INTRODUCTION

There is an increase in number of pregnancies with Covid-19 cases in the past 5 months [1]. Covid 19 in pregnancy specifically is a difficult scenario. Pregnancy is a state of elevated diaphragm and reduced tidal volume, this leads to exacerbated hypoxia and drop in pulse oxygen levels as compared to non pregnant women. In addition the nasal mucosa and alveolar lining is congested as a result of increased peripheral vascularity in pregnancy. Furthermore there are fewer treatment options of covid 19 in pregnancy and the teratogenic potential of antiviral drugs remains unidentified. The teratogenic influence of covid-19 on pregnancy is also unknown.

Due to the upregulation of Angiotensin-converting enzyme (ACE)-2 and the SARS-CoV-2 receptor during pregnancy, there is an increased the risk of covid -19 infection [2-4]. SARS-CoV-2 and SARS-CoV-1 enter the host cell by binding their S proteins to ACE receptors located on the surface of the host cells [5,6]. ACE2, a dimer, functions as a carboxyl to lyse the single residues of ANG I to generate the single residues of ANG 1–9 and ANG II which is broken down as ANG 1–7. ANG 1–7 has vasodilatory function which can oppose the contractile effects of ANG II. ACE2 further plays a pivotal role in post-infection regulation activities like immune response, cytokine secretion, and viral genome replication [7-9].

Pregnancy with Covid also poses a difficult ICU scenario as pregnancy in itself a hypercoagulable state and covid increases the D-Dimers secondary to microthrombi. The pregnant hypoxic lady is also difficult to intubate. Steriods used to treat covid patients if used in pregnancy can lead to congenital anomalies like cardiac defects and cleft lip and cleft palate [10].

An overzealous use of anticoagulants like heparin and aspirin may also lead to retroplacental haemorrhage and clots collecting in the choriodecidual space can shear out the placenta leading to premature placental separation and in third trimester result in abruptio placenta [11]. The fetomaternal interphase is specifically affected by the hypercoagulability in microcirculation at choriodedcidual interphase. In addition these microinfarcts in the primary and secondary and tertiary fetal stem villi are responsible for decreased feto-maternal gas exchange across the placental blood barrier. This results in fetal asphyxia and accumulation of toxic metabolites in fetal circulation.

The fetus mounts a protective sympathetic response and there is a compensatory increase in erythropoesis and vascular redistribution in fetus to vital organs evidenced by fetal Doppler studies in Covid pregnancies in third trimester. The cardiovascular changes, the increase in metabolic rate and oxygen consumption, the decrease in functional residual capacity, and ventilation perfusion mis match, lead to the occurrence of hypoxic respiratory failure in these patients [12]. Hence this study was done to identify the common clinical presentations of Covid in pregnancy correlate it with the fetomaternal outcome in Covid pregnancies.
MATERIALS AND METHODS

In this prospective study all antenatal women attending the outpatient department of Saveetha Medical College were offered a voluntary COVID screening and fetomaternal outcome was recorded in all women with singleton pregnancies. This study was approved by the ethical and research board. Written consent was obtained in all cases. A first trimester scan was done to measure CRL (Crown Rump Length) to date the pregnancy in all cases.

The research was included in 28 Covid-19 with pregnancies as the study group. Pregnant women were recruited between 1 April 2020 and 31 July 2020 after getting written informed consent from participants in local language. Multiple Pregnancies and pregnancies with congenital anomalies were excluded. Detailed maternal factors like age, gestational age, parity, pre-pregnancy body mass index, previous low birth weight, haemoglobin levels, chronic hypertension, gestational diabetes and previous preedampsia were recorded subsequently. Covid-19 symptoms like fever, running nose, headache, anosmia and breathlessness were recorded. Temperatures, Pulse rate, Blood pressure, oxygen saturation were measured at the time of admission. All women were admitted in separate Labor room meant exclusively for Covid Care. Post partum care was given in the same ward till postpartum day 5.All newborns were tested for Covid-19.

Placental problems like infarcts, retroplacental calcifications, small placenta, and premature separation were also reported. Placenta from 28 normotensive, nonproteinuric pregnant women with standard pulsatility index (<1.55) of uterine artery was studied as a control group. On the day of delivery, the placenta was weighed and 12 full thickness blocks of placenta were made from center and periphery. The blocks were incubated in 4% buffered formalin for 12 hours and sections were taken at 5 microns spacing. Placential specimens were scored for staining in trophoblast, stromal cells, vessel walls and Hofbauer cells.

RESULTS

Covid -19 pregnancy is associated with miscarriages, preterm labor and intrauterine deaths. Placental lesions commonly observed are perivillous fibrinous exudates, microthrombi and micro infracts. All newborns were Covid negative and hence transplacental transfer is not recorded in this preliminary report (Table 1) (Figures 1-4).

| S.No | Age | Gestational age | Medical Co-morbidities | Associated Obstetrical Problems | Procedure done/ outcome | Baby weight / sex | Apgar score ( after 1 min , after 5 min ) | Histology |
|------|-----|----------------|------------------------|---------------------------------|-------------------------|-------------------|--------------------------------------|-----------|
| 1    | 23y | G2 A1 with 22 weeks intrauterine death | Hypothyroidism | Previous abortion at 1 trimester | MTP with Misoprostol 400 micrograms p/v 4hrly | Nil | Nil | Placental microthrombi |
| 2    | 33Y | G2 P1 L1 With 38 Weeks | Nil | Cephalopelvic disproportion | LSCS With ST | 2.690kg / boy | 8/10,9/10 | Chorioangiosis |
| 3    | 27y | Primi with term gestation | Nil | Failed Induction | LSCS With ST | 2.630kg / girl | 8/10,9/10 | Focal Perivillous fibrinous exudates |
| 4    | 32y | G2 P1 L1 With 38 Weeks | Nil | Previous LSCS with Cephalopelvic disproportion | LSCS With ST | 2.5kg, boy | 8/10,9/10 | Chorioangiosis |
| 5    | 32y | Primi with term gestation | Nil | Cephalopelvic disproportion, moulding | LSCS With ST | 2.560kg / girl | 8/10,9/10 | Chorioangiosis |
| 6    | 23y | Primi with 12 weeks | Nil | nil | Suction and evacuation | Nil | Nil | Placental microthrombi and empty fetal villi |
| 7    | 30y | G3 P1 L1 A1 with term gestation | nil | Previous LSCS with Cephalopelvic disproportion | Emergency LSCS | 3.220kg , boy | 8/10,9/10 | Hyalinization and focal fibrosis |
| 8    | 27y | Primi with 40 weeks | Nil | Oligohydramnios , post dated pregnancy | Emergency LSCS | 3.150kg , girl | 8/10,9/10 | Increased syncytial giant cells |
| 9    | 21y | G4 P1 L1 A2 38weeks +1 day | Nil | Previous 2 miscarriages in first trimester | Normal vaginal delivery with episiotomy | 3.00 kg , boy | 8/10,9/10 | Chronic inflammation increased neutrophils infiltrates |
| 10   | 21y | Primi with 40 weeks | Nil | Cephalopelvic disproportion | Emergency LSCS | 3.1 kg , girl | 8/10,9/10 | Chorioangiosis |
| No. | Age | P/A | Gestation | Edema | Antepartum | Delivery | Birthweight | Apgar | Histological Findings |
|-----|-----|-----|-----------|-------|------------|----------|-------------|-------|----------------------|
| 11  | 28y | G2 P1 L1 With term gestation | Bilateral pedal edema | nil | Normal vaginal delivery with episiotomy | 2.95 kg, boy | 8/10,9/10 | Focal perivillous fibrinous exudates |
| 12  | 28y | Primi with term gestation | nil | Severe oligohydramnios, IUGR, fetal distress | Emergency LSCS | 2.49 kg, boy | 8/10,9/10 | Microthrombi, focal fibrosis and hyalinization |
| 13  | 32y | G3 P2 L2 with 36 weeks | nil | Previous LSCS | LSCS With ST | 2.930 kg, girl | 8/10,9/10 | Focal fibrosis and neutrophilic infiltration |
| 14  | 32y | Primi with 38 weeks | nil | Minor Cephalopelvic disproportion, history of cord around the neck | Emergency LSCS | 1.66 kg, girl | 8/10,9/10 | Microthrombi and infarcts |
| 15  | 23y | Primi with 39 weeks + 6 days | nil | Cephalopelvic disproportion | Emergency LSCS | 3.070 kg, boy | 8/10,9/10 | Chronic neutrophilic exudates |
| 16  | 28y | Primi with 40 weeks | nil | Cephalopelvic disproportion | Emergency LSCS | 2.970 kg, boy | 8/10,9/10 | Chronic neutrophilic exudates |
| 17  | 25y | Primi with 14 weeks with intrauterine death | Hyperemesis | nil | MTP with Misoprostol 400 micrograms p/v 4hrly | 3.65 kg, boy | 8/10,9/10 | Perivillous hyalinization |
| 18  | 28y | G3 P1 L1 A1 37 weeks + 4 days | nil | Previous LSCS, Cephalopelvic disproportion | Emergency LSCS with sterilisation | 2.794 kg, girl | 8/10,9/10 | Perivillous fibrosis |
| 19  | 24y | G4 A3 37 weeks + 2 days | nil | Bad obstetric history | Emergency LSCS | 3.364 kg, girl | 8/10,9/10 | Perivillous fibrosis, microthrombi neutrophilic cell infiltrates |
| 20  | 24y | G2 P1 L1 37 weeks + 5 days | nil | Previous LSCS | Emergency LSCS with sterilisation | 2.210 kg, boy | 8/10,9/10 | Perivillous fibrosis |
| 21  | 26y | G4 P2 L2 D2 | nil | Previous LSCS, Premature rupture of membranes, transverse lie | Emergency LSCS with sterilisation | 2.75 kg, boy | 8/10,9/10 | Perivillous fibrosis |
| 22  | 32y | Primi with term gestation | nil | Cephalopelvic disproportion | LSCS | 2.020 kg, girl | 8/10,9/10 | Microthrombi and empty fetal villi |
| 23  | 26y | G3 P2 L2 with term gestation | nil | nil | Normal vaginal delivery | 2.84 kg, girl | 8/10,9/10 | Microinfarcts |
| 24  | 22y | Primi with term gestation | nil | Cephalopelvic disproportion | LSCS | 2.09 kg, girl | 8/10,9/10 | Chorioangiosis |
| 25  | 25  | G2 P1 L1 at term | N/A | N/A | Normal Delivery with episiotomy | 2.605 kg, girl | 8/10,9/10 | Microthrombi |
| 26  | 28  | G2 P1 L1 at 38+3 | nil | Cephalopelvic disproportion | Elective repeat LSCS | 3.040 kg, boy | 8/10,9/10 | Perivillous Fibrosis |
| 27  | 27  | G2 P1 L1 AT 38 weeks | nil | Previous LSCS, intrauterine fetal growth restriction | Emergency LSCS | 2.630 kg, girl | 8/10,9/10 | Microinfarcts and perivillous fibrosis |
| 28  | 28  | G2 P1 L1 at 34 weeks | HELLP syndrome, thrombocytopenia | Previous LSCS | Emergency LSCS | 1.8 kg, boy | 8/10,9/10 | Microinfarcts and autoamputation of tertiary fetal stem villi |
DISCUSSION

This is a preliminary study of effects of COVID-19 on human pregnancy and placenta. Animal studies with mouse corona virus has been demonstrated to cause placental lesions and result in intrauterine fetal hypoxia. Most human studies done recently for transplacental transfer have not shown to affect the fetus. Recently, there was a case report where the newborn was found positive for Covid -19 IgM antibodies and high IL-6 levels.

In our study of 28 patients we did not find newborn transfer. Some possible explanations could be that ACE-2 receptors are down regulated in fetus and newborn and the presence of different colonies of viruses and bacteria in mucosa of lungs and the airway limiting the growth of the SARS virus by direct competition and interaction. The presence of maternal antibodies and the various changes that their immune system undergoes after environmental exposure can explain why newborns are relatively safe from the virus. We have demonstrated placental vascular malperfusion in our case. This could be a part of systemic vasculitis and microthrombi deposition as happens in all organs affected with COVID vasculopathy. This is an antiviral immune response and placenta too exhibits villitis of unknown etiology in COVID-19 infected mothers. In our series of 28 patients other causes of placental vasculitis like preeclampsia and gestational diabetes were ruled out as exclusion criteria. Thus, these placental changes of focal microthrobi and villitis and infarcts can be attributed to COVID -19. These changes were also seen in miscarriages, intrauterine deaths and preterm placenta of COVID-19 pregnant women. Further studies are required to study the pathophysiology of Intrauterine fetal demise and miscarriages in COVID -19 with pregnancy.

CONCLUSIONS

Placental affection in COVID-19 IS a part of systemic vasculitis of COVID-19 pathophysiology. The microthrombi and microinfracts can lead to fetal malperfusion. The systemic Cytokine response can lead to Fetal inflammatory response syndrome (characterized by IL-6> 11pg/ml) even if there is no direct transfer of virus transplacentally. This immense sympathetic stimulation leads to secretion of neurotoxins as a part of inflammatory cascade and induce fetal mononuclear production of TNF alpha, IL-6 and IL-1. This may be a cause for miscarriages and fetal deaths in COVID -19. Further studies on newborn inflammatory markers are required to confirm our preliminary findings.

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