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Association of Serum Ferritin Level with Severity of COVID-19 Infection During Third Trimester of Pregnancy

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Abstract **Original Research Article**

Background: World has been passing through COVID-19 pandemic by a newly emergent coronavirus named SARS-CoV-2 since December 2019 and officially declared as a pandemic by WHO on 11th March 2020. Till mid-March 2022, around 460 million people already suffered from COVID-19, among them around 6 million people died and globally death rate was 2%. In Bangladesh till mid-March 2022, around 1.9 million people suffered from COVID-19 and around 29 thousand people had died. As pregnancy is a physiological immunosuppressive state, so pregnant women might be more susceptible to this infection. Studies on COVID-19 during pregnancy have showed, this infection occurred more during third trimester of pregnancy (about 64%). Reviewing several other studies on COVID-19 infection we found that, elevated serum ferritin level was associated with its severity; and ferritin could effectively discriminate severity and non-severity with sensitivity 96% and specificity 70%. We conducted this study to evaluate association of serum ferritin level with severity of COVID-19 infection during third trimester of pregnancy. ***Objectives:*** To evaluate association between rise of serum ferritin level and severity of COVID-19 infection during 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 77 cases were included in this study after matching eligibility criteria. After collecting intravenous blood, serum ferritin level was measured. ***Results:*** Among 77 cases of third trimester COVID-19, 19 cases (24.7%) were asymptomatic, 31 cases (40.3%) were mild, 19 cases (24.7%) were moderate and 8 cases (10.4%) were severe COVID-19. Non-severe COVID-19 group included 50 cases of asymptomatic & mild COVID-19; and their mean serum ferritin level was 51.48 ng/ml. Severe COVID-19 group included 27 cases of moderate & severe COVID-19; and their mean serum ferritin level was 478.37 ng/ml. Comparison between mean values of these two groups showed p-value ≤0.05 (0.0000000002), reached from independent samples t-test. ***Conclusion:*** Current study concluded that, rise of serum ferritin level is significantly associated with severity of COVID-19 infection during third trimester of pregnancy.

Keywords: Serum Ferritin, COVID-19 infection, third trimester of pregnancy.

INTRODUCTION

World has been passing through COVID-19 pandemic, a global public health emergency by a newly emergent coronavirus named SARS-CoV-2, since December 2019; started from Wuhan, China [1]. It has officially declared as a pandemic on 11th March 2020 by WHO [2]. Till mid-March 2022, around 460 million people already suffered from COVID-19, among them around 6 million people died (Worldometer 2022) and globally death rate was 2% [5]. In Bangladesh, SARS-CoV-2 infected first case was found on 8th March 2020 in Dhaka [3]. Till mid-March 2022, around 1.9 million Bangladeshi people suffered from COVID-19 and around 29 thousand people died (Worldometer 2022).

SARS-CoV-2 is a member of coronavirus family, which is closely related to SARS-CoV which caused SARS pandemic in 2002-2004. So, this virus was named SARS-CoV-2 accordingly. The disease was named COVID-19 (Coronavirus disease 2019) by WHO. This virus is spherical shaped around 100nm diameter. It consists of capsid (outer protein shell) and inner core containing single-stranded RNA; also contains four kinds of proteins (envelope, membrane, nucleocapsid and spike proteins) and lipid. Due to spike protein this virus looks like a corona. Spike protein binds with angiotensin-converting enzyme-2 (ACE2) receptor on human cells to cause infection. It is a positive-sense RNA virus, as RNA acts as mRNA for protein synthesis [4].

SARS-CoV-2 virus spreads from person to person via respiratory droplets and aerosols. It binds via its spike protein to angiotensin-converting enzyme-2 (ACE2) receptor located on type-II alveolar cells, intestinal epithelium and vascular endothelium [1]. This illness is usually a disease of acute resolved but it can also be fatal with 2% mortality rate. Death is due to massive alveolar damage and progressive respiratory failure [5]. There may also hypercoagulability and disseminated intravascular coagulation (DIC) due to direct endothelial injury by virus or by persistent systemic inflammation. Some patient may experience cytokine storm which is also a cause of fatality. About 5-15% of all patients with COVID-19 infection may progress to severe or critical illness requiring intensive care. [1] Co-morbidities like diabetes mellitus, hypertension, cardiovascular diseases, chronic respiratory disease, cancer etc. may be associated with severity of this infection [6].

Pregnancy is a physiological immunosuppressive state to tolerate intra-uterine allogenic fetal tissue, where cell-mediated cytotoxic immune response modulated towards increased humoral and innate immune responses [7]. So pregnant women might be more susceptible to this infection [8]. Study on COVID-19 infection during pregnancy showed in 64% cases, this infection was occurred in third trimester of pregnancy [9].

Several studies on COVID-19 infection showed, elevated serum ferritin level was associated with severity of this infection. Ferritin is an iron storage protein, gives determination of mobilizable stored iron. But as an acute-phase protein, it also could be raised in conditions other than iron storage, such as severe inflammation. Patient with elevated serum ferritin level had a higher incidence of severity of this infection. Cao *et al.,* (2020) discussed serum ferritin could effectively discriminate severity and non-severity with sensitivity 96% and specificity 70% [10]. Another study showed that mild elevation of serum ferritin could occur early prior to pulmonary symptoms [11]. Raised ferritin level was associated with inflammatory states in SARS-CoV-2 infection and therefore, ferritin could be a useful parameter to predict disease severity and the extent of the cytokine storm [12].

Unfortunately till mid-March 2022, limited information was available regarding serum ferritin level in pregnant women with COVID-19 infection. So, the purpose of this study was to evaluate association of rise of serum ferritin level with severity of COVID-19 infection during third trimester of pregnancy. If any association could be found, measurement of serum ferritin level might be used as a simple, effective and less costly test tool in the early stage of COVID-19 infection during pregnancy. Thus, early assumption of case fatality could be possible and early intervention could be initiated to prevent further disease progression and reduction of case fatality could be possible.

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 77 pregnant women during third trimester of pregnancy with COVID-19 infection were included in this study. After taking informed written 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 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	27	35.1	27.36±5.00
26 – 30	32	41.6	
31 – 35	15	19.5	
36 – 40	3	3.9	
Total	77	100	
Parity			

Pregnancy with COVID-19 infection			
Age Range (Years)	**Frequency (n)**	**Percentage (%)**	**Mean± SD**
Nullipara	30	39	
Primipara	29	37.7	
Multipara	17	22.1	
Grand multipara	1	1.3	
Total	77	**100**	

[Nullipara (pregnancy never reached age of viability), primipara (1 viable pregnancy), multipara (2-3 viable pregnancy) & 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	1	1.3	26.93±3.99
18.5 – 24.9	Normal	26	33.8	
25 – 29.9	Overweight	30	39	
30 – 34.9	Obesity, class I	19	24.7	
35 – 39.9	Obesity, class II	1	1.3	
Total		**77**	**100**	

Table 3: Study subjects according to gestational age

Term/ Preterm pregnancy	Gestational age (Weeks)	Frequency (n)	Percentage (%)	Mean± SD
Term Pregnancy	**37-42**	**33**	**42.9**	
Preterm pregnancy	**28 - 36^{+6}**	**44**	**57.1**	34.75±3.55
Very preterm	28 – 31^{+6}	16	20.8	
Late preterm	32 - 36^{+6}	28	36.3	
Total		**77**	**100**	

(Term pregnancy, Preterm pregnancy, very preterm, late preterm) [13]

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

Symptomatic or asymptomatic	Frequency (n)	Percentage (%)
Asymptomatic	**19**	**24.7**
Symptomatic	**58**	**75.3**
Mild	31	40.3
Moderate	19	24.7
Severe	8	10.4
Total	**77**	**100**

(Mild, moderate, severe COVID-19) [14]

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

Severity of COVID- 19 infection	n	Mean Serum ferritin level (ng/ml)	SD	P value
Non-severe group (Asymptomatic & mild COVID-19)	50	51.48	46.53	0.0000000002
Severe group (Moderate & severe COVID-19)	27	478.37	408.18	
Total	**77**			

(Mild, moderate, severe COVID-19) [14]
P value reached from independent samples t-test

DISCUSSION

Currently world has been passing through a pandemic called COVID-19 since December 2019, caused by a newly emergent coronavirus named SARS-CoV-2 causing respiratory tract infection [1]. Pregnancy is a physiological immunosuppressive state to tolerate intra- uterine allogenic fetal tissue [7]. So, pregnant women might be more susceptible to this infection [8]. During pregnancy, COVID-19 infection found more at third trimester of pregnancy about 64% with median gestational age 32 weeks [9]. So, this study was conducted in pregnant women during third trimester of pregnancy with COVID-19 infection admitted in Department of Obstetrics & Gynaecology (COVID-19 unit), BSMMU & DMCH.

In this study, 77 pregnant women during third trimester of pregnancy with COVID-19 infection were enrolled according to inclusion and exclusion criteria.

Socio-demographic characteristics showed, 41.6% cases were in 26-30 years, 35.1% cases were in 18-25 years, 15% cases were in 31-35 years and 3.9% cases were in 36-40 years. Mean age was 27.36 years. Parity showed, 39% cases were nullipara (pregnancy never reached age of viability), 37.7% cases were primipara (1 viable pregnancy), 22.1% cases were multipara (2-3 viable pregnancy) and 1.3 % cases were grand multipara (4 or more viable pregnancy).

Body Mass Index (BMI) showed, 39% cases were overweight, 33.8% cases were from normal BMI, 24.7% cases were from class-I obesity, 1.3 % cases were both from underweight and class-II obesity. Mean BMI was 26.93 (kg/m2).

Gestational age showed, 57.1% cases were preterm pregnancies; where 20.8% cases were very preterm and 36.3% cases were late preterm pregnancies. 42.9% cases were term pregnancies. Mean gestational age was around 34 weeks.

Here severity of COVID-19 infection showing, 24.7% cases were asymptomatic COVID- 19 infection. 75.3% cases were symptomatic COVID-19 infection, among them 40.3% cases were mild, 24.7% cases were moderate and 10.4% cases were severe COVID-19 infection. Similarly, [15] found 25% COVID-19 infection during pregnancy were asymptomatic, 50% cases were mild, 38.9% cases were moderate and 11.1% cases were severe COVID-19 infection.

Total 77 COVID-19 infected pregnant women during third trimester cases were enrolled in two groups; non-severe and severe COVID-19 groups. Mean serum ferritin levels of both groups were measured. Non-severe COVID-19 group included 50 cases of asymptomatic & mild COVID-19 cases and mean serum ferritin level was 51.48 ng/ml. Severe COVID-19 group included 27 moderate & severe COVID-19 infected cases and mean serum ferritin level was 478.37 ng/ml. Comparison between mean values of these two groups showed P value ≤ 0.05 (0.0000000002), reached from independent samples t-test. There is significant association between rise of serum ferritin level and severity of COVID-19 infection during 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 [15, 16].

Limitations of the study

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

CONCLUSION

Current study concluded that, rise of serum ferritin level is significantly associated with severity of COVID-19 infection during third trimester of pregnancy. So, measurement of serum ferritin level may be used as a simple, effective and less costly test tool in the early stage of COVID-19 infection during pregnancy. Thus, early assumption of case fatality could be possible and early intervention could be initiated to prevent further disease progression and reduction of case fatality could be possible.

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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