

Clinical Features, Obstetric-Neonatal Outcomes, Placental Pathology And Potential Of Intrauterine Vertical Transmission In Pregnant Patients With COVID-19 In A Tertiary Care Centre: A Retrospective, Descriptive Study.

Dr Moushmi Parpillewar Tadas¹, Dr Rasika Gadkari², Dr Meena Mishra³,
Dr Nita gade⁴, Dr Nisha Meshram⁵, Dr Purnima Tiwari⁶, Dr Shuchita Mundle^{7*}

¹ Associate Professor, Department of Obstetrics and Gynaecology, Government Medical College and Hospital, Nagpur, Maharashtra state, India.

² Professor, Department of Pathology, All India Institute of Medical Sciences, Nagpur, Maharashtra state, India.

³ Professor, Department of Microbiology, All India Institute of Medical Sciences, Nagpur, Maharashtra state, India.

⁴ Associate Professor, Department of Microbiology, All India Institute of Medical Sciences, Nagpur, Maharashtra state, India.

⁵ Assistant Professor, Department of Pathology, All India Institute of Medical Sciences, Nagpur, Maharashtra state, India.

⁶ Senior Resident, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Nagpur, Maharashtra state, India.

^{7*} Professor, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Nagpur, Maharashtra state, India.

Corresponding author:

*Dr Shuchita Mundle, Professor, Department of Obstetrics and Gynaecology, All India Institute of Medical Sciences, Nagpur, Maharashtra, India.

Abstract

Background: Currently effects of Covid-19 on pregnancy are little known. To identify maternal and neonatal risks associated with Covid-19 in pregnancy, determine possibility of vertical transmission, and describe outcome a retrospective descriptive study was done. Associations were evaluated for all Covid-19 patients, and disease classified as mild versus moderate/severe disease.

Methods: Covid RT-PCR-positive women who were admitted from 1st of May to 31st August 2020 were included. Cases were classified according to their severity, investigations done and treated according to MOHFW, India guidelines. Data were collected, analysed in terms of maternal and neonatal outcomes. Amniotic fluid, cord blood, neonatal throat swabs tested for possibility of vertical transmission. Placental histopathology was done to study the Covid-specific changes.

Results: Total 181/221 delivered during study period. There were 215 (97.28%) mild, 5 (2.71%) moderate and 1 (0.45%) severe cases. 210(95.02%) were diagnosed in third trimester. Mean gestational age was 36.79 ±5.24 weeks and 3 out of 4 in moderate/severe category delivered preterm. 132 (59.73%) were asymptomatic. There was 1 ICU admission and 1 maternal death. The mean birth weight was 2.7 ±0.59kg. There were 7 stillbirths, 14 NICU admissions and 1 neonatal death. No samples of amniotic fluid and cord blood tested positive for Covid RT-PCR. Placental histopathology showed fibrinoid deposition, features of maternal vascular malperfusion and fetal vascular malperfusion.

Conclusions: The majority of the Covid infected women are asymptomatic, are in mild category and there is no adverse maternal and neonatal outcome due to disease. The adversity of maternal and neonatal outcomes depends on severity of disease and severity of disease is dependent on presence of co-morbidities. No evidence of vertical transmission was found in the tested samples.

Keywords: Covid-19, pregnancy-related morbidity, maternal and neonatal outcome, amniotic fluid, cord blood RT-PCR, vertical transmission, placental histopathology

Date of Submission: 15-08-2023

Date of Acceptance: 25-08-2023

I. Introduction

The world is now facing a new coronavirus disease 2019 (COVID-19, which started in December 2019 in Wuhan, China), a major epidemic threat that the world has ever faced¹. Since then, the virus has spread all over the world². Regarding the impact of COVID-19 infection on a pregnant woman, there are concerns relating to the potential effect on maternal, fetal and neonatal outcomes; therefore, pregnant women require special attention concerning prevention, diagnosis, and management. Reports from various influenza studies have suggested that during pregnancy, there are higher chances of mortality and morbidity as compared to a non-pregnant woman and similar results were also obtained for the other two coronaviruses- SARS-CoV and MERS-CoV.³ In other types of coronavirus infections like SARS and MERS, there are severe complications during pregnancy, especially in the third trimester like severe pneumonia, admission to ICU, and need for mechanical ventilation with high fatality rate. Currently, however, there is no evidence that pregnant women are more susceptible to COVID-19 infection or they are more prone to developing severe pneumonia.⁴ The symptoms reported in a few studies vary for pregnant women, which are inconsistent across studies. For instance, Liu et al.⁵ identified cough, shortening of breath, fatigue and fever as the most important symptoms of COVID-19 among pregnant women, whereas cough and fever were reported by Zhu et al.⁶ Most of the studies reported a mild to moderate flu-like symptoms of cough, sore throat, and fever. Few of women had difficulty in breathing or shortness of breath. These have been classified as features of severe acute respiratory illness (SARI) by the WHO. Pregnant women, especially those with associated medical diseases (diabetes, asthma, etc) may present with pneumonia and marked hypoxia. However, according to some studies, infection with COVID-19 during pregnancy can cause complications for both the mother and the fetus; including preterm delivery, respiratory distress, fetal distress, coagulopathy accompanied by liver dysfunction and death of the mother.⁷

The treatments provided to the COVID-19 infected pregnant women were also varied. Oxygen support, antiviral therapy, and antibiotic therapy were the treatments provided to the infected pregnant women by some while some reported that antibiotic therapy was avoided but oxygen support and antiviral therapy were provided.^{5,6} Furthermore, a study carried out in India on 141 Covid-positive patients reported mild respiratory symptoms; many patients with co-morbidities had good maternal and fetal outcome⁸. One of the major concerns is whether SARS- CoV- 2 can be vertically transmitted from mothers to their fetuses, thus causing congenital infection. There are conflicting studies regarding vertical transmission. At present, information regarding the epidemiology, clinical features, treatment, vertical transmission potential of COVID-19 is rapidly changing.

The Coronavirus pandemic has put the whole medical world in a state of dilemma regarding the manifestations, symptoms, treatment in the scenario of emerging new Covid strains and everchanging management protocols. To study the clinical characteristics, laboratory and radiological investigations, treatment, vertical transmission, placental changes, maternal and fetal outcomes and to describe the associations and risk factors for morbidity associated with Covid-19; we undertook a collaborative study.

II. Material and methods

This is a retrospective descriptive study carried out in collaboration at the Department of Obstetrics and Gynecology of Government Medical College, Nagpur, Maharashtra, India and the departments of Obstetrics and Gynecology, Pathology and Microbiology of All India Institute Of Medical Sciences, Nagpur. Institutional Ethics Committee approval was taken for conducting the study at both institutes.

Study period: All Covid positive women who delivered at Department of Obstetrics and Gynecology of Government Medical College, Nagpur from 1st of May to 31st August were included in the study.

In the initial stage of the pandemic, women with symptoms of the disease (fever, cough, shortness of breath), who were in close contact with known Covid patients, who had a history of travel from high-risk areas, women coming from containment zone who had their expected date of delivery within five days were screened and tested according to Indian Council of Medical Research's (ICMR) guidelines. Their throat swab sample was collected and subjected to RT-PCR test at State Level Viral Research & Diagnostic Laboratory, Government Medical College, Nagpur. All women who tested positive were delivered at the dedicated Covid Care Hospital (CCH) which is well equipped with labour room, operation theatre and Intensive Care Unit (ICU) facility. In the later part of the pandemic, ICMR approved private laboratories to do the tests and Municipal Corporation made it compulsory to test all pregnant women near their expected date of delivery, so all pregnant women who tested positive at other facilities with RT-PCR who were referred to this facility were also included in the study.

All women were divided into three categories mild, moderate and severe depending on their symptoms, co-morbidities and radiological findings as per ICMR guidelines and managed according to the management protocols given by Ministry of Health and Family Welfare (MOHFW), Government of India⁹. Asymptomatic women who were far from their expected date of delivery, after all, investigations (Complete blood count CBC, renal function test RFT, liver function test LFT, Electrocardiogram ECG) were discharged for home quarantine or shifted to quarantine centre. Symptomatic women, in addition to above investigations, were advised X-ray chest and oxygen saturation monitoring. Symptomatic women with co-morbidities and who had X-ray changes

and low oxygen saturation were advised Erythrocyte sedimentation rate ESR, C - reactive protein CRP, Lactate dehydrogenase LDH, S. ferritin, D-dimer and CT scan. Patients were accordingly treated with anti-COVID-19 treatment protocol, which consisted of oxygen therapy, hydroxychloroquine (200 mg 2 times a day for 10 days), azithromycin (500 mg on day 1, and 250 mg per day for 4 days), vitamin C (500 mg per day for 10 days) and zinc tablet (15mg per day for 10 days). Antiviral therapy (Faviparavir), Injection Remdesivir, steroids and low molecular weight heparin were used when indicated in consultation with the physician. Amniotic fluid, cord blood and placenta were collected and sent to All India Institute Of Medical Sciences, Nagpur for Covid-RTPCR testing after maintaining a proper cold chain.

After delivery babies were isolated from their mother and kept in nursery and throat swab RT-PCR was done at 24 and 72 hours. The baby was discharged if both swabs were negative. All women and their neonates were followed unto discharge and final outcome was noted.

Data collection

Data of all the patients was collected from their records like demographic factors, symptoms, history of contact, pre-existing medical disease, pregnancy-related disorder, laboratory investigations, classification of category, mode of delivery, the fetal outcome in terms of APGAR score, admission to NICU, birth weight, and duration of hospital stay were noted and filled in pre-designed forms.

Inclusion criteria:

1. Patients were considered to be eligible to be included in the study if they were RT-PCR positive Covid-19 testing and delivered at our facility during the study period
2. Patients who were admitted in labour who were untested, but subsequent testing during the delivery became positive.

Exclusion criteria:

1. If they were patients who had symptoms suggestive of Covid but had negative Covid-19 testing.
2. If they were positive but away from term and discharged before delivery.

All maternal and fetal data was recorded and the outcome noted. The maternal adverse outcome included length of hospital stay of more than 10 days, ICU admission, need for mechanical ventilation, supplemental oxygen and maternal death. The adverse neonatal outcome included low birth weight, stillbirth, low APGAR score, NICU admission and neonatal death.

Statistical analysis

Data was entered in MS Excel, coded and analysed in statistical software STATA, version 10.1, 2011. Descriptive statistics were used to summarize quantitative variables with mean and standard deviation, while frequency and percentages were used to summarize categorical (qualitative) variables. Inferential statistics included tests of significance and P values. Significance of Mean difference in two groups was tested by two-independent sample t-test with equal variances. Significance of difference in proportions in two groups was assessed by Pearson's Chi-square test or Fisher's exact test (for small frequencies). Binary multiple logistic regression analysis was also performed to identify predictors of adverse fetal outcome adjusting for maternal and fetal characteristics. A P-value < 0.05 was considered statistically significant.

III. Results

During the study period 221 pregnant patients who tested positive for Covid-19 RT-PCR were admitted to the Obstetrics and Gynaecology department of the Government Medical College and Hospital, Nagpur. Three spontaneous abortions and 37 undeliverable discharges were made up of the 181 babies delivered here. There were 2891 deliveries during the study period, making the incidence of Covid-19 positivity 6.26%.

Table No. 1 displays demographic information. The mean age was 26.82 ± 4.23 years. The moderate/severe category had an average age of 33.6 years.

Table no 1. Showing demographic characteristics

Maternal characteristics	No. of cases (n-221)
Maternal age (years)	26.82 ± 4.23(19- 40)
Parity	
Nullipara	8 (3.62%)
Primi	90(40.72%)
Multi	123(55.66%)
Residence	
Rural	52 (23.08%)
Urban	169(73.92%)
Education status	

Illiterate	2(0.9%)
Primary	5(2.26%)
Secondary	140(63.35%)
Graduate	65(29.41%)
Professional	9(4.07%)
Occupation	
Not working	198(89.59%)
Working	23(10.49%)
Duration of hospital stay	
≤7days	153(68.78%)
8-14 days	58 (26.70%)
>14 days	10 (4.52 %)
Gestational age at diagnosis (in weeks)	
1 st trimester	3(1.36%)
2 nd trimester	8(3.62%)
3 rd trimester	210(95.02%)
Mean	36.79± 5.24
History of contact	
Yes	27 (12.21%)
No	194 (87.78%)
Referred From	
Quarantine Centre	20 (9.05%)
Sub-centre	2 (0.90%)
Primary health centre	8 (3.62%)
Rural hospital	18(8.14%)
District hospital	67 (30.77%)
Private hospital	48 (21.72%)
Other medical colleges	4 (1.81%)
Booked of this college	54 (23.98%)

Table 2 displays the severity classification, typical symptoms, indicators, and treatments. 215 patients (97.28%) fell into the mild category, 5 (2.26%) into the intermediate category, and 1 (0.45%) into the severe category. Out of the mild 59.73% were asymptomatic, and among those who were symptomatic, fever, cough, sore throat, diarrhoea, myalgia, and 49 (27.07%) were accompanied by labour pains. Shortness of breath, fever, and cough were the most prevalent symptoms in the severe category, which included 5 out of 6 patients. Few people experienced more than one symptom. All patients in the moderate/severe category required oxygenation and three of them received injections of Remdesivir, prednisone, and LMWH, two of them required high flow nasal cannula oxygenation (HFNO), and one of them in the severe category needed endotracheal intubation. Zinc and vitamin C tablets were given to all patients. On MOHFW recommendations, the treatment procedures were developed.

Table no 2. Showing severity classification, symptoms, abnormal signs and treatment

Covid 19 cases(n=221)	Mild (n=215)	Moderate and severe (n=6)
Severity		
Mild	215 (97.28%)	
Moderate	-	5 (2.71%)
Severe	-	1 (0.45%)
Symptoms		
Asymptomatic	132 (59.73%)	1(0.45%)
Symptomatic	39(17.64%)	5(2.71%)
Fever	16 (7.23%)	1(0.45%)
Cough	17 (7.69%)	2 (0.90%)
Sore throat	11 (4.97%)	3 (1.35%)
Shortness of breath	1 (0.45%)	4 (1.80%)
Myalgia	1 (0.45%)	1(0.45%)
Diarrhoea	3 (1.35%)	-
Labour pains	49 (22.17%)	
Abnormal signs		
Fever (>38 ⁰ C)	12	2
Tachycardia (P>100/min)	0	3
Tachypnea (RR>20/min)	0	4
Decreased O2 saturation(<92%)	0	1
Treatment		

Hydroxychloroquine	0	2
Azithromycin	4	2
Favipiravir	16	4
LMWH	17	4
Steroids	15	4
Remdesivir	0	5
Oxygenation	0	1
Ventilation	0	1

Maternal outcomes (Table 3)

The majority of the Covid-positive women had chronic conditions such hypertension, type 2 diabetes mellitus (DM), anaemia, and sickle cell anaemia. HIV and thyroid problems were present in few. Some had multiple co-morbidities. A total of 20 women had problems associated with pregnancy, including hypertensive disorders, gestational diabetes, preterm labour, foetal growth restriction, previous caesarean section, liquor abnormalities, malpresentation, and multiple pregnancies. Few of them suffered from more than one disorders. In moderate to severe category one patient had chronic hypertension, three had premature labour, and two had undergone previous Caesareans and the average gestational age at delivery was 36.35 weeks, and 3 out of 4 babies were born prematurely.

As they were away from term, 38 (17.19%) women were discharged undelivered. Out of the remaining 181 women who gave birth, 95 (42.99%) underwent a Caesarean section, compared to 85 (38.46%) who delivered vaginally and 1 (by forceps). Three of the four instances in the moderate/severe category were delivered vaginally, and one by caesarean. None of the caesareans were performed because of the illness; instead, the majority were carried out for obstetric reasons such previous caesareans, foetal distress, malpresentation, etc.

152 individuals (68.78%) spent less than 7 days in the hospital on average. Comorbidities such hypertensive diseases, anaemia, thrombocytopenia, and others increased the length of hospital stay. Patients with moderate to severe disease experienced prolonged hospital stays as a result of the illness. Patients were hospitalised in the early phases of the pandemic after being diagnosed until their test results were negative, which increased the hospital stay. The average hospital stay was 7.6 to 8.26 days.

In the mild category, one women experienced postpartum psychosis. Wound infection affected one patient who was in the moderate category. There was one case of maternal mortality. She was admitted to the intensive care unit with septicaemia, severe pneumonia, acute respiratory distress syndrome, mechanical ventilation, and substantially impaired liver and kidney functions. A case fatality rate of (1/220) 0.55% was recorded.

Table no 3. Showing maternal outcome (morbidity and mortality)

Medical complications	Cases (n=221)
Anaemia (Hb<11gm %)	36
Severe	7
Moderate	29
Thrombocytopenia	48
Mild/moderate	45
Severe	3
Hypothyroidism	16
HIV	2
Pregnancy morbidity	
Pre-eclampsia/eclampsia	26
Gestational DM	10
Fetal growth restriction	29
Preterm	17
Multiple pregnancies	6
Previous lscs	59
Malpresentations	8
Liquor abnormalities	11
Mode of delivery	
Undelivered	38(17.19%)
Spontaneous abortions	2(0.90%)
Vaginal	85(38.46%)
Cesarean	95 (42.99%)
Instrumental	1(0.45%)
Labour complication	

APH	2
PPH	2
Retained placenta	1
ICU admission	1
Mortality	1
Duration of hospital stay	
≤7days	152(68.78%)
8-14 days	59 (26.70%)
>14 days	10 (4.52 %)

In order to treat their acute anaemia or postpartum haemorrhage, fourteen women required blood transfusions.

For severe thrombocytopenia during labour, platelet transfusions were given to six women. Table 4 displays the preliminary laboratory test outcomes for subjects that tested positive for Covid-19. Neutrophilia (>7700/mm³ or >70% of leukocytes) and lymphocytopenia (<1000mm³ or <8% of leukocytes) were found in 39 (17.56%) and 21 (9.43%) patients, respectively. Neutrophil to lymphocyte ratio was 4.06 to 2.02 on average. All the inflammatory markers were significantly deranged in all patients. There was no patient who had coagulation disorders or cytokine storm in our study. A CT scan was performed in 5 cases, and results suggestive for COVID-19 were discovered in 3 cases. Radiologic imaging, such as an X-ray, was performed in 179 patients, with abnormalities being discovered in 31 of them.

Table no. 4 showing Laboratory investigations

Investigation	Results
Haemoglobin (gm%)	10.42±1.42 (5-13.7)
WBC count (10 ³ /mm ³)	8.77±3.29 (2.8 - 22)
Leukocytosis (>11 000/mm ³)	46 (20.72%)
Absolute Neutrophil count(10 ³ /mm ³)	6.64±2.77
Neutrophilia (>7700/mm ³)	39 (17.56%)
Absolute Lymphocyte count (10 ³ /mm ³)	1.86±1.01
Lymphocytopenia (<1000/m ³)	21(9.45%)
NL ratio	4.06± 2.02 (0.7-12.4)
Platelet count (10 ³ x mm ³)	197.88±82.84 (2.45 - 484)
Thrombocytopenia(<150x10 ³ x mm ³)	48(21.62%)
Blood urea mg/dl	19.89± 12.47 (10-105)
Serum creatinine mg/dl	0.71± 0.27 (0.4- 2.5)
Serum bilirubin mg/dl	0.58±0.43 (0.1-2.6)
Inflammatory markers(n=7)	
Serum LDH	448.71±208.65
Serum ferritin	450.06±805.98
D-Dimer	3.28±3.47
C- Reactive protein	52.85±23.90
Radiological investigations	Findings suspicious of Covid
X-ray	31/222
CT-Scan	2/5

Neonatal outcomes (Table 5)

The average birth weight was 2.7± 0.59 kg, however it was 2.42 kg for moderate/severe cases. Seven stillbirths occurred. Intrauterine growth restriction and pre-eclampsia are the primary causes of stillbirth. Due to low birth weight, preterm, respiratory distress syndrome, meconium aspiration syndrome, hypoxic-ischemic encephalopathy, or hyperbilirubinemia, fourteen babies were sent to the NICU. On the fourth day of life there was one neonatal death due to acute birth asphyxia. Three of the neonates in the moderate/severe group had no morbidity, while one stillbirth occurred in that group. Four newborns tested positive for Covid after birth; these babies were all healthy when they were discharged from the hospital, and their mothers Covid reports had

come after delivery and they had not been separated from them. None of the newborns who were separated from their mothers tested positive.

Table no 5. Showing neonatal outcome

Neonatal outcome	Case(n-187)*
Birth weight (Kg)	2.7±0.59
Stillbirth	7
NICU admission	14
Neonatal death	1
Throat swab RT-PCR positive at birth	4

(* 6 were twin pregnancies)

Less gestational age at birth, a longer hospital stay, and lower haemoglobin and platelet counts were found to be linked with worse foetal outcomes when the bivariate analysis was used to evaluate the relationship between adverse foetal outcomes and other covariates. Out of 16 characteristics, one maternal characteristic—the presence of pregnancy-related disorders (OR=2.55, P=0.04)—and one foetal characteristic—birth weight (OR =0.01, P=0.008)—were found to be significantly associated with the foetal outcome, according to the multivariate analysis shown in Table 6. Each pregnancy-related disease that is present raises the risk, whereas a higher birth weight lowers the likelihood of unfavorable foetal outcomes.

Table no 6. Showing Multivariate analysis for testing association between adverse fetal outcome and other factors Logistic regression

Number of obs = 172

LR chi2(16) = 35.09

Prob > chi2 = 0.0039

Log-likelihood = -17.557073

Pseudo R2 = 0.4998

Maternal and fetal characteristics	Odds Ratio	Std. Err.	z	P> z	[95% Conf. Interval]
Age	1.817375	1.994587	0.54	0.586	.211467 15.61876
Duration of stay	1.111338	1.239359	0.09	0.925	.124908 9.887851
Education	2.400704	2.553113	0.82	0.410	
Parity	.5968251	.675297	-0.46	0.648	.2986058 19.3009
Gestational age	1.574808	.9802575	0.73	0.466	.064972 5.482348
Pregnancy-related morbidity	2.549256	1.15996	2.06	0.040	.4649301 5.33418
H/o contact	1.169542	1.640633	0.11	0.911	.0748084 18.28443
Pulse	.9551641	.0622433	-0.70	0.481	.8406388 1.085292
Systolic BP	.9413577	.1317579	-0.43	0.666	.0748084 18.28443
Diastolic BP	.8467982	.0851038	-1.65	0.098	.7155098 1.238494
SPO2	.6404209	.3241568	-0.88	0.379	.2374759 1.727076
Birth weight	.0142732	.0227533	-2.67	0.008	.0006275 .3246743
Haemoglobin	.5939483	.3046618	-1.02	0.310	.2173355 1.62318
WBC count	.8076522	.1649072	-1.05	0.295	.5412841 1.205101
Platelet count	.9937793	.007587	-0.82	0.414	.9790196 1.008761

Amniotic fluid, cord blood and placental testing

We could collect forty-four samples of amniotic fluid, and cord blood and do testing. None of the samples was found RT-PCR positive for Covid.

Fourteen placentas from patients with Covid -19 were examined (Table 7). Twelve patients were delivered at term (37-40 weeks), 2 delivered between 35-36weeks, and 1 had intrauterine fetal demise (IUID at 35W5D). Three placenta weights were small for gestational age, (372g, 370g, 399g g.). Two placentae were large for gestational age (615g, 712g g.). Indications for pathologic evaluation were to find out changes in the

placenta specific to Covid -19. One case additionally had anaemia, 2 had pregnancy-induced hypertension, 2 had oligohydramnios, 1 had IUGR and 1 had heart disease and 1 had IUFD.

Features of maternal vascular malperfusion (MVM) were present in 10/15 cases. Features included distal villous hypoplasia (5/15), accelerated villous maturation (9/15), decidual arteriopathy (1/15), and villous infarctions (9/15).

Features of fetal vascular malperfusion (FVM) were present in 15 of 15 cases. Specifically, 11 of 15 COVID-19 placentas showed clustered avascular villi, 15 of 15 showed fibrin deposition in fetal vessels, 1 of 15 showed delayed villous maturation, and 9 of 15 placentas showed chorangiomas.

None of the placentae showed changes of acute/ chronic maternal/fetal inflammatory changes. Only one placenta showed focal lymphocytic infiltrate in the membrane (the patient who had IUFD). Additional findings in the COVID-19 cases included, 1 case with the maternal stromal vascular lesion, all 14 cases showed features of maternal malperfusion, 11 showed calcifications, 10 had increased syncytial knots, and 3 showed haemorrhage.

Table7. Showing details of placental histopathology

S. No	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Age(Yrs)	33	29	27	24	NA	NA	20	20	N A	NA	NA	25	27	NA
Asso. Abnormality.	IU D	N	N	oligoh ydram nios	Nil	PET	Nil	ane mia	PE T	Nil	Heart Diseas e	Ni l	Nil	oligo, iugr
Gestational age(weeks)	35 W5 D	39	39	38	39	38 W4D	40 W4D	41	39	39W 4D	36W 2D	38 W 5 D	37W 3D	37W 4D
Live / Still Birth	SB	LB	L B	LB	LB	LB	LB	LB	L B	LB	LB	L B	LB	LB
Birthweight(gms)	260 0	2700	27 50	2700	310 0	2700	3300	2600	24 00	3700	2700	27 00	3000	2400
Placental weight. (gms)	488	615	60 6	467	555	372	534	479. 5	37 0	712	540	52 0	569	399
Cord diameter(cms)	1.5	1	1. 5	1.2	1.3	1	1	1	1.2	2	1	1	1	1
Placental hypoplasia	N	N	N	N	N	N	N	N	N	N	NA	N	N	N
Placento-megaly	N	N	N	N	N	N	N	N	N	Y	NA	N	N	N
Mat. stromal vascular lesions	N	N	N	Y	N	N	N	N	N	N	NA	N	N	N
Superficial implantation	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Maternal malperfusion	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Fibrin deposition FVM	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Calcification	Y	Y	N	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y
Avascular villi FVM	Y	Y	N	Y	N	Y	Y	Y	Y	Y	Y	Y	N	Y
Distal villous hypoplasia MVM	N	Y	N	N	N	Y	Y	N	Y	N	N	N	Y	N
Accelerated villous maturation MVM	Y	Y	N	N	Y	Y	Y	Y	Y	Y	N	N	N	Y
Increased syncytial knots	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	N	N	N	Y
Villous infarcts MVM	Y	N	N	Y	N	Y	Y	N	Y	Y	Y	N	Y	Y
Decidual arteriopathy MVM	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
Loss of maternal vascular integrity	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Fetal Stromal Vascular Lesions														
Villous capillary lesion (Chorangioma) FVM	N	N	Y	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y
Chorangioma	N	N	N	N	N	N	N	N	N	N	N	N	N	N

Delayed villous maturation FVM	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Changes of fetal malperfusion	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Placental inflammatory immune response															
Acute maternal inflammatory response	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Chronic maternal inflammation	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Acute fetal inflammatory response	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Chronic fetal inflammation	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Chronic maternal/fetal inflammatory response	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
Other placental Pathology	FLIM	N	N	N	N	N	N	N	N	N	Haemorrhage	Haemorrhage, villous fibrosis	HV, ET	N	Haemorrhage

Note: **HV**-hyalinized villi, **ET**-, extravillous trophoblast; **FLIM**- Focal lymphocytic infiltrate in membrane

IV. Discussion

To our best knowledge, this is one of the first large studies of maternal and fetal outcomes of 181 cases of the studied 222 cases who were admitted to our facility. Many studies have focused on infected patients from the general population; however, details of COVID-19-related pregnancy outcomes are published in small numbers.

As per the data from other viral illnesses such as influenza, SARS and MERS, pregnant women are more likely to develop viral pneumonitis, with higher morbidity and mortality⁸. In our study majority of the woman (82%) were asymptomatic, similar to the Indian study.⁸ In our study fever and cough were the most common symptoms followed by a sore throat. This was similar to other studies.^{16,17,18,19}

Various studies have reported that co-morbidities are more susceptible to Covid -19 and increased unfavourable outcomes.^{20,21} Approximately more than one- third of confirmed cases in the present study had co- morbid diseases. These women had adverse outcomes in terms of an increased rate of caesarean delivery, increased hospital stay, therefore; we can conclude that physicians should be cautious in the management of pregnancies complicated by co- morbidities and a multidisciplinary approach should be accepted.

Out of the 222 patients admitted 95.02% were in the third trimester as they came in labour and tested positive. Out of these 181 were delivered during the study period. In many initial studies, they reported cesarean births in all cases due to uncertainty in the outcome and vertical transmission of disease^{3,22,23,24} Rate of cesarean delivery was higher in our study than that of vaginal delivery (42.99% versus 38.46% respectively) as most of the cases were admitted with pregnancy and medical morbidities that required cesarean. Most of the studies had similar findings.^{8,25}

Regarding the effect of the disease on pregnancy very little is known. Few studies have reported increased incidence of preterm delivery^{25,26,28} more severe pneumonia, increased maternal respiratory distress and fetal distress.²⁷ In our study we found that 3 of the 4 patients of moderate to severe category delivered preterm and one delivered at term. Bivariate analysis showed lower gestational age is associated with adverse fetal outcomes.

In our study most of the patients were asymptomatic hence only were given supportive treatment with multivitamins, symptomatic women in the mild category were given antibiotics and supportive treatment. The patients who received antivirals were mostly postnatal women as they are contraindicated during pregnancy. Patients in the moderate to severe category required LMWH, and oxygen therapy and one patient required mechanical ventilation. Few studies have mentioned the treatment received by Covid pregnant females^{19, 24, 29}

A single large study carried out in Maharashtra found an overall CFR of 0.8% in this part of the region⁹ which is comparable to our study. Previous studies have revealed that the clinical symptoms and laboratory findings of infected pregnant women are atypical in comparison with nonpregnant adults.³⁰ Neutrophilia, lymphocytopenia, increased neutrophil to lymphocyte ratio, interleukin 6, D- dimer, hepatic

function tests, and acute phase reactants are the most common findings in the general population. In our study, we found lymphopenia (9.45%), neutrophilia (17.56%) and thrombocytopenia (21.62%) and elevated inflammatory markers in moderate /severe disease patients. The leukocytosis and elevated neutrophil-to-lymphocyte ratio were reported in a study.³⁰ In another study laboratory findings included high leukocyte count, elevated neutrophil ratio, lymphopenia, and elevated CRP, D-dimer, and LDH.³ Bivariate analysis showed low platelet count is associated with adverse fetal outcomes in our study.

Radiologic imaging has been widely used in the diagnosis and management of Covid. Due to limited resources, we could do CT scans of moderate/ severe cases only which had an abnormality in more than half cases.

One of the issues of importance is the vertical transmission. Some studies done have not found vertical transmission^{22,23,24,27} while some meta-analyses have concluded that vertical transmission of severe acute respiratory syndrome coronavirus 2 is possible and seems to occur in some cases.^{31,32} In our study amniotic fluid and cord blood samples were found RTPCR negative. Also, the maximum newborn's RT-PCR was negative and the positive babies were not separated from their mothers as their reports came positive after delivery.

Hypoxia induced by maternal Covid-19 infection may lead to MVM³³, features or diagnoses of MVM were noted in 10 cases. Similar changes were seen in studies by Sharpe et al³³, and Shanes et al³⁴. Usually, features of MVM are associated with hypertensive disorders of pregnancy but only two of our patients had preeclampsia. FVM is associated with a lack of blood flow within the placenta; features of FVM were present in all 15 cases. Some studies had control groups and they showed increased FVM in Covid-19 placentas³⁴. None of the placenta showed changes of acute/ chronic maternal/fetal inflammatory changes, Chen Shuo³⁵ had similar findings but the study by Shane et al³⁴ and Zaigham et al³⁶ had few cases of acute and chronic inflammatory changes. The abnormal blood flow of the placenta is related to a large amount of fibrin deposition under the chorion and between the villi. Fibrin deposition was present in all 14 cases in our study. Similarly, Zaigham et al³⁶ found massive perivillous fibrinoid deposition in a majority of placentas with Covid-19, and Chen Shuo³⁵ et al had similar findings.

V. Conclusions

The results suggest that majority of the Covid infected women are asymptomatic and are of mild category and there is no adverse maternal and neonatal outcome due to disease, in this part of the world and at this phase of the pandemic. There was no increased incidence of spontaneous abortions, intrauterine deaths or fetal distress due to the disease. The adversity of maternal and neonatal outcomes depends on the severity of the disease and the severity of the disease in turn is dependent on the presence of co-morbidities. Low gestational age, low haemoglobin, and low platelet count are associated with adverse fetal outcome. There was no evidence of vertical transmission of the disease in our study. Features of MVM, FVM and fibrinoid deposition were consistent findings in histopathological examination of the placenta. Regular screening of women to detect the coronavirus infection early and vaccination will reduce complications, reduce the severity, and improve maternal and fetal outcomes.

Strengths and limitations

The study's strength is the large number of patients and parameters studied. The limitations are no comparison group. As we got a smaller number of severe cases we could not assess the exact outcome in severe cases.

Areas of research

Most of the women in our study were in third trimester, so the effect of Covid -19 if infected in early pregnancy may be followed and its effect on foetus are not known. Large microbiological studies involving amniotic fluid, cord blood and histopathological study of Covid-19 placenta with a control group are future areas of research.

Acknowledgement

The authors would like to thank Dr Suresh Ughade, Ex- professor and Statistician for his statistical help.

Author's contribution: MPT collected data, analyzed it and wrote the manuscript. SRM conceptualized the study, coordinated the sample testing, analyzed the data, reviewed the manuscript, RG and NM did the placental histopathology, MM and NG did the amniotic fluid and cord blood sample testing, and PT helped in coordinating the sample testing. The final draft was approved by all the authors.

Funding sources: None

Conflicts of interest: The authors declare that they have no conflicts of interest.

References

- [1]. Who, Novel Coronavirus (Covid-19) Situation. 2020, World Health Organization, Geneva, Switzerland.
- [2]. Worldmeter. Covid-19 Coronavirus Pandemic (Real Time Database). 202003.04.2020]; Available From: <https://www.worldometers.info/coronavirus/>.
- [3]. Wang Z, Wang Z, Xiong G. Clinical Characteristics And Laboratory Results Of Pregnant Women With Covid-19 In Wuhan, China. *Int J Gynaecol Obstet* 2020; 150 : 312-17.
- [4]. Muhidin S, Behboodi Moghadam Z, Vizheh M. Analysis Of Maternal Coronavirus Infections And Neonates Born To Mothers With 2019-Ncov; A Systematic Review. *Arch Acad Emerg Med* 2020; 8: E49.
- [5]. La Verde M, Riemma G, Torella M, Cianci S, Savoia F, Licciardi F, Et Al. Maternal Death Related To Covid-19: A Systematic Review And Meta-Analysis Focused On Maternal Co-Morbidities And Clinical Characteristics. *Int J Gynaecol Obstet* 2021; 154 : 212-9.
- [6]. Lokken Em, Taylor Gg, Huebner Em, Vanderhoeven J, Hendrickson S, Coler B, Et Al. Higher Severe Acute Respiratory Syndrome Coronavirus 2 Infection Rate In Pregnant Patients. *Am J Obstet Gynecol* 2021; 225: 75.E1-16.
- [7]. Zhu H, Lin Wang, Chengzhi Fang, Sicong Peng, Lianhong Zhang, Guiping Chang Et Al., Clinical Analysis Of 10 Neonates Born To Mothers With 2019-Ncov Pneumonia. *Translational Paediatrics*, 2020. 9(1): P. 51-60.
- [8]. Arun Harishchandra Nayak, Deepali Swapnil Kapote, Michelle Fonseca, Niranjan Chavan, Rahul Mayekar, Meenal Sarmalkar, Et Al. Impact Of The Coronavirus Infection In Pregnancy: A Preliminary Study Of 141 Patients. *The Journal Of Obstetrics And Gynecology Of India (July-August 2020)* 70(4):256–261
- [9]. Rahul K. Gajbhiye, Niraj N. Mahajan, Rakesh B. Waghmare Et Al. Clinical Characteristics, Outcomes, & Mortality In Pregnant Women With Covid-19 In Maharashtra, India: Results From Pregcovid Registry. *Indian J Med Res* 153, May & June 2021, Pp 629-636
- [10]. Gajbhiye Rk, Modi Dn, Mahale Sd. Pregnancy Outcomes, Newborn Complications And Maternal-Fetal Transmission Of Sars-Cov-2 In Women With Covid-19: A Systematic Review Of 441 Cases. *Medrxiv* (2020). Doi: 10.1101/2020.04.11.20062356
- [11]. Schwartz Da, Dhaliwal A. Infections In Pregnancy With Covid-19 And Other Respiratory Rna Virus Diseases Are Rarely If Ever, Transmitted To The Fetus: Experiences With Coronaviruses, Parainfluenza, Metapneumovirus Respiratory Syncytial Virus, And Influenza. *Arch Pathol Lab Med* (2020) 144(8):920–8. Doi: 10.5858/Arpa.2020-0211-Sa
- [12]. Zaigham M, Andersson O. Maternal And Perinatal Outcomes With Covid-19: A Systematic Review Of 108 Pregnancies. *Acta Obstetrica Gynecologica Scandinavica* (2020) 99(7):823–9. Doi: 10.1111/Aogs.13867
- [13]. Alzamora Mc, Paredes T, Caceres D, Webb Cm, Valdez Lm, La Rosa M. Severe Covid-19 During Pregnancy And Possible Vertical Transmission. (2020) 37(8):861–865. Doi: 10.1055/S-0040-1710050
- [14]. Robbins Jr, Bakardjiev Ai. Pathogens And The Placental Fortress. *Curr Opin Microbiol* (2012) 15(1):36–43. Doi: 10.1016/J.Mib.2011.11.00
- [15]. <https://www.mohfw.gov.in/pdf/updatedclinicalmanagementprotocolforcovid19dated03072020.pdf>
- [16]. Na Li, Lefei Han, Min Peng, Yuxia Lv, Mm, Yin Quyang, Mm, Kui Liu, Mm, Et Al. Maternal And Neonatal Outcomes Of Pregnant Women With Covid-19 Pneumonia: A Case-Control Study *Clin Infect Dis*. 2020 Mar 30
- [17]. Dehan Liu, Lin Li, Xin Wu1, Dandan Zheng, Jiazheng Wang, Lian Yang Et Al. Pregnancy And Perinatal Outcomes Of Women With Coronavirus Disease (Covid-19) Pneumonia: A Preliminary Analysis. *American Journal Of Roentgenology*. Doi.Org/10.2214/Ajr.20.23072
- [18]. Lian Chen, M.D. Qin Li, Phd. Danni Zheng, M.Med.Sc. Hai Jiang, M.Med.Sc. Yuan Wei, M.D. Letter To The Editor. *Clinical Characteristics Of Pregnant Women With Covid-19 In Wuhan, China*. *New England Journal Of Medicine* 382;25 *Nejm.Org* June 18, 2020
- [19]. Dilek Sachin, Atakan Tanacan, Seyit A. Erol, Ali, Anuk, Elif G.Y, Eyi, A. Seval Ozgu - Erdinc Et Al, A Pandemic Centre' s Experience Of Managing Pregnant Women With Covid - 19 Infection In Turkey: A Prospective Cohort Study. *Int J Gynecol Obstet* 2020; 1–9
- [20]. Yang J, Zheng Y, Gou X, Ke Pu, Zhaofeng Chen, Qinghong Guo Et Al. Prevalence Of Comorbidities In The Novel Wuhan Coronavirus (Covid- 19) Infection: A Systematic Review And Meta- Analysis. *Int J Infect Dis*. 2020. 20.
- [21]. Guan W- J, Ni Z- Y, Hu Y, Wen-Hua Liang, Chun-Quan Ou,, Jian-Xing He, Et Al. Clinical Characteristics Of Coronavirus Disease 2019 In China. *N Engl J Med*. 2020
- [22]. Chen H, Guo J, Wang C, Fan Luo, Xuechen Yu, Wei Zhang, Jiafu Li 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;395(10226):809–15.
- [23]. Yu N, Li W, Kang Q, Zhi Xiong, Shaoshuai Wang, Xingguang Lin, Yanyan Liu Et Al. Clinical Features And Obstetric And Neonatal Outcomes Of Pregnant Patients With Covid-19 In Wuhan, China: A Retrospective, Single-Centre, Descriptive Study. *Lancet Infect Dis*. 2020;20(5):559–64.
- [24]. Wu Y-T, Liu J, Xu J-J, Chen Y-F, Yang W, Chen Y, Et Al. (2020) Neonatal Outcome In 29 Pregnant Women With Covid-19: A Retrospective Study In Wuhan, China. *Plos Med* 17(7): E1003195. <https://doi.org/10.1371/journal.pmed.1003195>