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Association of Covid 19 antibodies in fetal growth restriction and small for gestational age among newborn babies

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Abstract

Introduction and Review of Literature: The novel coronavirus termed SARS cov 2 is a major public health challenge over the world. Since December 2019 the outbreak of COVID 19 infection has become a major epidemic all over the world. However there have been only few studies in pregnant woman relating to the clinical course and outcomes of COVID 19 infection during pregnancy and potential risks to unborn child. There are certain evidences which showed that hypoxia and decreased in ACE2 content in pregnant women with SARS-cov 2 infection affect fetal development. Also the immune response in pregnant women infected with SARS-cov 2 infection affects fetal and neonatal development. Moreover till now there is a limited evidence of intrauterine vertical transmission of SARS-COV 2 infection in pregnant women and the potential risk to the mother and baby have become a matter of major concern. A systemic review on outcomes of SARS, MERS and COVID 19 during pregnancy supported miscarriage, preeclampsia, cesarean and periatal deaths were more common in the general population. A study by Dan Dang and his team showed that there are potential effects of SARS-cov 2 infection during pregnancy on fetuses and newborns which are worthy attention. A study by zhu et al. reported highest postnatal morbidity in 10 neonates including 6 cases of respiratory dyspnea 4 cases with digestive symptoms and 1 case of death. A case series by piuli shah showed there have been developments of IUGR in the newborn of pregnant lady who developed COVID 19 infection during her third trimester and delivered significantly IUGR baby by c- section.

Aims and Objective(s) of the Study:

Our study aims to detect antibodies against COVID 19 among the intrauterine growth restriction infants and small for gestational age infants and to see the association of the asymptomatic COVID 19 infection among the mothers or if there was any exposure to COVID 19 to mother antenatally.

Proposed Methodology (Not more than 2-3 pages)

Subjects

Inclusion Criteria

- All neonates with both symmetrical and assymetrical IUGR components
- All neonates who are small for gestational age.

Exclusion Criteria

- Neonates with chromosomal abnormalities
- Parents not willing for the study

Cases will be selected based on inclusion and exclusion criteria and detailed clinical examination and anthropometry will be done. Neonate will be categorised as symmetrical or assymetrical IUGR based on the ponderal index.

Neonates who are small for gestational age will also be included in the study. Parents are informed about the procedure and consent is obtained regarding the same. Blood Serum samples will be analysed for IgG and total antibodies by using recombinant protein representing the SARS – COV2 S1 RBD antigen.

Keyword: Fetal Growth Restriction, Small for Gestational Age, SARS - Covid 19, Antibody detection.

Introduction

Coronavirus disease 2019 (Covid 19) by SARS – COV2 has been swiftly spreading around the world, prompting WHO to declare pandemic on March 11, 2020. Covid 19 has a wide range of disease manifestations which have been described as 5 different patterns- Asymptomatic, mild to moderate, severe, critically ill and mortality. At the onset of coronavirus disease 2019 pandemic the WHO designated pregnant women as a vulnerable group based on preliminary reports of increased risk of still birth, preterm birth, fetal growth restriction and extrapolation from experience with previous respiratory virus outbreaks, including severe acute respiratory syndrome (SARS), middle east respiratory syndrome (MERS) and influenza. The clinical manifestations of COVID 19 can be divided into 3 stages – stage 1 is characterized by the symptoms of mild flu like syndrome and the majority of patients remain in stage 1 and small proportion of cases may progress further leading to pulmonary impairement becomes evident in stage 2 which is characterized by development of viral pneumonia with present tachypnea , cough and fever with presence or absence of hypoxia. Stage 3 is characterized by most severe phase which is characterized by systemic manifestations of hyperinflation with cytokine storm syndrome (CRS) leading to lung injury and multiorgan failures. A systemic review study shows that there is increased abortions in mother with COVID 19 positive result which several case studies and case reports have identified during the pandemic. Placental inflammation during the viral infection may result in fetal growth restriction and induce abortion. There has been no any consistent evidence of vertical transmission of virus from mother to fetus which requires further investigation. Major maternal factors for fetal growth restriction are extremes of reproductive age group, maternal malnutrition, chronic diseases which causes interfering with placental flow and oxygenation like chronic cardiovascular disease , pregnancy induced hypertension , sickle cell anemia in mother, maternal diabetes , collagen vascular disease, maternal exposure to alcohol and tobacco. Placental and umbilical anatomical factors which are known to cause fetal growth restriction are placental malformations like chorioangioma, infarction, circumvallet placenta , placental mosaicism, placental infarction or focal lesions, placental abruption, placenta previa, insufficient

uteroplacental perfusion, single umbilical artery. Certain fetal factors causing fetal growth restriction are CNS and skeletal malformations, chromosomal abnormalities, congential infections – TORCH infections and multiple gestations.

A case report shows that there was a dramatic presentation of arrested fetal growth due to placental ischemic changes in mothers infected with COVID 19. Initial studies have shown that covid 19 increases the risk of preterm birth and low birth weight and also the need for hospitilisation in NICU. Although in a small series of pregnant women with severe COVID 19 a pre eclampsia like syndrome a variant of clinical manifestation of preeclamsia was reported. During pregnancy several viral infections have been known to increase the risk of fetal malformation, preterm birth and IUGR without significant long term impact on the off spring health.

Methods

This study was conducted at Rajarajeswari medical college and hospital, postnatal wards and neonatal intensive care unit in Department of pediatrics Bangalore, Karnataka.

Study Design And Subjects

The study is a prospective study done among neonates with both symmetrical and assymetrical IUGR and SGA babies admitted to Rajarajeswari medical college and hospital. – a tertiary care hospital.

Twenty five babies were included in the study which meet the inclusion criteria that is- all neonates with symmetrical and assymetrical IUGR (definition from cloherty to be added) components which was either detected by at least 2 intrauterine growth assessment or after clinical examination and anthropometry of neonates were plotted on fentons growth charts after birth and calculation of ponderal index and . Also this study includes SGA babes. SGA describes a neonates whose birth weight is less than 10^{th} centile for gestational age or less than 2 standard deviation below the mean for infants gestational age. Informed consent was obtained from parents. This study excluded the neonates with chromosomal abnormalities and also major congenital abnormalities. Also excludes the neonates born to mothers who are vaccinated against covid 19. This study also excludes neonates born to mother with PIH, TORCH infections, thyroid abnormalities and anemia and Parents of neonates not willing for study was also excluded.

Maneuver

This is a prospective study performed in a tertiary care center in Banglore over 3 months. All neonates who fulfilled the inclusion criteria were included in the study. Demographic data with delivery details were obtained from maternal case records and was documented in a preformed proformas.

Serum samples were collected from the neonates who fulfilled the criteria for the study and using a chemiluminescentmicroparticles immunoassay (CMIA) method detection of IgG antibodies against SARS-COV 2 including neutralizing antibodies to the receptor binding domain (RBD) of S1 subunit of the spike protein. IgG antibodies was analysed since it crosses the placenta and also indicates the past infection in mother. IgG antibodies against COVID 19 was considered positive if levels were more than 50Au/ml and negative if less than 50 Au/ ml.

Ethical Statement

Ethical approval for the study was sought and obtained from the health research and ethics comitee of rajarajeswari medical college and hospital.

The data obtained were treated with utmost confidentiality. Written informed consent was obtained from parets of neonates who were included in the study

Statistical Analysis

Microsoft excel statistical package for social science version 23.0 was used for analyzing the data. The data collected was analysed using the descriptive statistics for summerising data using mean and standard deviation and inferential statistics using unpaired T test and Z test. The level of statistical significance was set at 5% which is p value < 0.05, Data was entered and was carefully checked to eliminated multiple or wrong entieres and outliers.

Result

Study Sample : IN total 30 neonates were recruited for the study , 5 neonates were excluded from study because 2 among them were born to mother with pregnancy induced hypertension, 2 babies were born to mother who were vaccinated against COVID 19, 1 baby was excluded as baby was TORCH positive.

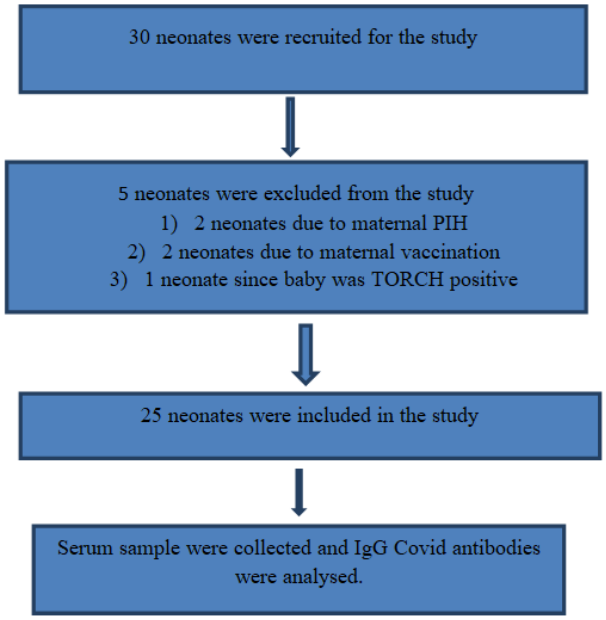

Table 1: Qualitative Variables: Frequency And Percentage

Sn.	Variables	Levels	Frequency	Percentage
1	Parity	i) Multipara	9	36%
		ii) primipara	16	64 %
2	Type of delivery	i) NVD	16	64%
		ii) LSCS	9	36%
3	Trimester details 1st trimester	a) H/O cold and cough		
		• Yes	0	0
		• No	25	100%
		b) H/O fever with/ without rashes		
		• Yes	1	4%
		• No	24	96%
		c) H/O covid exposure		
		• Yes	0	0
		• No	25	100%
		d) H/O RTPCR positive	0	0

	2nd trimester	• Yes • No	25	100%
		a) H/O cough and cold		
		• Yes	6	24%
		• No	19	76%
		b) h/o fever with / without rashes		
		• Yes	0	0%
		• No	25	100%
		c) h/o covid exposure		
		• Yes	0	0%
		• No	25	100%
		d) h/o RTPCR positive		
		• yes	0	0%
		• no	25	100%
	3rd trimester			
		a) H/O cough and cold		
		• Yes	3	12%
		• No	22	88%
		b) h/o fever with / without rashes		
		• Yes	2	8%
		• No	23	93%
		c) h/o covid exposure		
		• Yes	0	0%
		• No	25	100%
		d) h/o RTPCR positive		
		• yes	0	0%
		• no	25	100%
4	Clinical covid status of mother	a) Negative	14	56%
		b) Positive	11	44%
5	Gender of baby	a) Female	11	44%
		b) Male	14	56%
6	Maternal RTPCR	a) Positive	0	0%
		b) Negative	25	100%
7	Covid 19 IgG Antibody status of baby	a) Negative	8	32%
		b) Positive	17	68%

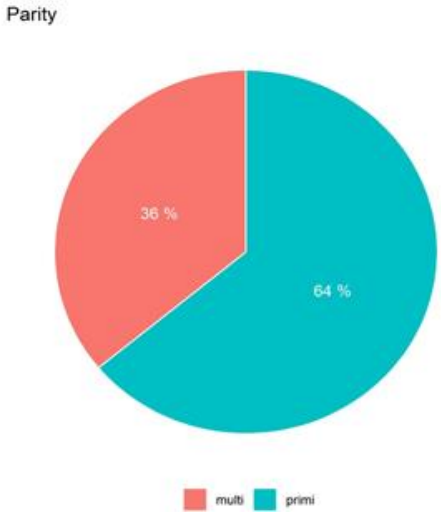

Figure 1

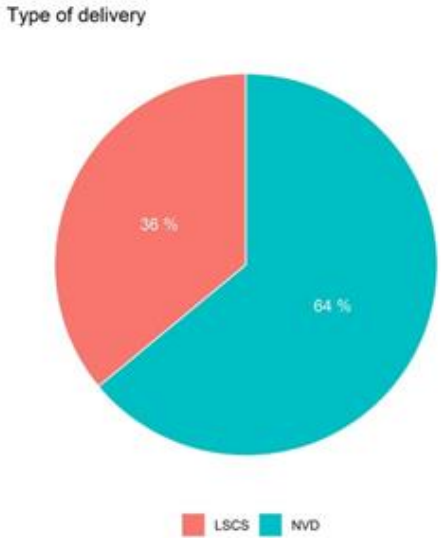

Figure 2

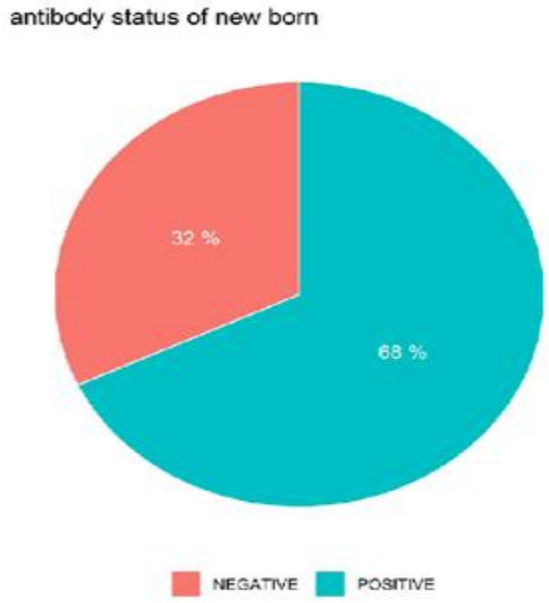

Figure 3

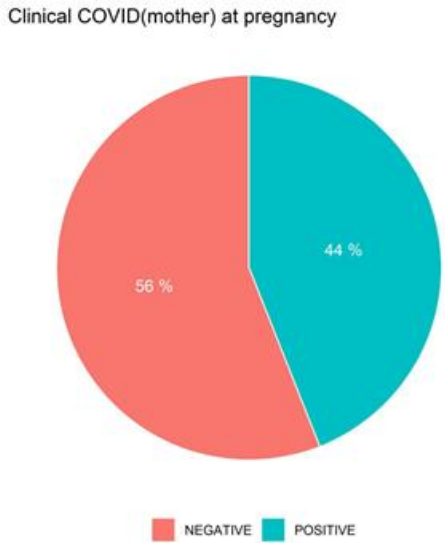

Figure 4

Table 2: Quantitative Variables: Descriptive Statistics

Sn.	Variable	N	Mean	SD	Median	Q1	Q3	Min	Max
1	Maternal age	25	23.56	2.80	24.0	22.0	26.0	19.0	30.0
2	Gestational age	25	36.46	2.08	37.0	36.0	37.57	28.0	38.29
3	Ponderal index	25	2.22	0.17	2.2	2.1	2.32	1.9	2.6
4	IgG level	25	659.66	1049.82	144.0	23.0	552.00	4.8	3440.0

Table 3: Comparison by Mother's Clinical Covid Status during Pregnancy

Summary: Quantitative

Sn.	Variable	Group	N	Mean	Median	SD	Q1	Q3	P. Value
1	Ponderal Index	a) Negative b) Positive	14 11	2.21 2.23	2.21 2.20	0.19 0.15	2.10 2.15	2.31 2.15	0.848
2	Log, Igg	a) Negative b) Positive	14 11	4.27 5.78	3.88 6.10	1.92 1.98	2.81 4.45	5.76 7.53	0.067

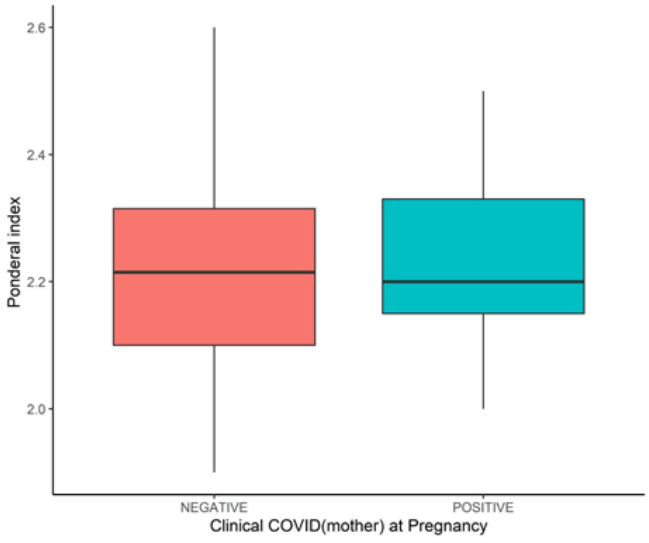

Figure 5

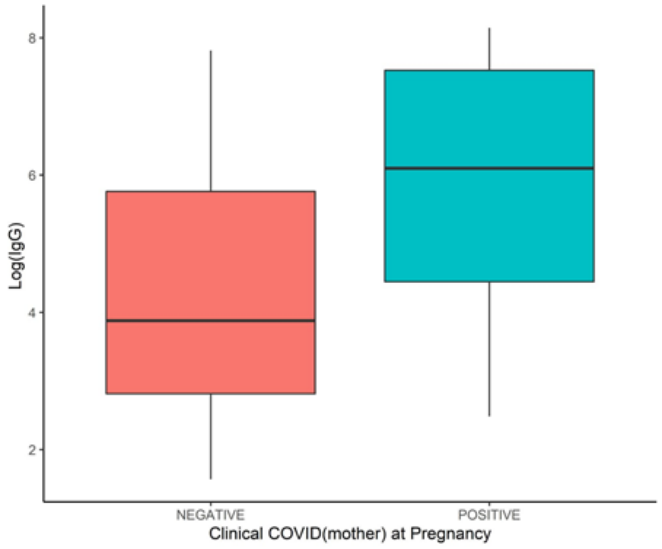

Figure 6

Table 4: Summary: Qualitative

Sn.	Variable	Levels	Negative	Positive	Chi. Square	P Value	P. Value. Fish
1	Antibody status of baby	a) Negative b) Positive	6(42.9%) 8(57.1%)	2(18.2) 9(81.8)	0.776	0.378	0.234

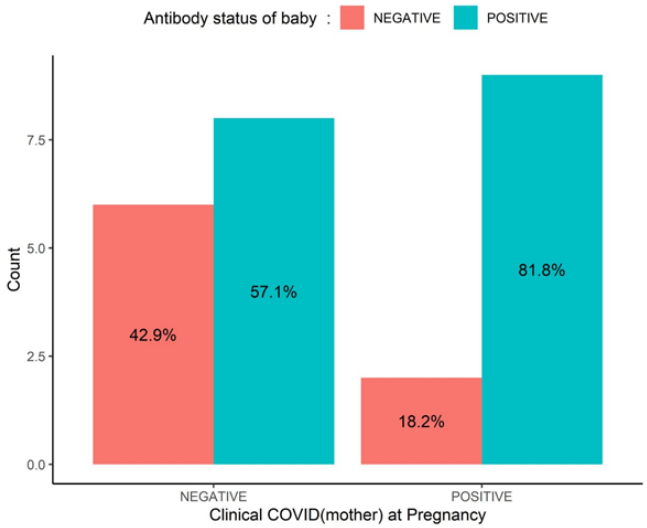

Figure 7

Study showed that 44% of mothers were clinically COVID positive during the pregnancy and all the mothers were tested negative by RT PCR analysis for covid at the time of delivery.

It was seen that 68% of infants who had fetal growth restriction were tested positive for covid 19 IgG antibodies.

It showed that statistical analysis of the clinically positive COVID 19 positive mothers had higher incidence of delivering IUGR babies which was trending to be significant with p value of 0.06.

Discussion

Our study aims to prove that COVID 19 infection is also the major leading cause for fetal growth restriction.It was noted that not many studies are conclusive of proving that COVID- 19 is becoming the most important etiological factor for causing fetal growth restriction. Pre covid era TORCH infections were considered the major infectious agent affecting the mothers and was also the leading cause for fetal growth restriction, and antibody detection against the TORCH infections in the infants serum sample gave the clue for cause of fetal growth restriction .Like wise our study also involves the detection of IgG covid 19 antibodies in the IUGR infants being the cause of FGR. Retrospective analysis of the maternal covid 19 symptoms, in our study, during the pregnancy gave the clinical positive mother. Also it was noted in the study that mothers who had symptoms of covid 19 during 2nd trimester had higher incidence of delivering IUGR babies. Euguchi et al studied the association of systemic immune response due to COVID 19 infection due to binding of SARS COV 2 spike protein binding to ACE 2 receptor which is seen in female reproductive tract and placental tissues, leading to elevation of inflammatory cytokines and chemokines. Histopathological studies of the placenta in pregnant women with COVID-19 revealed the presence of SARS-CoV-2 in about 27 % of cases .The histopathological findings of the placenta affected by COVID-19 were similar to those observed in previous outbreaks by other coronaviruses (SARS and MERS) . However, the presence of SARS-CoV-2 was confirmed by PCR of placental tissue/amniotic membrane, and immunohistochemistry and in-situ hybridization assays of formalin-fixed paraffin-embedded tissue sections later. Hosier et al were first to publish a study of 3 third trimester placental from pregnant women with COVID 19 reported a high degree of fibrin deposition and

syncytial knots accompanied by a chorioangioma or massive placental infarction. A study showed that , the major placental pathologies of COVID-19 patients have been described as foetal vascular malperfusion (FVM), foetal vascular thrombosis, maternal vascular malperfusion (MVM), massive infection with generalized inflammation (presence of M2 macrophages, cytotoxic and helper T cells, and activated B-lymphocytes), fibrin deposition and intervillous thrombosis. The placental abnormalities, such as MVM, observed in the cases of pregnant women with COVID-19 have been associated with IUGR. Previously, the presence of intense infiltration of macrophages in the placenta and elevated levels of placental inflammatory markers have been reported to be associated with a reduction in foetal growth rate. Hence, SARS-CoV-2 related placental pathology may be induced by the local activation of both innate and acquired immune effectors at the maternal-foetal junction and pro-inflammatory cytokine milieu. Careful follow up of pregnant women with COVID-19, including asymptomatic cases, should be considered. The impact of COVID-19 on pregnancy outcomes is still poorly understood. Studies in pregnant women during previous outbreaks of other coronaviruses (SARS and MERS) have observed an increased risk for miscarriage, Preterm birth, and IUGR. The initial pregnancy outcomes reports of pregnant women infected with COVID-19 suggest an increase in the risk of PTB and LBW ,particularly in the latter half of the pregnancy (≥ 20 weeks gestation) . Prematurity could be spontaneous or induced in pregnant women with COVID-19, and the severity of COVID-19 may be a factor inducing PTB. A study by wong et al showed that the placental abnormalities such as maternal vascular malperfusion as observed in case of pregnant women with COVID 19 have been associated with IUGR. Sharpe et all showed that presence of intense infiltration of macrophage in placenta and elevation levels of placental inflammatory marker have been reported to be associated with reduction of fetal growth rate. Also a study by rotshenker – olshinka et al showed, 83.3% of pregnant women diagnosed with IUGR and abnormal fetal Doppler flow measurement have placental pathologies compatable with Maternal vascular malperfusion secondary to viral etiology. Immunologically, SARS-CoV-2 infection is known to induce a decrease in CD4+ andCD8+ T and natural killer (NK) cell levels, more evidently in critically illpatients. Despite decreased T cells, the immune response of COVID-19 ischaracterized by the increased Th17 response, with a concurrent reduction of regulatory T (Treg)/Th17 cell ratios. Studies have suggestedthat the uncontrolled release of pro-inflammatory cytokines inCOVID-19 cases is due to the exaggerated Th17 response. A recent study of the inflammatory cytokine profiles in three different groups of patients with respiratory infections, including hospitalized-but-stable COVID-19 patients, COVID-19 patients requiring intensive care unit (ICU) admission, and patients with severe community-acquired pneumonia requiring ICU support, revealed that the inflammatory cytokines, including IL-1β, IL-6, IL-8, and soluble TNF receptor 1 (sTNFR1) were significantly elevated in COVID-19 cases when compared to patients who required ICU support withoutCOVID-19. Notably, the balanced Treg/Th17 immune responses are critical for embryonic implantation and healthy pregnancy, while reduced levels of Treg cells and increased levels of Th17 cells are associated with obstetric complications, such as miscarriage, preeclampsia, and Preterm birth. Hence,

intrauterine fetuses in mothers with SARS-Cov-2 infection can be exposed to pro-inflammatory milieu either directly induced by fetal or placental tissue or indirectly by maternal immune responses. In COVID-19 cases, shifted Th17 immunity has been reported to induce pro-inflammatory cytokine excess. Pro-inflammatory immune responses are dominant during implantation and parturition in normal pregnancy, systemically and locally. Recently, in a systemic review evaluating the pregnancy outcomes of nine Chinese studies with pregnant women with COVID-19 (n = 92),increased prevalence of PTB of about 63.8%, LBW with prevalence of 42.8% , prevalence of fetal distress was also increased of about 61.1%, and neonatalICU admissions were noted to be about 76.9%. Unfortunately, the majority of the studies did notreport the nature of FGR precisely.

Limitation

The sample size in the study is small and hence it requires more sample size to prove the significance. Also there was unavailability of confirmed COVID 19 positive data proved by RTPCR among the mothers who had clinical symptoms of covid 19 during antenatal period.

Conclusion

Our study is one of the first to evaluate the association of COVID 19 during pregnancy which could be the cause of IUGR. It was found that there was a strong association between the maternal infection with covid 19 during pregnancy leading to fetal growth restriction in intrauterine life.

Although clear pathogenesis is not understood for causation of FGR due to COVID 19 but we do believe that in this era of covid 19, it could be most important infectious agent leading to FGR.

The limitations of the study may provide insight into future studies on whether there is a real relationship between maternal covid 19 infections leading to fetal growth restriction.

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