Organization (WHO) declared it as pandemic in March 2020. Very less data is available over the impact of virus on pregnancy. Our objective is to evaluate the clinical features, obstetrical complications and neonatal outcomes in a pregnancy with coronavirus infection.

METHODS

125 laboratory confirmed SARS-CoV-2 pregnant women were studied. Detailed clinical features, maternal complications, pregnancy and neonatal outcomes were analysed.

RESULTS

Out of 125 confirmed pregnant women, 57 patients delivered by caesarean section, 40 delivered vaginally while 28 patients were doing well with their ongoing pregnancy. 88 patients were asymptomatic, 12 had fever, and 17 patients had cough and sore throat while 08 patients had mild diarrhoea and pain in abdomen. 109 patients showed lymphopenia. All neonates tested negative at birth. As there is still no definite treatment for the disease, we treated our patients symptomatically with hydroxychloroquine, azithromycin, vitamin C and all our patients responded well to the treatment.

CONCLUSIONS

No major complications were observed in studied cohort like severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Our study depicted the mild course of infection in pregnancy without causing any life-threatening complications. No confirmed case of vertical transmission was seen. All women responded well to hydroxychloroquine and symptomatic treatment.

KEY WORDS

Coronavirus, Pregnancy, SARS CoV-2, Hydroxychloroquine, WHO

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BACKGROUND

At the end of 2019, several patients were diagnosed with pneumonia of unknown cause, epidemiologically associated with the same seafood market. The Chinese Centre for Disease Control and Prevention immediately launched an emergency response. The WHO also responded promptly and declared the outbreak of a Public Health Emergency of International Concern (PHEIC). The causative agent of the unidentified pneumonia has been confirmed as a novel coronavirus. Coronavirus is a single stranded RNA virus, belonging to Coronaviridae family that can cause various diseases with enteric, respiratory, hepatic and neurological symptoms.¹ The new coronavirus was officially renamed as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) by the International Committee on Taxonomy of Virus and the disease it causes namely coronavirus disease 2019 (Covid-19) has quickly become of tremendous concern worldwide. Person to person transmission may occur through contact, respiratory tract or possibly by fecal-oral-route. Currently, there is no definite treatment although some potential drugs are under investigation.² Due to the severity of this outbreak and the potential of spreading on an international scale, the WHO declared a global health emergency on 31 January 2020; subsequently, on 11 March 2020, they declared it a pandemic situation. At present, we are not in a position to effectively treat Covid-19, since neither approved vaccines nor specific antiviral drugs for treating human coronavirus infections are available. Reverse-transcriptase quantitative polymerase chain reaction (RT-qPCR) detection methods based on nucleic amplification are often used in the case of SARS-CoV, MERS-CoV and other viruses because of high sensitivity and specificity, particularly in the acute phase of infection.

The coronavirus has intruded the humans through gene mutations leading to the pandemic. Previous epidemics of many emerging viral infections have typically resulted in poor obstetrical outcome including maternal morbidity and mortality, intrauterine vertical transmission, perinatal infections and death. Pregnant women do not appear more likely to contract the infection than the general population in case of coronavirus infection. However, pregnancy itself alters the body's immune system and response to viral infections in general, which can occasionally be related to more severe symptoms and this will be the same for Covid-19 according to the Indian Council for Medical Research-National Institute for Research in Reproductive Health (ICMR-NIRRH).³ Physiological changes in pregnant women not only increases the susceptibility to the virus, but also increases the severity of disease. The cardiovascular changes, the increase in metabolic rate and oxygen consumption, the decrease in functional residual capacity and the mismatch between basic ventilation and perfusion, all of these factors caused by pregnancy are easily led to the occurrence of hypoxic respiratory failure in women after infection with SARS-CoV2.⁴ There is currently no data suggesting an increased risk of miscarriage or early pregnancy loss in relation to Covid-19. Follow up of positively diagnosed pregnant women during in the first and second trimesters should be encouraged, to understand the impact of the new coronavirus infection on the pregnant mother, the fetus and the course of pregnancy.

METHODS

It was a prospective observational study, conducted in the Department of Obstetrics and Gynaecology, Government Medical College, Kota, Rajasthan. It is a tertiary care centre with around 15000 deliveries per year and is the main referral centre for the entire Hadoti region of the Rajasthan. The study was conducted over laboratory confirmed Covid-19 positive pregnant women admitted in the hospital from April 2020 to September 2020. Since our first positive patient reported on 21 April 2020, and till first week of September we got total 125 positive patients, all patients were observed for data collection. All enrolled patients were explained about the purpose of the research work and an informed consent was obtained before conducting the study. All patients' despite of their age and parity admitted in our hospital underwent testing for Covid-19. The oropharyngeal swabs were collected and tested for SARS-CoV-2 by use of real time reverse transcriptase –Polymerase Chain Reaction. For all confirmed positive cases we enquired the following information

- Detailed travel history.
- H / o exposure to people with symptoms of Covid-19.
- Symptoms of Covid-19.
- Residence in hotspot area.
- Immune-compromised condition.

After admission these patients were given following care; daily vitals (blood pressure, pulse rate, respiratory rate, oxygen saturation, temperature) charting, input-output charting, X-ray chest with abdominal shield, electrocardiograph and fetal heart rate monitoring. Complete blood counts, c-reactive proteins, liver function tests, renal function tests, blood sugar charting done for all patients. Testing repeated for each patient in every 48 hours till 2 consecutive negative reports obtained. After making the clinical diagnosis obstetrical management was done apart from individualised symptomatic and supportive treatment for each patient in the form of oxygen inhalation, analgesics, nebulisation, intravenous fluid, (intravenous antibiotics post operatively). Tablet hydroxy chloroquine 400 mg twice a day given to all patients. Induction of labour done as per obstetrical indication, while conducting the deliveries and Caesarean section, it was done with all due precautions and wearing personal protective equipment's. The course of pregnancy, mode of delivery, neonatal outcome, maternal complications all were recorded and analysed statistically. The neonates were also tested for Covid-19 infection, they were separated from mother after delivery till her test came negative, feeding of newborns done as per government guidelines. None of the studied patients received convalescent plasma therapy.

All the Covid-19 positive postpartum patients who were referred from the remote areas were excluded in the study.

Statistical Analysis

Data was collected and entered in Microsoft Excel sheet to prepare master chart. Linear variables were summarised as mean and standard deviations. Nominal and categorical data was presented as proportions (%). MDCalc 12.2 .1.0 version software was used for all statistical calculations.

RESULTS

Total 125 laboratory confirmed antenatal women were enrolled in the present study. 113 patients were in their third trimester while 12 patients were in their first trimester. Out of 125, 88 patients were asymptomatic while 12 patients were having fever, 17 patients had mild cough and sore throat, and 08 patients had mild diarrhoea and pain in abdomen. X-ray was suggestive of features of pneumonitis in 12 patients while no one had progressed to critical pneumonia requiring ventilator care and no maternal deaths were observed. 109 patients had lymphopenia and leukocytosis was observed in 87 patients. Out of 125, 40 patients had normal vaginal delivery, 57 women underwent Caesarean section, whereas 28 patients were continuing their pregnancy well till date. 97 live births were recorded with a 1-minute Apgar score of 8 - 9 in 90 new-borns. 07 cases of fetal distress were observed.

Age	No. of Patients	Percentage
< 20 yrs.	02	01.6 %
20 - 30 yrs.	80	64.00 %
30 - 40 yrs.	43	34.40 %
Gravida		
1	70	56.00 %
2	32	25.60 %
3	18	14.40 %
4	05	4.00 %
Gestational Age		
< 32 wks.	12	9.6 %
32 - 36 wks.	25	20.00 %
36 - 40 wks.	74	59.20 %
> 40 wks.	14	11.20 %

Table 1. Characteristics of the Study Participants (N = 125)

Majority of the patients were in the age group of 20 - 30 years, more than half of studied cohort were primigravida. The gestational age of maximum patients i.e. 59.20 % was between 36 weeks to 40 weeks. 12 patients were in their first trimester of pregnancy, rest of women were in their third trimester.

Complaints	No. of Patients	Percentage
Asymptomatic	88	70.40 %
Fever	12	09.60 %
SARI-mild	17	13.6 %
SARI-severe	-	-
GI/T complaints	08	06.40 %

Table 2. Complaints at the Time of Admission

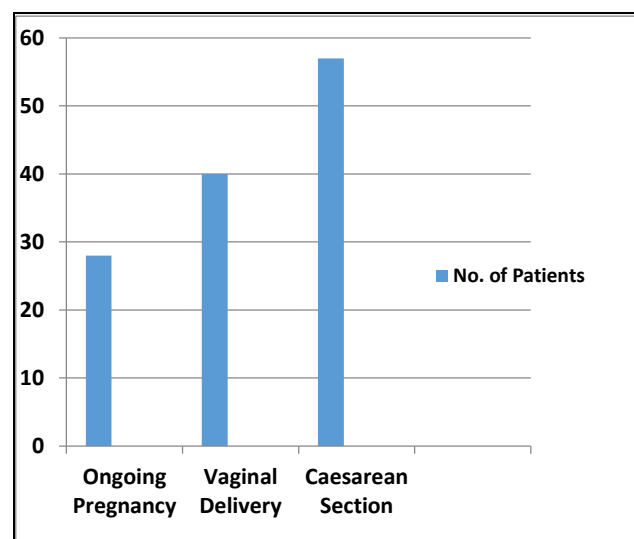
Amongst 125 women, 88 were asymptomatic, 12 patients had history of fever, 17 patients were having mild cough and sore throat while 08 patients had mild pain in abdomen and diarrhoea. Fortunately, signs of severe acute respiratory infections (SARI) were not observed in the admitted women.

Lymphocyte Percentage	No. of Patients	Percentage
< 10 %	09	7.20 %
10 - 15 %	55	44.00 %
15 - 20 %	45	36.00 %
20 - 40 %	16	12.80 %

Table 3. Maternal Lymphocyte Counts

Leucocyte Count	No. of Patients	Percentage
4000 - 11000	43	34.40 %
11000 - 20000	67	53.60 %
20000 - 30000	15	12.0 %
> 30000	00	0

Table 4. Maternal Leucocyte Counts



Graph 1. Obstetrical Outcome

Birth Weight	No. of Newborns
< 2 Kg	07
2 Kg - 2.5 Kg	45
2.5 Kg - 3 Kg	27
> 3 Kg - 3.5 Kg	18

Table 5. Baby Details

Lymphocytopenia was observed in 109 patients, leucocytosis found in 82 patients, anaemia was present in 18 patients, which was corrected by blood transfusion and haematinics. Apgar score for 90 new-borns was > 8 / 10 at 1 minute and 5 minutes. All new-borns were tested through oropharyngeal swab for RT -PCR and all were reported negative. 57 out of 125 patients underwent Caesarean section, 40 patients delivered vaginally, and 28 patients were continuing their pregnancy well till date. Surgery done under spinal anaesthesia; no complications observed during surgery with average time being 40 minutes to 55 minutes.

DISCUSSION

Covid-19 caused by SARS-CoV2 virus, a potentially fatal disease represents great global public health concern. In March 2020 WHO declared this outbreak as pandemic. The virus infects the lower respiratory tract and causes pneumonia in humans, seems that the symptoms are milder than SARS & MERS.⁵ As of now, not much information about the mortality, pathobiology, cellular responses, viral impact over course of pregnancy and fetus, teratogenicity and potential treatment about this disease is known; a probable course of events can be postulated based over the past few studies and still many studies are going on. There has been considerable concern about the effects of SARS-CoV-2 infection during pregnancy on the fetus and newborn.

Studies have shown that in the outbreak of influenza virus during 1957-1958 the mortality of pregnant women was 10 % which was twice as high as that of non-pregnant women.⁶ During the outbreak of SARS in 2003, several small clinical reports stated that pregnant women infected with SARS had worse outcomes than non-pregnant women.⁷

Thomas et al.⁸ assessed longitudinal changes among more than 52 participants at 3 time points during pregnancy and 2 time points during postpartum. Indicators observed were

WBC, analysis of the function of natural killer cells (NK cells), cluster of differentiation (CD4) T cell response, cytokines in maternal blood, levels of defensins, steroid hormones and so on. The result showed that when compared with postpartum, the late gestation was characterized by a decrease number and activity in the NK cells which may affect the viral clearance rate and lays foundation for the onset and deterioration of infectious disease.^{9,10}

Angiotensin-convertase enzyme (ACE) is the core of rennin angiotensin system (RAS) and has long been considered as a key regulator of blood pressure in mammals. In recent studies, scholars believe ACE-2 is the "doorknob" for SARS-CoV-2 entering the door of the host cells.¹¹ and the up regulation of ACE-2 is likely to increase the susceptibility of Covid-19. A high expression of ACE-2 in pregnant women also increase the susceptibility of pregnant women to SARS-CoV-2.⁶

Chen et al.¹² retrospectively analysed the clinical data of 9 labour confirmed Covid-19 pregnant women and explored the potential of vertical transmission of virus. The result showed that clinical characteristics of these patients during pregnancy were similar to those of non-pregnant adults and SARS CoV-2 test of amniotic fluid, umbilical cord blood, neonatal throat swabs and breast milk samples were negative. However if we do not find proofs of vertical transmission it's not enough to make us relax. Studies have shown that mother's response to infection tends to promote the fetus inflammatory response syndrome which we define as (FIRS) is characterized by high levels of inflammatory cytokines in placenta such as IL-1, IL-6, IL-8 & TNF- α but a lack of cultivable microorganism. These cytokines have been shown to affect the central nervous system and circulatory system and tend to cause fetal abnormal morphology in animal models including ventricular expansion and bleeding.^{13,14,15} Hence active treatment should be given to prevent more serious effect of infection on mother as well as fetus. The lack of cellular structure of the virus contributes to its great variability which also makes people still weak in antiviral treatment. Since 2013, the Food and Drug Administration (FDA) has approved only 12 drugs to treat viral infections. Currently there is no specific drug for SARS-CoV-2. So, people only have to choose existing drugs based on the past experience of antiviral and strive to develop vaccines or direct acting antiviral drugs or host directed therapies at the same time.¹⁶

However, due to proven teratogenicity, many antiviral drugs are prohibited in pregnancy. Chloroquine was first synthesized in 1934 by Hans Anderserg in Bayer, Germany through structural modification of the oldest antimalarial drug, quinine. Hydroxychloroquine is a new antimalarial drug developed by scientists on the basis of chloroquine in 1944 with less side effect profile. Previous studies have clearly suggested that chloroquine has shown immunomodulatory and broad spectrum antiviral effects and such mechanism ensures its therapeutic effects in a variety of infectious disease and has begun to show new therapeutic range. Evidence and clinical trials have confirmed the inhibitory effect of chloroquine on HIV / MERS-CoV, SARS-CoV and other viruses. Moreover, the dose of antiviral is lower than the blood concentration for the treatment of malaria and no toxicity was found to host cells.¹⁷ Martin et al.¹⁸ showed that the inhibitory effect of chloroquine on cells of SARS-CoV 2 infection can be demonstrated before or after the cells are exposed to the virus, which means that chloroquine shows an effect both on prevention and on treatment of SARS CoV.

Andrea Cortegiani et al. stated that there is sufficient pre-clinical rationale and evidence regarding the effectiveness of chloroquine for treatment of Covid-19 as well as evidence of safety from long term use in clinical practice for other indications¹⁹ to justify ethical research on topic.²⁰

Satyajit et al. concluded in their study that considering the global health crisis for the Covid-19 pandemic, the option of using hydroxychloroquine drug in the treatment of SARS-CoV-2 might be the logical approach to follow. However, we need to wait for the results that would come out of larger prospective, randomized, dose determining, controlled clinical trials before making clinical recommendations.²¹

Chen et al. retrospectively studied 9 pregnant patients in their 3rd trimester with Covid-19 infection, and they found that the symptoms of Covid-19 pneumonia were diverse in pregnant women with the main symptom being fever and cough. They found no evidence of vertical transmission in late pregnancy.

Zhang et al. retrospectively compared 16 Covid-19 positive pregnant women against 45 non Covid pregnant women and found that in case of critical illness timely termination of pregnancy will not increase the risk of premature birth and asphyxia but is beneficial to the treatment and rehabilitation of maternal pneumonia. Covid-19 infection has not been found in neonates delivered from pregnant women with Covid-19 infection.²²

Our study is having few limitations, first is the small sample size of the studied patients. Second, no direct testing of intrauterine tissue samples such as amniotic fluid, cord blood or placenta was done to confirm the intrauterine infection. Third, possibilities of fetal inflammatory response was not explored.

CONCLUSIONS

An unprecedented global health burden has been created by coronavirus pandemic. There has been sparse information regarding the impact of infection over the course of pregnancy and the neonates. Unlike fatal complications of SARS and MERS, our study depicted the mild course of infection in pregnancy without causing any life-threatening complications or maternal deaths. There was no confirmed case of intra uterine vertical transmission of SARS-CoV-2 observed as all the new-borns tested negative for the infection. All pregnant women responded well to hydroxychloroquine and symptomatic treatment.

Data sharing statement provided by the authors is available with the full text of this article at jemds.com.

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