ORIGINAL RESEARCH

Comparison of Inflammatory Parameters in Coronavirus Disease 2019-infected Pregnant Women and Age-matched Nonpregnant Women

Deepika Naidu[1], Meena Priyadharshini[2], Krithika V Senthilkumar[3], Usha Sekkizhar[4], Jeevithan Shanmugam[5]

Abstract

Aim: This study aims to compare inflammatory parameters in coronavirus disease-2019 (COVID-19)-infected pregnant women and age-matched nonpregnant women.

Materials and methods: It was a cross-sectional study, and data were collected retrospectively. Pregnant women (cases) with COVID infection admitted to the hospital between July 2020 and December 2020 were included in the study. Age-matched nonpregnant women who were also COVID-positive were taken as controls. Their demographic data, comorbidities, and inflammatory markers were compared. The results were compared using descriptive analysis (clinical profile and outcome of patients). Bivariate analysis was done using Chi-square/Fischer exact test; *t*-test was used to compare the mean biochemical/pathological parameters between the groups. The clinical outcomes (intensive care unit [ICU] admission, O_2 requirement, and mortality) were also noted.

Results: A total of 228 women (116 pregnant and 112 nonpregnant) were enrolled in the study. The average age of cases was 27 years, while that of controls was 29 years. There was no statistically significant difference in the incidence of comorbidities (anemia, hypertension, diabetes mellitus, asthma, and hypothyroidism) between the two groups. Compared to the controls, pregnant women did not have any significant difference in the levels of D-dimer, lactate dehydrogenase, and serum ferritin, but there were significant differences ($p < 0.05$) in the values of total count neutrophils, lymphocytes, interleukin-6, and international normalized ratio. We did not have any mortality in either group, and only one patient from the study group needed ICU admission.

Conclusion: We were able to point out the inflammatory markers that were significantly altered in COVID-positive pregnant women. The markers may help us understand the severity and clinical outcome of the disease better in the future, so that appropriate preventive measures can be taken.

Clinical significance: From our study, we were able to identify the markers that were significantly altered due to COVID-19 infection in pregnant women. These markers may play a role in predicting the outcome of the disease and help in deciding an effective treatment plan.

Keywords: Coronavirus disease-2019, Cross-sectional study, Interleukin-6, Inflammatory markers, International normalized ratio, Lymphocytes, Neutrophil, Pregnant, Pregnant vs nonpregnant.

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Introduction

The coronavirus disease-2019 (COVID-19), which is caused by SARS-CoV-2, was discovered in 2019. The first case of COVID-19 was reported in Wuhan, China, in December 2019. As of June 2021, over 177 million people have been infected leading to over 3.8 million deaths worldwide. It was declared an international public health emergency on January 30, 2020, by the World Health Organization (WHO).[1]

The physiological changes during pregnancy make a woman more susceptible to serious infections.[2] Maternal resistance to hypoxia is reduced due to anatomical changes such as increase in the transverse diameter of the thoracic cage and an elevation of the diaphragm.[3] A pregnant women's immunity is reduced, putting them at risk of contracting COVID-19. Pneumonia is an important cause of morbidity and mortality among pregnant women.[4] In addition, hypertension and diabetes, the most common complications occurring during pregnancy, have chronic negative health effects on both mothers and their babies.[5] Thus, pregnant women are considered in the high-risk group during the current COVID-19 pandemic.[6]

COVID-19-infected patients show abnormal laboratory test results as it causes a significant inflammatory state (cytokine storm). This inflammatory response maybe proportional to the severity of the disease. To date, most studies[7,8] on COVID-19-infected pregnant women describe their clinical characteristics like symptoms, maternal and fetal outcomes, CT findings, and mother-child transmission, and there are fewer studies assessing pregnant women with COVID-19 with comorbidities. The purpose of this study was to compare inflammatory markers among pregnant COVID-19 patients and age-matched control groups of COVID-19-positive nonpregnant

[1–3]Department of Obstetrics and Gynecology, KMCH IHSR, Coimbatore, Tamil Nadu, India

[4]Department of Medicine, KMCH IHSR, Coimbatore, Tamil Nadu, India

[5]Department of Community Medicine, KMCH IHSR, Coimbatore, Tamil Nadu, India

Corresponding Author: Deepika Naidu, Department of Obstetrics and Gynecology, KMCH IHSR, Coimbatore, Tamil Nadu, India, Phone: +91 9789860408, e-mail: dr.naidudeepika@gmail.com

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women. The clinical outcomes among these patients were also studied. The parameters taken into account were need for oxygen therapy, intensive care unit (ICU) admission and mortality.

Materials and Methods

This cross-sectional retrospective study was carried out among pregnant women admitted in our hospital during the period between July 2020 and December 2020. Our hospital, Kovai Medical College and Hospital (Institute of Health Sciences and Research), is a 750-bed Medical College and General Hospital in Tamil Nadu. All pregnant women who were confirmed to be COVID-19 positive were taken as "cases." Age-matched nonpregnant women who tested positive for COVID-19 were taken as "controls." A total of 228 patients were recruited for the study.

After Institutional Human Ethics Committee approval, data from the medical records of the patients were entered and analyzed using a semi-structured questionnaire which contained the following data:

- Demographic data including name, age, residential address
- History of known medical or surgical illness
- Obstetric history including gravid status, coexisting obstetric complications (in pregnant cases)
- Patient's vital signs at the time of admission—pulse rate, blood pressure, oxygen saturation (SpO_2), and respiratory rate
- Hematological and inflammatory parameters on the day of admission—hemoglobin (Hb), white blood cell count (WBC), differential leukocyte count (DLC), platelet count (PLT), D-dimer, international normalized ratio (INR), interleukin 6 (IL-6), lactate dehydrogenase (LDH), serum ferritin, and C reactive protein (CRP)
- Clinical outcome of the disease—oxygen requirement, ICU admissions, and mortality

The above-mentioned tests are routinely performed in our institution as a part of COVID-19 protocol, so no patient was excluded for insufficient data. Patients who were COVID-19 negative were excluded from the study. Most of the patients were asymptomatic and were found to be COVID-19 positive when the test was done routinely before planning delivery or if the patient came in labor. The blood tests were done on the day of admission.

Statistical Analysis

The data collected were analyzed using SPSS software version 26. Descriptive analysis was done for clinical profile and outcome of patients. Bivariate analysis was done using Chi-square/Fischer exact test; *t*-test was used to compare the mean biochemical/pathological parameters between both groups. $p < 0.05$ was considered to be statistically significant.

Results

A total of 228 patients were included in the study. Pregnant women with COVID positivity were 116 in number and were taken as "cases." Age-matched nonpregnant COVID-positive women were taken in the "control" group. One-hundred and twelve women were in this group.

Age: For both case (study) and control groups, patients between the ages of 20 and 40 years were taken. The average age in the study and controls group were 27.6 (SD ± 3.8) years and 29.8 (SD ± 6.4), years respectively.

The average systolic blood pressure in the study group was 111.9 mm Hg, whereas in the control group, it was 111.1 mm Hg. The mean diastolic blood pressure was 71.7 mm Hg (study) and 71.3 mm Hg (controls). The average pulse rate was 89.6 and 87.9 in the study and control groups, respectively. The mean oxygen saturation in both groups was at 98%. There was no statistically significant difference between the two groups in terms of blood pressure, pulse rate, and saturation rate. Only the respiratory rate showed a significant difference with a *p* value of <0.001 (21.2 vs 18.9) (Table 1).

The prevalence of anemia among the study group was 16.4% (19/116). Diabetes and hypertension were seen in 25% (29/116) and 5.2% (6/116), respectively. Hypothyroidism was seen in 21.6% (25/116), and 0.9% (1/116) suffered from asthma. In the control group, anemia was seen in 23.2% (26/112) and hypothyroidism in 6.3% (7/112). The percentage of patients suffering from diabetes, hypertension, and asthma was 3.6% (4/112) each. The difference in the prevalence of diabetes mellitus and hypothyroid between the groups was significant. There was no difference in the prevalence of anemia, hypertension, and asthma (Table 2).

While comparing the inflammatory markers in both the groups, the following results were noted. The mean white blood cell count in the groups was 9,530.5 (study) and 5,949.1 (controls). There was a statistically significant difference between the groups ($p = 0.002$). Similarly, there was a significant difference in the neutrophil and lymphocyte count in both the groups [(neutrophils: 72.8 vs 60.4%; lymphocytes: 21.4 vs 32.3%)]. The *p* value for both these parameters was <0.001. The interleukin-6 levels also showed a difference that was statistically significant with *p* value of 0.044. The mean value in the study group was 7.3 pg/mL and 5.4 pg/mL among the controls. The INR value showed a significant difference with *p* value <0.001 (1.02 vs 1.04).There was no statistically significant difference in the D-dimer (1.67 vs 0.65), LDH (224.84 vs 225.34), and serum ferritin (63.74 vs 58.34) values between the two groups (Table 3).

Of all the patients included in the study, only one patient (0.8%) needed ICU care. She was a term-pregnant patient with

Table 1: Comparison of vital parameters in both groups

Vital signs	*Study group*	*Control group*	*p value*	*Sig.*
Systolic blood pressure	111.9 ± 9.64	111.1 ± 8.97	0.448	0.504
Diastolic blood pressure	71.7 ± 7.8	71.3 ± 7.7	0.390	0.533
Pulse rate	89.6 ± 8.7	87.9 ± 10.6	2.780	0.097
Respiratory rate	21.2 ± 0.8	18.9 ± 2.6	71.195	<0.001
SpO_2	98 ± 1.2	98 ± 1.1	0.003	0.954

p <0.05 is significant, *p* <0.001 is highly significant

Table 2: Comparison of prevalence of comorbidities in both groups

Condition	*Study group N (%)*	*Control group N (%)*	*Chi-square value*	*p value*
Anemia	19 (16.4%)	26 (23.2%)	1.680	0.244
Diabetes mellitus	29 (25%)	4 (3.6%)	21.137	<0.001
Hypertension	6 (5.2%)	4 (3.6%)	0.348	0.749
Hypothyroid	25 (21.6%)	7 (6.3%)	11.058	0.001
Asthma	1 (0.9%)	4 (3.6%)	1.950	0.207

p <0.05 is significant, *p* <0.001 is highly significant

Table 3: Comparison of inflammatory markers in both groups

Parameters	*Study group*	*Control group*	*t value*	*p value*
White blood cells	9530.51 ± 2857.25	5949.10 ± 2238.80	9.872	0.002
Neutrophils	72.80 ± 6.95	60.49 ± 11.84	27.453	<0.001
Lymphocytes	21.40 ± 6.46	32.39 ± 10.84	28.691	<0.001
IL-6	7.30 ± 12.40	5.41 ± 5.01	4.116	0.044
D-dimer	1.67 ± 1.06	0.65 ± 1.04	2.983	0.085
LDH	224.84 ± 67.97	225.34 ± 51.73	0.151	0.698
Ferritin	63.74 ± 52.24	58.34 ± 63.84	0.649	0.421
INR	1.02 ± 0.05	1.04 ± 0.05	13.396	<0.001

p <0.05 is significant, p <0.001 is highly significant

no comorbidities and presented with persistent fever spikes. The parameters done during the routine work up were within normal limits. She was taken up for emergency cesarean section in view of nonreassuring fetal status. In the immediate postoperative period, she had a fall in saturation to 92%, and heart rate also dropped to 55/minute. She was immediately shifted to ICU and was started on antivirals, anticoagulants, steroids, and oxygen therapy. CT chest had shown 10% lung involvement. Patient's condition improved in 3 days, and she was shifted back to ward in a stable condition. She was discharged 2 days later. No patient in the control group had any adverse outcome.

Discussion

A cross-sectional retrospective study was done on patients admitted in our institution during the period between July 2020 and December 2020. Our study showed that infected pregnant women had significantly higher levels of white blood cell count, neutrophils, interleukin-6, and INR. The lymphocyte count was markedly decreased in pregnant women. These findings were similar to a study by Deng et al.,[9] where they found that inflammatory markers were higher in pregnant COVID-19 patients. Studies have shown that hyperinflammation plays an important role in COVID-19-related mortality and that elevated markers positively correlated with severity of infection.[10]

In our study, we saw that there was a statistically significant difference in the total count and neutrophil count. Chen et al.[7] reported that lymphopenia was present in 51 of 116 COVID-19-infected pregnant women, while Liu et al.[6] found that among 15 pregnant COVID-19 patients, 12 had a decreased lymphocyte count and 10 had increased CRP values. These findings were similar to our study.

Tanacan et al.[11] compared the levels of various cytokines between COVID-19-infected pregnant women and COVID-19-negative pregnant women. They concluded that COVID-19 infection may have an impact on the cytokine profile of pregnant women, and disease severity may depend on cytokine levels. Another study by Sabaka et al.[12] showed that IL-6 may serve as a potential predictor in severe COVID-19 and might also help in identifying patients requiring hospitalization. This was similar to the finding in our study where IL-6 was significantly higher in the infected pregnant women group ($p = 0.044$), but further studies with larger numbers are needed to evaluate the feasibility in using IL-6 as a screening tool for the course of COVID-19 disease.

We found a significantly higher respiratory rate (RR) among pregnant women (21 vs 18). There is not much literature defining a normal RR in nonpregnant and pregnant individuals. Teli et al.[13] and Dennis and Hardy[14] reported a RR of 26 and 18, respectively, in term-pregnant patients. The high RR may be attributed to the anatomical changes that take place during pregnancy, thus causing an increase in the RR.

Blitz et al. and Agarwal et al. from Agra, India,[15,16] showed that there was no significant difference in ICU admissions between pregnant and nonpregnant women with COVID-19. Similarly, in our study, only one patient in the pregnant group needed ICU care (supplemental O_2).

In our study, the inflammatory markers (total count, neutrophils, interleukin-6, and INR) were significantly raised, and lymphocytes were significantly reduced in COVID-19-infected pregnant women when compared to infected nonpregnant women. Multidisciplinary approach helped us in identifying critically ill patients and initiating treatment. But more such studies with larger numbers will be required to assess the usefulness of these markers in predicting the outcome of the patients. Also, the long-term effects of the COVID-19 infection and its treatment needs to be further investigated. The additional complications due to diabetes or hypertension needs to be studied in detail.

Conclusion

The inflammatory markers are significantly raised in pregnant women, in comparison to nonpregnant women. The severity of increase may help the treatment plan and help us be aware of possible complications. Therefore, COVID-19-infected pregnant women should be treated as a high-risk group. A good multidisciplinary approach is essential for positive maternal and fetal outcomes.

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This study has been approved by the hospital's Institutional Human Ethics Committee. Patient privacy was maintained at all times. Written informed consent from patient participants was not needed as per our Institution's guidelines.

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