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Original Research Article

Comparison of Mean Serum Ferritin Levels between Non-severe and Severe COVID-19 Infection Groups During Third Trimester of Pregnancy

Dr. Kazi Sanzida Haque[1*], Prof. Dr. Tripti Rani Das[2], Dr. Shah Noor Sharmin[3], Dr. Rakiba Sultana[4], Dr. Mossa. Nupur Aktar[5], Dr. Marfoonnahar Smriti[6], Dr. Tasnim Binte Ahmed[7], Dr. Sabikun Naher Urmy[8]

[1]Resident Surgeon, Department of Obstetrics & Gynaecology, Cumilla Medical College Hospital, Cumilla, Bangladesh
[2]Professor, Department of Obstetrics & Gynaecology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[3]Medical Officer, Department of Obstetrics & Gynaecology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh
[4]Residential Medical Officer, Birolpolita 20 Bed Hospital, Magura Sadar, Magura, Khulna, Bangladesh
[5]Assistant Registrar, Department of Obstetrics and Gynaecology, Shaheed M. Monsur Ali Medical College Hospital, Sirajganj, Bangladesh
[6]Registrar, Department of Obstetrics and Gynaecology, Mugda Medical College and Hospital, Dhaka, Bangladesh
[7]Histopathologist, Department of Pathology, Mugda Medical College and Hospital, Dhaka, Bangladesh
[8]Resident Physician, Department of Medicine, Sheikh Sayera Khatun Medical College Hospital, Gopalganj, Bangladesh

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***Corresponding author:** Dr. Kazi Sanzida Haque
Resident Surgeon, Department of Obstetrics & Gynaecology, Cumilla Medical College Hospital, Cumilla, Bangladesh

Abstract

Background: Despite the fact that, ferritin is commonly regarded as a representation of total body iron reserves; its predictive value is also connected to COVID-19 severity. COVID-19 disease can manifest itself in pregnant women in a variety of ways. Comorbid conditions have a significant impact on the progression of COVID-19 severity. Several studies have showed that, serum ferritin level was associated with severity of COVID-19 infection. So, we conducted this study to evaluate the comparison of mean serum ferritin levels between non-severe and severe COVID-19 infection groups during third trimester of pregnancy. ***Objectives:*** The aim of this study is to compare the mean serum ferritin levels between non-severe and severe COVID-19 infection groups in third trimester of pregnancy. ***Methods:*** This cross-sectional study was carried out in Department of Obstetrics and Gynaecology, COVID-19 Unit, BSMMU and DMCH. Sampling method was purposive. Total 154 cases were included in this study after matching eligibility criteria. After collecting intravenous blood, serum ferritin level was measured. ***Results:*** Among 154 cases, 24.7% cases were asymptomatic, 40.3% cases were mild, 24.7% cases were moderate and 10.4% cases were severe COVID-19 infection during third trimester of pregnancy. The non-severe COVID-19 infection group consisted of 100 cases of asymptomatic and mild COVID-19 infected patients, with a mean serum ferritin level of 51.48 ng/ml. The severe COVID-19 infection group consisted of 54 cases of moderate and severe COVID-19 infected patients, with a mean serum ferritin level of 478.37 ng/ml. The independent samples t-test revealed a p-value of ≤0.05 (0.0000000002), when comparing the mean values of these two groups. ***Conclusion:*** Serum ferritin level rises significantly in severe COVID-19 infection during third trimester of pregnancy.

Keywords: Ferritin, COVID-19, Third trimester.

INTRODUCTION

The unique coronavirus disease 2019 (COVID-19), which was first appeared in December 2019 in Wuhan (Hubei, China). It has surprisingly dominated the entire globe, with several countries experiencing the second wave [1]. Cases infected with this severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) frequently present with severe pneumonia and targeted organ injuries involving the liver, heart and kidneys, despite the rapidly evolving clinical course and presentation [2].

With the surging devastating effects of this pandemic, the focus of scientific research was on establishing appropriate therapy regimens to battle the

virus. Meanwhile, early risk stratification techniques and biomarkers to predict disease development and to identify high-risk individuals; at an early stage of infection were desperately needed [3]. This could help to maximize management goals and overcome the scarcity of medical and material resources, which were especially noticeable during this worldwide catastrophe.

The inflammatory cytokine storm, which is associated with severity and mortality, is characterized by the abrupt and excessive release of pro-inflammatory cytokines, including inflammatory cytokines released by macrophages, particularly the interleukins IL-6, IL-10 and tumor necrosis factor (TNF) [4]. With this important event in the pathophysiological pathway in mind, biochemical measurement of plasma inflammatory markers and positive acute phase reactants such as ferritin, could help to predict disease development [5]. Ferritin is found in most tissues as a cytosolic protein, while a mitochondrial version exists and nuclear localization has been hypothesized [6]. Despite being widely recognized as a representative of total body iron stores, its prognostic utility is associated with acute and chronic inflammatory processes, and it is nonspecifically elevated in a variety of such disorders, including chronic kidney disease, rheumatoid arthritis, autoimmune disorders, and among others [7].

COVID-19, a disease caused by SARS-CoV-2, is highly contagious and causes death worldwide. Early findings in pregnant women have showed that, the clinical course of COVID-19 is often mild (86%), severe (9%) or critical (5%); similar to the clinical course distribution reported in the non-pregnant population [8]. Infections with SARS-CoV-2 appear to generate significant lung symptoms such as pneumonia, acute respiratory distress syndrome, pervasive micro-emboli and coagulation disruptions. As a result, an increase in morbidity and mortality among pregnant women is a legitimate cause for concern. Pregnancy-related physiological changes such as hypercoagulation, changes in cell-mediated immunity [9], lower lung capacity and pulmonary secretion clearance may enhance both the susceptibility and clinical severity of pneumonia. Common pregnancy associated symptoms, such as physiological dyspnea, may delay a diagnosis if pathologic dyspnea due to COVID-19 is not recognized. Diabetes, hypertension, arrhythmia, gestational diabetes and hypertension, pre-eclampsia are all comorbid illnesses that increase morbidity and mortality. However, it was unclear, if the current scenario was caused by the clinical course of COVID-19 disease or an underlying comorbid condition [10].

In earlier investigations, many laboratory indicators were explored to better understand the pathophysiology of the disease and to assess how these markers play a role during the COVID-19 process [11]. Furthermore, recent studies have showed that, patients with COVID-19 had lower hemoglobin levels and higher ferritin levels. Ferritin levels were pathologically high in 5,700 patients hospitalized for COVID-19 in a study conducted in the United States of America (USA) [12]. Anemia associated with high ferritinemia is a significant risk factor for death, regardless of the underlying diseases. Elevated ferritin levels in COVID-19 may anticipate an impending inflammatory response or be connected with viral spread in the human body and impact iron metabolism. In this regard, iron is an important micronutrient for both human cells and pathogens. The natural immune response may decrease iron turnover during infections to limit the pathogen's utilization of it. This mechanism, however, can also result in anemia, which limits oxygen transport to tissues and leads to multi-organ failure [13]. As a result, we believe, it is critical to investigate the relationship between iron metabolism and COVID-19 development. The purpose of this study is to see, if ferritin levels can predict the severity of COVID-19 infection during third trimester of pregnancy.

METHODOLOGY

This cross-sectional study was carried out in the Department of Obstetrics and Gynecology, COVID-19 Unit, Bangabandhu Sheikh Mujib Medical University (BSMMU) and Dhaka Medical College Hospital (DMCH), Dhaka. This study was conducted from March 2021 to February 2022. Total 154 pregnant women during third trimester of pregnancy with COVID-19 infection were included in this study. After taking consent and matching eligibility criteria, data were collected from patients on variables of interest using the predesigned structured questionnaire by interview and observation. Statistical analyses of the results were be obtained by using window-based Microsoft Excel and Statistical Packages for Social Sciences (SPSS-24).

RESULTS

Table-1: Socio-demographic characteristics of study subjects

Pregnancy with COVID-19 infection			
Age Range (Years)	**Frequency (n)**	**Percentage (%)**	**Mean± SD**
18 – 25	54	35.1	27.36±5.00
26 – 30	64	41.6	
31 – 35	30	19.5	
36 – 40	6	3.9	
Total	**154**	**100**	

Pregnancy with COVID-19 infection			
Age Range (Years)	**Frequency (n)**	**Percentage (%)**	**Mean± SD**
Parity			
Nullipara	60	39	
Primipara	58	37.7	
Multipara	34	22.1	
Grand multipara	2	1.3	
Total	**154**	**100**	

[Nullipara (pregnancy never reached age of viability), primipara (1 viable pregnancy), multipara (2-3 viable pregnancy) and grand multipara (4 or more viable pregnancy)]

Table 2: Body Mass Index (BMI) of study subjects

BMI (kg/m2)	Classification	Frequency (n)	Percentage (%)	Mean± SD
<18.5	Underweight	2	1.3	26.93±3.99
18.5 – 24.9	Normal	52	33.8	
25 – 29.9	Overweight	60	39	
30 – 34.9	Obesity, class I	38	24.7	
35 – 39.9	Obesity, class II	2	1.3	
Total		**154**	**100**	

Table 3: Study subjects according to gestational age

Term/ Preterm pregnancy	Gestational age (Weeks)	Frequency (n)	Percentage (%)	Mean± SD
Term Pregnancy	**37-42**	**66**	**42.9**	
Preterm pregnancy	**28 - 36^{+6}**	**88**	**57.1**	34.75±3.55
Very preterm	28 – 31^{+6}	32	20.8	
Late preterm	32 - 36^{+6}	56	36.3	
Total		154	100	

Table 4: Study subjects according to severity of COVID-19 infection

Symptomatic or asymptomatic	Frequency (n)	Percentage (%)
Asymptomatic	**38**	**24.7**
Symptomatic	**116**	**75.3**
Mild	62	40.3
Moderate	38	24.7
Severe	16	10.4
Total	**154**	**100**

Table 5: Mean serum ferritin levels in non-severe and severe COVID-19 infected groups

Severity of COVID- 19 infection	n	Mean Serum ferritin level (ng/ml)	SD	P value
Non-severe group (Asymptomatic & mild COVID-19)	100	51.48	46.53	0.0000000002
Severe group (Moderate & severe COVID-19)	54	478.37	408.18	
Total	**154**			

P value reached from independent samples t-test

DISCUSSION

Jie Yan *et al.*, [14] found fever in 50.9% of pregnant women, cough in 28.4%, and dyspnea in 7.8%, with only 6.9% of them being severe. Delahoy *et al.*, [15] examined 598 pregnant women's surveillance data and discovered fever in 59.6% and coughing in 52%. According to Mohr Sasson *et al.*, [16], 54.5% of 11 pregnant women had respiratory symptoms, while 27% had fever, and respiratory symptoms were more common than fever. However, in the preceding investigations, admission symptoms were not assessed after clinical classification. Pierce-Williams *et al.*, [17] also reported application clinical symptoms of 44 severe and 20 critical pregnant women, with an average of 7 days between the beginning of symptoms and hospital application.

In this present study, according to socio-demographic factors, 41.6% of cases are between the ages of 26-30, 35.1% are between the ages of 18-25, 15% are between the ages of 31-35 and 3.9% are between the ages of 36-40. The average age was 27.36

years. 39% are nullipara, 37.7% are primipara, 22.1% are multipara, and 1.3% are grand multipara. According to Body Mass Index (BMI), 39% were overweight, 33.8% were normal BMI, 24.7% were class-I obesity, and 1.3% were both underweight and class-II obesity. The average BMI was 26.93 kg/m2.

Fever and respiratory symptoms are typical COVID - 19 symptoms, but uncommon symptoms include GIS (abdominal pain, diarrhoea, and nausea-vomiting) and symptoms and indicators of brain involvement [18]. This was an interesting finding because fever, which is a common symptom of COVID-19 during the pandemic time, was not present in pregnant admissions, indicating that the clinic could be severe. The absence of fever in pregnant women in the severe group can be explained by an increase in immune suppression and a decrease in fever response in tandem with an increase in illness severity in immunocompromised pregnant women [19]. It was emphasized that dyspnea, tachypnea and low peripheral oxygen saturation are essential criteria in determining illness severity and may be used to predict the need for intensive care. A single-center investigation found that data such as heart rate, respiration rate and mean arterial pressure did not differ among ICU patients, and the patient did not require intensive care [20].

In our study, depending to the gestational age, preterm pregnancies accounted for 57.1% of all instances, with 20.8% being very preterm and 36.3% being late pregnancies. 42.9% of the cases were full-term pregnancies. The average gestational age was approximately 34 weeks. In addition, the severity of COVID-19 infection, asymptomatic cases made up 24.7% of the total; 75.3% of cases had symptomatic COVID-19 infection, with 40.3% having mild, 24.7% having moderate, and 10.4% having severe COVID-19 infection.

Yuming *et al.*, [21] observed that the primary laboratory findings in 146 pregnant women were lymphopenia and increased CRP, with 5.5% having severe cases. Scott *et al.*, [26] investigated 69 COVID-19 positive pregnant women, 15 of whom required respiratory assistance, and found that the lymphocyte rate was lower in those who needed respiratory support, but the WBC, neutrophil, and PLT rates were comparable. CRP levels were raised in 63 individuals during their hospitalization, although there was no statistically significant difference between groups. Andrikopoulou *et al.*, [22] found that ferritin and leucopenia levels were considerably higher in moderate or severe illness groups, while differences in ALT, AST, LDH, IL-6, CREA, platelets, lymphocytes and D-dimer levels were not statistically significant.

In a multicenter study in France, 617 COVID-19 infected pregnant women classified as 79.2% non-severe, 15.2% receiving respiratory support (receiving nasal oxygen and/or mechanical ventilation support) and 5.6% critical group (receiving invasive mechanical ventilation or ECMO) were examined. The severity of the disease was found to be associated with the presence of over 35 years of age and comorbid conditions. In the neonatal nasal COVID-19 RT-PCR test screening, only two newborns had the test positive. While there was no COVID-19-related neonatal death, a mother who was followed in the ICU in the critical form group was lost due to COVID-19 [23, 24].

Our study suggests that, according to mean serum ferritin levels in non-severe and severe COVID-19 infected groups; the non-severe COVID-19 infected group consisted of 100 cases of asymptomatic and mild COVID-19 infected patients, with a mean serum ferritin level of 51.48 ng/ml. The severe COVID-19 infected group consisted of 54 moderate and severe COVID-19 infected patients, with a mean serum ferritin level of 478.37 ng/ml. The independent samples t-test revealed a p-value of ≤ 0.05 (0.0000000002), when comparing the mean values of these two groups. There was a significant link between an increase in serum ferritin level and the severity of COVID-19 infection during the third trimester of pregnancy. Similar to Tanacan *et al.*, (2021) and Chen *et al.*, (2021), who discussed about significant association of serum ferritin level with COVID-19 infection during pregnancy [25, 26].

Limitations of the study

The present study was conducted in a very short period due to time constraints and funding limitations.

CONCLUSION

Serum ferritin level rises significantly in severe COVID-19 infection during third trimester of pregnancy.

RECOMMENDATION

This study can serve as a pilot to much larger research involving multiple centers that can provide a nationwide picture, validate regression models proposed in this study for future use and emphasize points to ensure better management and adherence.

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