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Original Article

Obstetrics and Gynaecology Section

Association of Maternal Nutritional Status with COVID-19 Infection and its Effects on Pregnancy Outcomes- A Retrospective Study

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ABSTRACT

Introduction: Need is felt to perform research for assessing the impact of maternal nutrition status on severity of Coronavirus Disease 2019 (COVID-19) in pregnancy and effect of COVID-19 on maternal outcomes as it has not been established.

Aim: To evaluate association of maternal nutritional status and pregnancy outcomes with COVID-19 infection in pregnancy.

Materials and Methods: A retrospective study was conducted among 260 antenatal patients admitted in COVID-19 level 3 hospital (Teerthanker Mahaveer Medical College and Research Centre), Moradabad, Uttar Pradesh, India, from April 2020 to May 2021 with COVID-19 infection. Records were studied for the effect of maternal nutrition status along with COVID-19 and outcome of pregnancy in terms of anthropometric markers Body Mass Index (BMI), nutritional markers (haemoglobin, total serum proteins) and biochemical markers (oral glucose tolerance test, vitamin D). Pregnancy outcomes were assessed in terms of severity of symptoms, Intensive Care Unit (ICU) admission, labour outcome and obstetric complications. Data were tabulated and examined using the Statistical Package for Social Sciences (SPSS) version 20.0.

Results: Mean age of the patients enrolled was 21.4±5.6 years. A statistically significant association was seen with high body mass index (88.24%), hyperglycaemia (82.35%), hypoproteinaemia (6.01±0.47) and hypoalbuminaemia (0.93±0.24). Statistically significant association between adverse pregnancy outcomes in terms of bleeding per vaginum (11.76%), preterm labour (54.92%), gestational diabetes mellitus (82.35%), hypertension (29.41%), Intrauterine Device (IUD) baby (35.29%) with increasing severity of COVID-19 infections.

Conclusion: COVID-19 adversely affects the maternal obstetric outcome. Maternal nutrition status factors associated with severity of COVID-19 were body mass index, deranged blood sugar levels and protein levels.

Keywords: Antenatal, Body mass index, Coronavirus disease 2019, Haemoglobin, Pregnancy outcomes, Total serum proteins

INTRODUCTION

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) causes the Coronavirus Disease 2019 (COVID-19), a global public health disaster [1]. Most cohort studies have concentrated on examining COVID-19's effects on the general population, and there is a lack of evidence on its impact on vulnerable populations around the world, such as pregnant women [2,3]. Preliminary studies have shown that COVID-19 infection has minimal effects on pregnancy outcomes. There is very limited data that can conclude the consequence of coronavirus disease in pregnant females and neonatal outcomes in India [4,5].

The state of maternal nutrition is one of the important environmental factors which alter the course of pregnancy. The growth of foetal tissues and other products of conception, as well as the metabolic changes that occur throughout pregnancy, put the pregnant mother under a lot of stress and raise her nutritional needs. Workers in the fields of nutrition and maternal and child health from around the world have occasionally pointed out the close relationship between maternal nutritional status on the one hand and the health of the pregnant woman and her offspring on the other [6].

Being a developing country, majority of the females in India belong to the poverty stricken areas of the country and deal with nutritional deficiencies such as anaemia, vitamin D deficiency, hypoproteinaemia and diabetes. These conditions lead to increased propensity to infections in the patient [7-9].

Pregnancy being a state of special immune tolerance predisposes the woman to various viral infections [10]. It leads to various changes in the immune and cardiopulmonary systems of a woman's body, which put her at an increased risk of getting viral infections and developing severe pneumonia. Extensive population-based cohort studies have shown that seasonal influenza epidemics increase the risk of severe complications in pregnant women [11-13]. Although negative outcomes such as Intensive Care Unit (ICU) admission or patient death can occur, recent systematic reviews and meta-analyses reveal that the clinical course of COVID-19 in most women is not severe, and the infection has no major impact on pregnancy [14]. Thus, there is contradictory data available with respect to effect of coronavirus in pregnant females and neonatal outcomes.

The nutritional status of pregnant females during the coronavirus pandemic and its effect on the neonate has not been established yet. There might be interplay of various variables related to maternal nutrition which affect the immunological responses, innate and adaptive, leading to increased degree of severity of illness in the pregnant female which should be looked into. Hence, a need was felt to perform a study for assessing the impact of the maternal nutrition status on severity of COVID-19 in pregnancy and its effect on maternal outcomes.

MATERIALS AND METHODS

This retrospective study was conducted among patients admitted in Teerthanker Mahaveer Medical College and Research Centre, Moradabad, Uttar Pradesh, India, from April 2020 to May 2021. The records of 260 antenatal females admitted from April 2020 to May 2021, aged between 18-45 years with a positive Reverse Transcription Polymerase Chain Reaction (RT-PCR) report for COVID-19 was studied. The study was approved by the Institutional Research and Ethics Committee (Ref No. TMMC&RC/IEC/19-20/037).

Inclusion and Exclusion critera: All antenatal females with gestational age >6 weeks with cardiac activity on ultrasound and well defined gestational sac with positive COVID-19 report by RT-PCR attending COVID-19 level 3 hospital were included in the study. Any pregnant COVID-19 positive patients without investigations or records as per the study protocol were excluded from the study maternal nutritional status was assessed using anthropometrical, nutritional and biochemical markers.

Anthropometrical Markers

Prepregnancy weight of the patients was noted from the records brought by each patient and her Pre-pregnancy Body Mass Index (BMI) was calculated by dividing the pre-pregnancy weight (in kg) with square of height (in metre). Patients were classified into underweight (less than 18.5), normal BMI (18.5-24.9) and overweight (25-29.9) according to World Health Organisation (WHO) classification [15].

Nutritional Markers

Haemoglobin, total protein levels and albumin globulin ratio were the nutritional markers for assessment of maternal nutritional status in the present study. Total protein levels were divided into normal (6-8.3 g/dL) and decreased (<6 g/dL) and normal albumin globulin ratio was taken as 1-2 [16]. Total protein levels and albumin globulin ratio levels were measured using Turbochem 100 auto analyser marketed by CPC. Patients with decreased haemoglobin values were classified into mild (10-10.9 mg/dL), moderate (7-10 mg/dL), severe (<7 mg/dL) and very severe anaemia (<4 mg/dL) according to the Indian Council of Medical research (ICMR) Classification of anaemia [17].

Biochemical Markers

Vitamin D levels and Oral Glucose Tolerance Test (OGTT) were Biochemical markers used to assess maternal nutritional status in the present study. Blood sugar assessment in the study was done according to DIPSI guidelines using OGTT wherein a single blood sugar test 2 hours after 75 gm glucose ingestion was used to assess the blood sugar status of the patient [18]. Value of more than 140 mg/dL was considered as significant. On the basis of multiple guidelines serum 25(OH) D level of <20 ng/mL has been defined as vitamin D deficiency [19]. Vitamin D levels were estimated by automated immunoassays using Architecti1000sr Make 2015.

Detailed evaluation of all patients fulfilling the inclusion and exclusion criteria were collected from case sheets in the record room regarding their age, gestational age, socio-demographic factors. Socio-economic class of the patients was calculated on the basis of Modified Kuppuswamy Scale [20]. The patient's prepregnancy weight was noted from the records and BMI was calculated. Patient's baseline details like blood pressure, temperature and pulse rate were recorded. Examination findings, routine and specific investigations were noted and the patient's progress till she was admitted in the hospital was followed.

Patients were classified into asymptomatic, mild symptomatic, moderately symptomatic and severe symptomatic according to Centre for Disease Control Guidelines [21]. Individuals who tested positive for COVID-19, but had no symptoms consistent with the disease were classified as asymptomatic. Patients with positive report for COVID-19 and generalised symptoms such as fever, cough, sore throat, malaise, loss of taste/ smell but no shortness of breath/ dyspnea were classified as mild symptomatic. Patients with evidence of lower respiratory tract infection on clinical assessment or imaging and oxygen saturation ≥94% at room air were moderately symptomatic. All of the patients with increased respiratory rate (≥30 breaths per min), decreased oxygen saturation at rest (≤93%), PaO_2/FiO_2 ratio <300 mmHg or critical disease were classified into severe symptomatic category. All the patients in the severe symptomatic category had severe pneumonia, required invasive mechanical ventilation and were admitted in the ICU. The course of hospital stay was recorded and various laboratory investigations of interest to the present study such as haemoglobin, total protein, Albumin/Globulin (A/G) ratio, vitamin D level, OGTT were studied for the purpose of maternal nutrition status. The ICU admission if any was recorded along with any condition like respiratory complications, foetal distress, antepartum haemorrhage, intrauterine death of baby, disseminated intravascular coagulation.

STATISTICAL ANALYSIS

Data were tabulated and examined using the Statistical Package for Social Sciences Version 20.0 (IBM SPSS Statistics for Mac, Armonk, NY: IBM Corp, USA). Descriptive statistical analysis had been carried out in the present study. Results on continuous measurements are presented as Mean±SD. The results on categorical data were tabulated as frequency distribution. The statistical power calculation was based on the assumption that the data were normally distributed. Chi-square test and Analysis of Variance (ANOVA) test were applied and significant difference between the groups and level of significance p-value was set at <0.05.

RESULTS

Mean age of the patients enrolled was 21.4±5.6 years. It was observed that 66.92% (n=174) were booked patients with complete antenatal visits as per WHO [Table/Fig-1].

Demographic characteristics	n	Percentage
Age (years)		
18-25 years	144	55.38%
26-35 years	109	41.92%
>35 years	7	2.69%
Booking status		
Booked	174	66.92%
Unbooked	86	33.08%
Residence		
Rural	178	68.46%
Urban	82	31.54%
Period of gestation		
First trimester (1-12 weeks)	12	4.62%
Second trimester (13-26 weeks)	64	24.62%
Third trimester (27 weeks onwards till the end of pregnancy)	184	70.77%
Modified Kuppuswamy Socio-economic status scale [20]		
Upper class	17	6.54%
Upper middle	19	7.31%
Lower middle	33	12.69%
Upper lower	32	12.31%
Lower	159	61.15%
Type of admission*		
Labour room admission	168	64.62%
General ward admission	75	28.84%
ICU admission	17	6.53%

[Table/Fig-1]: Socio-demographic profile of the COVID-19 pregnant patients (N=260).
*patients less than 32 weeks gestational age with no other significant risk factors were admitted in the general ward. Patients more than 32 weeks gestational age were admitted in the labour room for foetal heart surveillance. Patients with severe symptomatic COVID-19 disease were admitted in the Intensive Care Unit (ICU)

Out of 260 patients enrolled in this study 237 belonged to asymptomatic/mild symptomatic group, six were moderately symptomatic and 17 patients were severely symptomatic. A statistically significant relationship was seen between BMI and severity of COVID-19 infection. Out of the severe symptomatic patients 88.24% (n=15) were overweight and had BMI between 25-29.9. A significant relation was also seen between OGTT, total protein, A/G Ratio with severity of COVID-19 infection [Table/Fig-2].

Variables	COVID-19 status			p-value (Chi-square test)
	Asymptomatic/Mild symptomatic (n=237)	Moderate symptomatic (n=6)	Severe symptomatic (n=17)	
	(n, %)	(n, %)	(n, %)	
BMI (kg/m^2)				
<18.5 (Undernourished)	29 (12.24)	1 (16.67)	0 (0.00)	0.69
18.5-24.9 (Normal)	196 (82.70)	5 (83.33)	2 (11.76)	**0.00001**
25-29.9 (Overweight)	12 (5.06)	0 (0.00)	15 (88.24)	**0.00001**
Anaemia				
<7 g/dL (severe)	5 (2.11)	0 (0.0)	3 (17.65)	0.37
7-10 g/dL (moderate)	124 (52.32)	4 (66.67)	9 (52.94)	0.78
10-11 g/dL (mild)	108 (45.57)	2 (33.33)	5 (29.41)	**0.0006**
Oral Glucose Tolerance Test (OGTT)				
<140 mg/dL	218 (91.98)	5 (83.33)	3 (17.65)	**0.00001**
>140 mg/dL	19 (8.02)	1 (16.67)	14 (82.35)	**0.00001**
Vitamin D				
Vitamin-D deficiency (<20 ng/dL)	191 (80.59)	4 (66.67)	13 (76.47)	0.65
Normal (20-40 ng/dL)	46 (19.41)	2 (33.33)	4 (23.53)	0.65
Total protein (Mean±SD)	6.92±0.1.02	6.46±0.79	6.01±0.47	**0.032** (ANOVA test)
Albumin/Globulin ratio (Mean±SD)	1.21±0.26	1.04±0.29	0.93±0.24	**0.02** (ANOVA test)

[Table/Fig-2]: Association of COVID-19 status with maternal nutritional status.
p-value <0.05 was considered as statistically significant

A statistically significant relation was observed between adverse pregnancy outcomes in terms of bleeding per vaginum, preterm labour, gestational diabetes mellitus, gestational hypertension, IUD with increasing severity of COVID-19 infections [Table/Fig-3].

Obstetric outcomes	COVID-19 status						p-value
	Asymptomatic/ Mild symptomatic (n=237)		Moderate symptomatic (n=6)		Severe symptomatic (n=17)		
	N	(%)	N	(%)	N	(%)	
Bleeding per vaginum	4	(1.68)	0	(0)	2	(11.76)	**0.004**
Preterm labour	0	(0)	0	(0)	9	(54.92)	**0.00001**
Oligohydramnios	21	(8.86)	2	(33.33)	4	(23.53)	**0.028**
Intrauterine Device (IUD) baby	0	(0)	0	(0)	6	(35.29)	**0.00001**
Gestational hypertension (including chronic hypertension superimposed with preeclampsia)	9	(3.79)	1	(16.67)	5	(29.41)	**0.00003**
Gestational diabetes	19	(8.02)	1	(16.67)	14	(82.35	**0.00001**
Mortality	0	0	0	0	14	(82.35)	**0.00001**

[Table/Fig-3]: Association of COVID-19 status with obstetric outcomes.
p-value <0.05 was considered as statistically significant
p-value was calculated using Chi-square test

It was observed that nine out of 17 (52.94%) patients in the severe symptomatic group had preterm labour in the present study. Total six out of nine (66.66%) patients went into spontaneous preterm labour, three patients (33.33%) were induced due to obstetric reasons (two patients had foetal distress and one had abnormal doppler findings on ultrasound).

DISCUSSION

Pregnant women are at a high risk of developing severe pneumonia due to altered cell-mediated immunity and changes in pulmonary function [22,23]. This has been demonstrated in the past during outbreaks involving viruses from the same family of COVID-19 such as SARS and Middle East Respiratory Syndrome (MERS) [24].

The mean age of patients enrolled in the present study was 21.4 years. A study assessing Coronavirus disease in pregnant women conducted by Yan J et al., [25] in China found the mean age of patients at admission to be 30.8 years, this discrepancy could be attributed to the culture of early marriage and childbirth of rural women in India. The same study found the mean gestational age on admission to be 38 weeks which was in concurrence with the present study.

As our hospital is located in the outskirts of the city most of the participants were in the lower socio-economic status in the present study. A study conducted by Little C et al., investigated the impact of socio-economic status on COVID-19 and found no significant difference in hospital admission rates between low and high poverty groups in COVID-19 afflicted patients [26]. Since the hospital is located in the outskirts of the main city, most of the patients coming to the hospital belong to the nearby villages and hence to the poorer strata of the society.

Only 6.53% patients in the present study required ICU admission as they were severely symptomatic. Villar J et al., in their study found that out of 706 COVID-19 infected pregnant women enrolled in his study 44% were asymptomatic and 18.9% were severely symptomatic and required ICU admission. The difference in severely symptomatic patients can be attributed to larger sample size in Villar J et al., study as compared to the current study. This difference can also be because most of the patients enrolled in the current study were young (mean age 21.4 years) as compared to Villar J et al., study (mean age was 30.2 years), so they had better immunity and hence better outcomes [27].

Authors found increased severity of symptoms and higher morbidity and mortality in patients with raised BMI. The 88.24% of the severe symptomatic COVID-19 participants were overweight (p-value=0.00001). Mohseni H et al., conducted a study wherein they found that mean BMI of groups increased with severity symptoms. The BMI of moderate symptomatic (27.57 kg/m^2), severe symptomatic (29.70 kg/m^2) and death persons (28.13 kg/m^2), was significantly higher than healthy (26.70 kg/m^2) and mild symptoms (26.57 kg/m^2) groups (p-value=0.001) [28]. Obesity is linked to an increase in the production of inflammatory cytokines such as tumour necrosis Factor- alpha, interleukins, and interferons. This leads to a state of chronic inflammation and compromised immunological

responses. This causes the symptoms to become more severe and is linked to an increased risk of deep vein thrombosis, pulmonary embolism, cardiovascular disease and stroke, and myocardial infarction [29].

Out of the 17 severe symptomatic patients enrolled in the present study, 17.65% had severe anaemia. The present study depicts increased severity of symptoms, higher rate of co-morbidities and increased mortality in the patients with decreased haemoglobin values. But due to lower number of patients in the severe symptomatic group no statistically significant association could be elicited between severity of anaemia and COVID-19 infection (p-value >0.05) in the current study.

A study conducted by Tao Z et al., in August 2020 demonstrated that anaemic patients with COVID-19 had an increased rate of comorbidities, more severe inflammatory responses, and organ damage when compared with the non anaemic controls [30]. Out of the 222 patients enrolled in the study, only 20 were severely symptomatic and 24.2 % of the patients with severe anaemia were moderate to severely symptomatic for COVID-19. However, the study subjects were non pregnant population [30]. Lower number of subjects in the moderate and severe symptomatic COVID-19 inflicted groups could be the reason for the difference of findings in the present study and the study by Tao Z et al., [30]. From the present study authors recommend further studies with higher sample sizes on this topic to assess the impact of anaemia on severity of COVID-19 infection

Around 82.35% of the severe symptomatic COVID-19 participants had >140 mg/dL OGTT and there was a statistically significant association found between COVID-19 status with deranged blood sugar values (p-value=0.00001). These findings were concurrent with the study conducted by Collin J et al., in Sweden in 2020 who found that pregnant women should exercise caution due to the potentially severe implications of SARS-CoV-2 infection, particularly those with additional risk factors such as obesity, hypertension, or gestational diabetes mellitus [31]. Hence, the present study shows a positive association between severity of symptoms of COVID-19 and deranged blood sugar values. A meta-analysis conducted by Huag I et al., in August 2020 found that patients with diabetes mellitus had more severe disease, poorer outcome and higher mortality in COVID-19 [32].

The present study revealed that 76.47% of the severe symptomatic COVID-19 participants had vitamin D deficiency and there was no statistically significant association found between COVID-19 status with vitamin D deficiency. Jain A et al., in their study refuted the results presented in the study as they depicted a strong difference in vitamin D levels and severity of the COVID-19 symptoms. But the study population included non pregnant patients. No studies assessing the impact of vitamin D deficiency on severity of COVID-19 have been performed in pregnant population as yet. Hence, the author recommends further research on this topic [33].

A statistically significant association was found between COVID-19 status with health determinant parameters like total protein and A/G ratio. Hypoproteinaemia is related with elevated inflammatory cytokines, prolonged Activated Partial Thromboplastin Time (APTT) and prothrombin time and deranged D-dimer values as a result of liver damage caused by hypercytokinaemia. These findings are in concurrence with the findings of Huang J et al., study where they compared the outcome of COVID-19 in patients with and without hypoalbuminaemia and found that patients with hypoalbuminaemia had a higher mortality rate (13.2%) as compared to patients with normal albumin (1%) [34].

A statistically significant relation was found between adverse pregnancy outcomes and severity of COVID-19. 11.76% severe symptomatic patients presented to us miscarriage. In patients with COVID-19 infection, Villar J et al., observed increased rates of pregnancy-induced hypertension, preeclampsia/eclampsia, sepsis as well increased admission to ICU [27]. Wong SF et al., in the case series on pregnant women with COVID-19 reported an overall case fatality rate of 25% and 57% patients who presented to him in the first trimester had spontaneous miscarriage [35].

Preterm delivery was attributed to both obstetric reasons (abnormal Cardiotocography (CTG), doppler changes, Oligohydramnios) and due to COVID-19 infection. Wong SF et al., in the study on pregnancy and perinatal outcomes in women with severe acute respiratory syndrome found that out of five pregnant women with SARS with period of gestation more than 24 weeks, four underwent preterm delivery, and intrauterine growth restriction was observed in them despite their recovery before delivery [35].

Total 14 out of 260 (5.38%) patients enrolled in the present study, developed Multi Organ Dysfunction Syndrome (MODS) and ultimately died. A study conducted by Takemoto MLS et al., reported that pregnant women who had COVID-19 were 22 times more likely to die than pregnant women who did not have COVID-19 infection. Total 11 out of 706 (1.6%) women with COVID-19 diagnosis died in his study. Four of these women had severe preeclampsia, out of these four, three had respiratory failure and the fourth developed pulmonary embolism. Five women developed severe respiratory failure antenatally, two of whom had caesarean deliveries and died despite extensive respiratory assistance. The remaining two women's symptoms worsened within 7 days of an uncomplicated delivery and they died soon after, despite ICU care [36].

From present study it is clearly obvious that maternal obesity with impaired glucose tolerance, hypoproteinaemia could directly impair the maternal defence system thereby leading to severe COVID-19 infection. The severity of COVID-19 may lead to increased rate of abortions, IUDs, more chances of hypertension in pregnancy, Preterm delivery and high chances of ICU admissions. This research brings new insight into association between maternal nutritional status and adverse pregnancy outcomes with COVID-19 infection.

Limitation(s)

In present study factors such as Heamoglobin and Vitamin D levels could not be assessed in detail due to lower sample size.

CONCLUSION(S)

Hence, the study shows that maternal nutrition status affects the severity of symptoms in COVID-19 and adversely affects the maternal obstetric outcome in pregnancy. The factors positively affecting the maternal nutrition status were BMI, deranged blood sugar levels and protein levels of the patient.

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