

# Covid-19 in Gravid Uterus – The Challenge in Antenatal Care and Its Outcome – A Tertiary Level Cross Sectional Analysis from Chennai, India

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## ABSTRACT

### BACKGROUND

With the emerging pandemic of corona virus disease 19 (Covid-19) infection around the world, the need to identify the course of this disease in pregnant women becomes the need of the hour. Its effect on pregnancy and the neonatal outcome is not well known because of lack of any reliable data. We wanted to evaluate the clinical features, laboratory manifestations and obstetric outcome of Covid-19 in the term of antenatal mothers who were either admitted in labour, induction of labour or elective caesarean section and rule out vertical transmission by doing a routine neonatal screening for Covid-19.

### METHODS

A descriptive cross-sectional study conducted at Sri Ramachandra Medical College & Research Institute, Chennai from March 2020 to September 2020 includes all antenatal women who were tested positive for severe acute respiratory syndrome (SARS- Cov2) reverse transcription - polymerase chain reaction (RT-PCR). 43 Covid positive patients were included in the study.

### RESULTS

Incidence of Covid positive antenatal women was found to be 1.7 %. Only 3 % were symptomatic with mild disease. Gestational diabetes mellitus accounted for (27 %), Class II obesity (7 %), hypertensive disorders of pregnancy (13 %) of the screen positive mothers. 20 % of the labouring women had meconium-stained liquor. Lymphopenia was seen in 73 % of cases. Elevated d-dimer in 13 %, requiring thromboprophylaxis. Negative RT-PCR for SARS-CoV-2 in the neonates ruled out vertical transmission.

### CONCLUSIONS

Covid-19 in pregnancy is more common in those with gestational diabetes, obesity, with development of complications like hypertension and meconium-stained liquor. The impact of Covid-19 is not as disabling as it is in the non-pregnant population.

### KEY WORDS

Universal Screening, In/Near Labour, Lymphopenia, Thromboprophylaxis, Meconium- Stained Amniotic Fluid.

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**BACKGROUND**

The outbreak of the novel corona virus (SARS-CoV-2), a strain of corona virus responsible for the Covid-19 pandemic heralded in Wuhan, China as the epicenter.<sup>1</sup> India declared the first diagnosed case on 30 January 2020. Human to human transmission is majorly responsible for this disease. The virus has been readily isolated from respiratory droplets or secretions, faeces, and fomites (objects). Transmission of the virus is known to occur most often through close contact with an infected person (within 2 meters) or from contaminated surfaces. Being a primary respiratory pathogen, multi-organ involvement has also been reported in some cases.

Coronaviruses are enveloped, positive-sense, single-stranded ribo nucleic acid (RNA) viruses of ~30 kb. They infect a wide variety of host species. They are largely divided into four genera;  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  based on their genomic structure.  $\alpha$  and  $\beta$  coronaviruses infect only mammals. Human coronaviruses such as 229E and NL63 are responsible for common cold and croup and belong to  $\alpha$  coronavirus. In contrast SARS-CoV, middle east respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2 are classified to  $\beta$  coronaviruses. The life cycle of the virus with the host consists of the following 5 steps: attachment, penetration, biosynthesis, maturation and release. Once viruses bind to host receptors (attachment), they enter host cells through endocytosis or membrane fusion (penetration). Once viral contents are released inside the host cells, viral RNA enters the nucleus for replication. Viral mRNA is used to make viral proteins (biosynthesis). Then, new viral particles are made (maturation) and released. Coronaviruses consist of four structural proteins; Spike (S), membrane (M), envelop (E) and nucleocapsid (N). Spike is composed of a transmembrane trimetric glycoprotein protruding from the viral surface, which determines the diversity of coronaviruses and host tropism.

Asymptomatic or pre-symptomatic infection	Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test or an antigen test) but who have no symptoms that are consistent with COVID-19.
Mild illness	Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, loss of taste and smell) but who do not have shortness of breath, dyspnoea or abnormal chest imaging.
Moderate illness	Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen (SpO2) $\geq$ 94 % on room air at sea level.
Severe illness	Individuals who have SpO2 < 94 % on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2 / FiO2) < 300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates > 50 %.
Critical illness	Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.
<b>Grading of Covid-19 Severity - (NIH Guidelines)</b>	

Spike comprises two functional subunits; S1 subunit is responsible for binding to the host cell receptor and S2 subunit is for the fusion of the viral and cellular membranes. Angiotensin converting enzyme 2 (ACE2) was identified as a functional receptor for SARS-CoV. ACE2 expression was high in lung, heart, ileum, kidney and bladder.

The symptom of patients infected with SARS-CoV-2 ranges from minimal symptoms to severe respiratory failure with multiple organ failure. On computerized tomography (CT) scan, the characteristic pulmonary ground glass opacification can be seen even in asymptomatic patients. The severity of SARS-CoV-2 in adults can be categorised as asymptomatic or pre-symptomatic, mild, moderate, severe and critical as per the NIH Covid-19 treatment guidelines. The following classification is applicable to the pregnant mothers as well.

Pregnant women are considered as clinically vulnerable group and are advised to continue shielding to minimize the risk of infection. Although shielding may be possible for other high-risk groups, pregnant women are still required to attend hospital appointments in person for regular antenatal care.<sup>2</sup> Despite the immunological changes in pregnancy, pregnant women are not likely to contract a severe disease according to the available evidence till date. Only an antenatal mother with a heavy viral load will be vertically transmitting the infection to the foetus as per the 2 case reports which have been published.<sup>3</sup> These reports showed the presence of IgM SARS CoV-2 in the neonate on the second day of life. The benefits of breastfeeding substantially outweigh the risk of potential transmission of Covid-19, hence mothers who are suspects or a confirmed case of Covid must be encouraged to initiate breastfeeding as per the world health organization (WHO).

The laboratory findings of Covid-19 include lymphopenia, thrombocytopenia with a normal total leucocyte count (TLC), increased acute phase reactant proteins like erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and ferritin with elevated lactate dehydrogenase (LDH) and d- dimer levels.<sup>4</sup> These finding overlap with that of the haematological changes in pregnancy and pathological conditions like HELLP, thereby masking the effect of the virus.

Universal screening for term pregnant mothers in/near labour, who are hospitalized for delivery has been recommended by the ICMR (Indian council of medical research). It enables the identification of asymptomatic patients and facilitates effective tracing and targeted isolation. These strategies will minimize the risk of further peaks in the pandemic and allow for a safer transition out of complete lockdown.

**Objectives**

1. To evaluate the clinical features, laboratory manifestations and obstetric outcome of Covid-19 in the term antenatal mothers who were either admitted in labour, induction of labour or elective caesarean section and
2. To rule out vertical transmission by doing a routine neonatal screening for Covid-19 on the second day of life.

**METHODS**

This cross-sectional study was conducted in Sri Ramachandra Medical College & Research Institute, Chennai from March 2020 to September 2020. The study was approved by the Institutional Ethics Committee. All term pregnant mothers

who were tested positive for SARS-CoV-2 RT-PCR as a universal screening protocol near/during labour were included.

The severity of the disease which was categorized as asymptomatic, mild, moderate, and severe infection was studied in them based on the clinical, laboratory and radiological findings.<sup>5</sup> The associated co-morbidities of the pregnant mother were also documented. All the neonates of COVID positive mothers were tested for the same on the second day of their life. No temporal separation between the mother and the baby was practiced and exclusive breastfeeding was encouraged with proper hand hygiene and sanitation being maintained.

Postpartum chest x-ray, d-dimer, serum ferritin, LDH levels were assessed, and both the mother and the new-born were discharged with an advice of home quarantine for two weeks in mild and asymptomatic cases.

**Statistical Analysis**

Categorical variables are expressed as N (%).

**RESULTS**

Out of 1706 antenatal mothers who were screened at/during labour, 31 mothers were tested positive that accounts for only (1.81 %) testing positive for the novel virus. Mild disease was present in 5 of them with fever being the only finding (16.1 %), while the remaining 26 pregnant mothers (83.8 %) were asymptomatic.

**Comorbidities in Covid Positive Mothers**

Class II obesity was present in 2 (7 %) of them. Six mothers were Rh negative without isoimmunisation. Hypertensive disorders of pregnancy were present in 4 mothers, out of which 3 were cases of severe pre-eclampsia (10 %) and the other was a case of gestational hypertension (3 %). Gestational diabetes mellitus (27 %) was present in 8 pregnant mothers with 6 of them on oral hypoglycaemic agents and the remaining 2 on medical nutritional therapy. Foetal growth restriction at 3<sup>rd</sup> centile was present in 2 mothers (7 %) with COVID positivity (Table 1).

Obstetric Characteristics	No. of Antenatal Mothers (N- 31)	Percentage (%)
Nulliparous	23	74.2
Multiparous	08	25.8
Obesity	02	6.5
GDM	OHA 05	16.1
	MNT 03	9.7
HDP	Non-Service 01	3.2
	Severe 03	9.7
Rh negative without ISO-immunization	06	19.4
FGR	02	6.5
Asymptomatic positive	26	83.8
Mild disease	05	16.1

*Table 1. Covid Positive Patients Characteristics*

**Obstetric Outcome**

Among the 31 antenatal mothers who were tested positive in labour, 23 mothers underwent a lower segment caesarean section (LSCS). Emergency LSCS was performed in 21 mothers

and elective LSCS was performed in 2 mothers. Eight labouring women had undergone a normal delivery with one of them having an instrumental delivery. Meconium-stained liquor (MSL) was an intraoperative finding in 7 (22.5 %) of them, out of which three of them had grade 3 MSL, two had grade 2 MSL and grade 1 MSL in the two other mothers (Table 2).

Intrapartum Characteristics	No of Antenatal Mothers (N = 31)	Percentage (%)
Elective LSCS	01	3.2
Emergency LSCS	22	70.9
Vaginal delivery	Spontaneous 07	22.6
	Instrumental 01	3.2
MSL	Grade 1 02	6.5
	Grade 2 02	6.5
	Grade 3 03	9.7

*Table 2. Obstetric Outcome*

**Laboratory Manifestations in Covid Positive Mothers**

Mild anaemia was a finding in 4 antenatal mothers who were treated already with hematinic and intravenous iron. Blood transfusion was given in 2 of the antenatal mothers with moderate anaemia. Differential leucocyte count showed lymphopenia in 23 (74.2 %) pregnant mothers. Thrombocytopenia was present in 4 of the labouring women, of which 3 were mild and one was moderate. D-dimer levels were elevated post-partum in 5 of them for whom thromboprophylaxis was given. Serum ferritin levels and chest radiograph was normal in the positive mothers. Serum lactate dehydrogenase was elevated in 4 mothers with levels more than 250 IU. Uric acid was elevated in those mothers with severe pre-eclampsia (Table 3).

Lab Investigations	No of Antenatal Mothers (N = 31)	Percentage (%)
Haemoglobin	Mild 04	12.9
	Moderate 02	6.5
Lymphocyte % in dc	23	74.2
D-dimer (†)	05	16.1
Platelets	Mild 03	9.7
	Moderate 01	3.2
LDH	04	12.9

*Table 3. Laboratory Parameters and Its Significance.*

**Neonatal Screening**

The neonates of COVID positive mothers were screened for SARS-CoV-2 RT-PCR on the second day of their life to rule out vertical transmission. None of the babies were showing evidence of positivity. There is a possibility of vertical transmission from the mother to the foetus as per new evidence, however further research is required as it has conflicting results.<sup>6</sup>

**DISCUSSION**

**Covid-19 & Pregnancy**

With over 35 million cases worldwide till date, majority of them display the mild version of the disease contributing to around 80 % of the confirmed cases.<sup>7</sup> Pregnancy despite being a partially immunocompromised state and posing a high risk of being prone to viral or bacterial pneumonia, there is no

abundant evidence to consider gravid mothers as “at risk” mothers. The association between the SARS-CoV-2 infection and disrupted ACE2 expression is likely to lead to dysregulation in ACE2 Ang-(1-7) axis.

Hence, we can hypothesize that SARS-CoV-2 impairs cardiovascular adaptation of mothers, normal hemodynamic regulation of placenta, foetal growth, and long-term cardiovascular health, as well as reproductive health of women in general. According to RCOG, there is currently not enough data to provide a correlation between the risk of miscarriage and Covid-19 or that the virus is teratogenic.

In our cross-sectional study, 83.8 % of the mothers who were screened at/during labour for the virus were asymptomatic with no chest findings and the remaining 16.1 % presented with low grade fever sans any chest symptoms.

### **Covid-19 & Comorbidity**

The risk of SARS-Cov-2 19 in pregnancy is mainly due to altered ACE expression. Dysregulated ACE2 expression has been associated with impaired maternal and foetal health, subnormal cardiovascular adaptation, impaired hemodynamic regulation, and foetal growth. Elevated angiotensin 2 was increasingly responsible for the development of pre-eclampsia. The study conducted by our department has showed that mothers with gestational diabetes mellitus are at risk of contracting the virus like the non-pregnant population. Severe pre-eclampsia has been diagnosed in 3 of the pregnant mothers with imminent signs and one of them had non severe features. Although there is no evidence that foetal growth restriction can occur as a consequence of SARS-CoV-2, however, at present, this is considered possible as two-thirds of pregnancies with SARS were affected by FGR as per the royal college of obstetricians and gynaecologists (RCOG) guidelines. In our descriptive study, foetal growth restriction at 3<sup>rd</sup> centile was noticed in 3 of those mothers with asymptomatic Covid-19.<sup>8</sup>

### **Covid-19 and Lymphopenia**

Lymphopenia or lymphocytopenia is the condition with low counts of lymphocytes in the blood. Although T cells could be initially increased at the onset of Covid-19, these patients tended to have low lymphocyte count; the condition that is associated with increased Covid-19 severity. Those with severe disease are observed to have hypercytokinemia or cytokine storm with increased levels of proinflammatory markers such as TNF- $\alpha$ , IL-6, IL-1 $\beta$ , IFN- $\alpha$ , IFN- $\gamma$ , IL-12, IL-18, IL-33, and so forth. The cytokine storm may come with a terrible attack of the immune system to the body, leading to organ failure and acute respiratory distress syndrome (ARDS), and subsequently, death in severe cases of Covid-19. Although pregnancy is innately associated with moderate reduction in lymphopenia, lymphopenia is a consistent predictor of Covid-19 associated mortality. In our study, although 74.2 % of the term pregnant mothers had lymphopenia in the differential count, majority of them were either asymptomatic or a case of mild disease.<sup>5</sup>

### **Meconium-Stained Amniotic Fluid**

Normal haemodynamics in placenta may be affected by viral-induced downregulation of ACE2 expression in Covid-19

pregnant women. However, placental sampling to be done to rule out ischemia. Meconium-stained amniotic fluid (MSAF) is a potential sign of fetal hypoxia as well as a potential toxin if the foetus aspirates with a gasping breath in utero or when it takes its first breaths following birth. Meconium-stained liquor, a sign of foetal hypoxia was an important finding in 7 of the 22 pregnant mothers who underwent caesarean section.<sup>8</sup>

### **Thromboprophylaxis**

The inflammatory cytokines produced by the SARS- Cov-2 19 is responsible for the multi-organ dysfunction and the thromboembolic disorders by releasing more thrombin. Elevated d-dimer which is an indirect measure of thrombin was seen in 5 of our patients with mild/asymptomatic Covid-19 and thromboprophylaxis was covered for the same. As per the RCOG guidelines, all pregnant women admitted with confirmed or suspected Covid-19 should receive prophylactic low molecular weight heparin (LMWH), unless birth is expected within 12 hours. If postpartum admission with confirmed/suspected Covid-19 within 6 weeks of birth, thromboprophylaxis to be given for the duration of admission or for 10 days post discharge or even longer if there is an existing co-morbidity.<sup>9</sup>

### **Symptomatic Antenatal Mothers Not a Part of the Screening Protocol**

According to RCOG, the risk factors associated with hospital admission for Covid-19 in pregnancy includes the following – BAME (Black/Asian or minority ethnicity), overweight or obesity, pre-existing comorbidity, and maternal age greater than 35 years. 12 antenatal mothers who were not in labour but were symptomatic for SARS-CoV-2 was tested and were admitted in the isolation ward. Eleven of the twelve antenatal mothers had mild disease with most of them having fever and the remaining having anosmia and cough. One mother presented with breathlessness and had the severe form of the disease. Moderate anaemia was present in three of them and they had required blood transfusion. Lymphocytopenia and elevated d-dimer was present in all of them and thromboprophylaxis was given. Eleven mothers with the mild disease were discharged when afebrile and symptomatically better and advised home quarantine for two weeks. The patient with severe Covid-19 disease had comorbidities such as morbid obesity and overt diabetes. She required resuscitative caesarean section and was put on invasive mode of ventilation for a week followed by tracheostomy and was discharged home after 3 weeks.

## **CONCLUSIONS**

Like the non-pregnant population, the incidence of the novel corona virus during routine screening at/near labour was found to be more common in those with co-morbidities such as gestational diabetes and obesity. Also, the affected mothers are more prone for hypertensive disorders of pregnancy with evidence of meconium-stained liquor as a marker of foetal hypoxia. Lymphopenia is another association with the infected mothers. There were no intrauterine foetal deaths or still births in any of them. The elevated d-dimer levels though not

present in a significant number of the mild/asymptomatic population, mandates thromboprophylaxis but at the same time we have not reported any case of venous thromboembolism till date in any of our patients. Overall, the impact of SARS-CoV-2 is not as disabling as it is in the non-pregnant population. However, we need further research on this aspect to come to a consensus.

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

Financial or other competing interests: None.

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