The Effect of Covid-19 Infection in Early Pregnancy on Hematological Parameters and Miscarriage Rate

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Abstract

Purpose

Based on the fact that Coronavirus Disease 2019 (Covid-19) is associated with many hemocytometric changes, in this clinical trial we aimed to investigate the effect of this underlying inflammatory process on the frequency of miscarriage.

Methods

This is a retrospective cohort study. Patients with laboratory-confirmed Covid-19 infection before the 20th gestational week were determined as the study group. Healthy pregnant women in their early pregnancy were determined as the control group. Hematological parameters of all patients included in the analysis were evaluated.

Results

A total of 176 pregnant women with confirmed Covid-19 infections were evaluated, of which 117 were included in the analysis. 117 healthy pregnant women were determined as the control group. There was no difference between the groups according to demographic characteristics. The median white blood cell (WBC) and lymphocyte levels were lower in patients with Covid-19 infection ($p<0.001$, $p<0.001$). The value of platelet/lymphocyte ratio (PLR) was higher in the group with Covid-19 infection (160.95 vs 132.42, $p<0.001$). It was also determined that the median plateletcrit level was lower in the group with Covid-19 infection ($p<0.001$). The miscarriage rate in the Covid-19 infection group and control group was 14.2% and 9.4%, respectively. ($p=0.220$).

Conclusion

Covid-19 infection presents with low lymphocyte count and plateletcrit values in pregnant women, and an increase in PLR rates in relation to the severity of the disease is observed. Although not statistically significant, Covid-19 infection was associated with increased miscarriage rates in our study.

Introduction

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection, which mainly presents with respiratory system symptoms, has the potential to turn into a multisystem disease and affects pregnant women as well as the entire population. Although it was stated that the effect of the infection on pregnant women at the beginning of the pandemic was similar to the general population, it has been observed that it may progress more severely in pregnant women in the following periods [1, 2].

Studies have shown that there is an increase in the frequency of preterm birth and cesarean section in cases with Coronavirus disease 2019 (Covid-19) infection during pregnancy [3]. The effect of Covid-19

infection on the frequency of abortion is not yet clear. Studies in the literature evaluating the relationship between SARS-CoV-2 infection and abortion risk are mostly in the form of case reports.

Complete blood count is the first laboratory test used in the evaluation of infectious diseases. During the Covid -19 pandemic, the relationship of many hematological parameters with the severity of the disease has been studied [4, 5]. Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), mean platelet volume (MPV), which can be easily reached through routine hematological parameters, are indicators of inflammatory status that have also been studied in obstetric practice [6]. NLR which is studied in the first trimester can give an idea about possible complications in pregnancy [7]. For example, increased NLR was found to be associated with severe preeclampsia, gestational diabetes, gestational cholestasis, hyperemesis gravidarum, early pregnancy loss and preterm labor [8, 9].

There are also studies in the literature investigating the relationship between the platelet indices and the risk of miscarriage [10–12]. Studies have shown that low MPV, lymphopenia, and high PLR are associated with early pregnancy losses [9, 11].

Although there are many studies in the literature on the course of Covid-19 infection in pregnant women, there is a need for good quality studies to illuminate its relationship with early pregnancy complications. Based on the fact that Covid-19 infection is a process that occurs with changes in hematological parameters that support inflammation, we planned to investigate the effect of this underlying inflammatory process on the frequency of miscarriage.

To the best of our knowledge, this is the first study to evaluate the risk of miscarriage in pregnant women with Covid-19 infection under 20 weeks of gestation, along with associated hematological parameters.

Materials And Methods

This is a retrospective cohort study. Pregnant women under 20 weeks of gestation who were evaluated for Covid-19 infection in Bursa City Hospital Gynecology and Obstetrics Department between December 2020 and June 2021 were included in the study. The study was approved by Bursa City Hospital Clinical Research Ethics Committee (Approval number: 2021-11/1). Patients with laboratory confirmed Covid-19 infection before the 20th gestational week were determined as the study group. Laboratory diagnosis of infection was made by real time polymerase chain reaction (RT-PCR) test. Body mass index, obstetric history, and hematological parameters of the patients were examined. In the study, blood samples taken from all study participants at the time of admission were evaluated. Only patients whose hematological parameters could be reached were included in the study. Neutrophil/lymphocyte and platelet/lymphocyte ratios were calculated for all patients included in the analysis. Pregnant women who had a Covid-19 infection before the 20th gestational week were determined as study group (Covid +), pregnant women who did not have a history of Covid-19 infection at <20 weeks as control group (Covid -). Data from 117 patients in both groups were included in the analysis. The patients in both groups were followed up through the hospital database until the 20th gestational week and beyond. Both groups were comparable with respect to demographic parameters. In the subgroup analysis, comparisons were made as the

control group, the inpatient group and the outpatient group. After RT-PCR positivity patients who had miscarriage at the time of admission to the hospital or during hospitalization were considered as miscarriage associated with Covid-19 infection.

Statistical analysis

The Shapiro–Wilk test was used to assess whether the variables followed a normal distribution. Variables were reported as mean±standart deviation and median (minimum:maximum) values. According to the normality test results, Independent samples t-test, Mann–Whitney’s U-test and Kruskal Wallis test were used to compare the groups. Comparison of abortion rates between covid infected and non-infected groups was made using the chi-square test. The relationships between age and hematological measurements were examined by correlation analysis and Spearman correlation coefficient was calculated. Statistical analyses were performed by using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). A p-value of 5% was considered statistically significant for all statistical comparisons.

Results

A total of 176 pregnant women who were confirmed to have Covid-19 infection by Polymerase Chain Reaction (PCR) test for SARS-CoV-2 on combined oropharyngeal and nasopharyngeal swabs were included in the study. 59 patients who did not have blood tests or whose blood tests could not be reached were excluded. 117 healthy pregnant women were determined as the control group (Figure 1). Demographic characteristics of the patients in the study and control groups are shown in Table 1. There was no difference between the groups according to demographic characteristics (Table 1).

Table 1
Demographic characteristics of the patients

	Covid(+) (n=117)	Covid(-) (n=117)	p-value
Age (years)	28(16:40)	27(18:42)	0.786
BMI (kg/m²)	26.03(17.36:44.77)	26.30(18.08:39.51)	0.782
Gestational age at admission	11(5:19)	9(5:18)	0.097
Gravida	2(1:6) (2.36±1.18)	2(1:6) (2.08±1.02)	0.075
Parity	1(0:4)	1(0:3)	0.172
Abortion history	0(0:3)	0(0:2)	0.124
<i>Data were reported as mean ±st. deviation and median(minimum:maximum)</i> <i>a: Mann Whitney U Test</i> <i>Abbreviations: BMI: Body mass index</i>			

The median white blood cell (WBC) level was found to be lower in the group with Covid-19 infection (6570 vs 8920, **p<0.001**). It was also determined that the lymphocyte level was lower in patients with Covid-19 infection (1360 vs. 2010, **p<0.001**). According to the NLR ratio, there was no difference between the groups (p=0.554). The value of PLR differed between the groups, and it was determined that it was higher in the group with Covid-19 infection (160.95 vs 132.42, **p<0.001**). While there was no difference between the groups according to MPV and PDW measurements (p=0.826 and p=0.914, respectively), it was determined that the median PCT level was lower in the group with Covid-19 infection (0.23 & 0.27, **p<0.001**) (Table 2).

Table 2

The effect of Covid-19 infection on hematological parameters

	Covid (+) (n=117)	Covid(-) (n=117)	p-value
WBC	6570(2470:13710)	8920(5040:14650)	<0.001^a
Lymphocyte	1360(220:4170)	2010(640:4080)	<0.001^a
NLR	3.17(0.44:28.73)	3.10(0.98:11.61)	0.554 ^a
PLR	160.95(73.62:1068.18)	132.42(69.77:339.06)	<0.001^a
MPV	10.20(7.5:13.6)	10.20(8.1:13.3)	0.826 ^a
PDW	11.40(8.4:22.4)	11.50(8.2:17.3)	0.914 ^a
PCT	0.23(0.03:0.38)	0.27(0.16:0.49)	<0.001^a
<i>Data were reported as median(minimum:maximum)</i>			
<i>a: Mann Whitney U Test</i>			
<i>Abbreviations: WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-lymphocyte ratio MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit</i>			

As a result of the comparisons made between patients who had a miscarriage and had a Covid-19 infection, and those whose pregnancy ended with a miscarriage but had no Covid-19 infection, the mean WBC level was lower in patients with Covid-19 group (6912.80 vs. 8603.63, **p=0.046**), median lymphocyte level was lower in patients with Covid-19 (1350). vs. 2150, **p<0.001**), median PLR was higher in Covid-19 infected patients (160.95 vs. 134.36, **p=0.038**) and median PCT level was lower in Covid-19 patients (0.23 vs. 0.29, **p=0.004**). There was no difference between the groups in terms of NLR, MPV and PDW levels (**p>0.05**) (Table 3).

Table 3

The effect of Covid-19 infection on hematological parameters in patients whose pregnancy ended with miscarriage

	Covid (+) (n=25)	Covid (-) (n=11)	p-value
WBC	6912.80±2202.33	8603.64±2373.38	0.046^b
Lymphocyte	1350(300:4170)	2150(1470:2830)	<0.001^a
NLR	4.07(1.32:28.73)	2.17(1.74:4.35)	0.054 ^a
PLR	160.95(73.62:670)	134.36(87.5:214.97)	0.038^a
MPV	10.2(9.2:13.6)	11(9.5:11.4)	0.068 ^a
PDW	11.3(9.2:22.4)	12.9(10.1:16.4)	0.068 ^a
PCT	0.23(0.03:0.38)	0.29(0.22:0.43)	0.004^a
<p><i>Data were reported as mean ±st. deviation and median(minimum:maximum)</i></p> <p><i>a: Mann Whitney U Test, b: Independent sample t-Test</i></p> <p><i>Abbreviations: WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-lymphocyte ratio MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit</i></p>			

In the subgroup analysis, it was determined that the median WBC levels of the outpatient and inpatient groups were lower than the patients who did not have Covid-19 infection (**p<0.001** and **p<0.001**, respectively). Lymphocyte values also differed between groups (**p<0.001**). In the subgroup analysis, it was determined that the median lymphocyte levels of the outpatient and inpatient groups were lower than the patients who did not have Covid-19 infection (**p<0.001** and **p<0.001**, respectively). It was determined that the median PLR values of the outpatient and inpatient groups were higher than the patients who did not have Covid-19 infection (**p=0.008** and **p<0.001**, respectively). Again, in the subgroup analysis, it was determined that the median PCT levels of the outpatient and inpatient groups were lower than the patients who did not have Covid-19 infection (**p=0.001** and **p<0.001**, respectively). On the other hand there was no difference in terms of NLR ratio, MPV and PDW levels between the groups (p>0.05) (Table 4).

Table 4

Relationship between disease severity and hematological parameters

	Covid (+)			
	Covid (-) (n=117)	Outpatient (n=62)	Inpatient (n=55)	p-value ^c
WBC	8920(5040:14650)	6640(2470:11950)	6140(2950:13710)	<0.001
Lymphocyte	2010(640:4080)	1520(220:3210)	1260(300:4170)	<0.001
NLR	3.10(0.98:11.61)	2.98(0.69:26.84)	3.42(0.44:28.73)	0.392
PLR	132.42(69.77:339.06)	153.77(79.66:1068.18)	176.55(73.62:709.09)	<0.001
MPV	10.20(8.1:13.3)	10.3(8.8:13.6)	10.1(7.5:12.5)	0.570
PDW	11.50(8.2:17.3)	11.35(8.9:22.4)	11.6(8.4:17.1)	0.991
PCT	0.27(0.16:0.49)	0.24(0.03:0.37)	0.23(0.1:0.38)	<0.001
<i>Data were reported as median(minimum:maximum)</i>				
<i>c: Kruskal Wallis Test</i>				
<i>Abbreviations: WBC: White blood cell, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-lymphocyte ratio MPV: Mean platelet volume, PDW: Platelet distribution width, PCT: Plateletcrit</i>				

It was determined that there was no relationship between age and hematological measurements in patient groups with and without Covid-19 infection.

While miscarriage was observed in 14.20% (n=25) of 176 patients who had Covid-19 infection, this rate was determined as 9.40% (n=11) in 117 patients who did not have Covid-19 infection, and no statistically significant difference was observed between the groups in terms of miscarriage rates (p=0.220).

Discussion

With the identification of the first cases in December 2019, the Covid-19 pandemic has affected the whole world as the first case in Turkey was described on March 11, 2020 [13]. The effect of this infection on pregnant women contains many uncertainties [14]. There are case reports in the literature reporting pregnancy loss before the 20th week during Covid-19 infection [3, 15–17]. However, studies on a large patient population in early gestational weeks are not available. The studies conducted mostly cover the 3rd trimester pregnant women. Unlike other studies in the literature, our study only included patients at early gestational weeks.

Hassanipour et al. reported a significant increase in neutrophils in patients and mortality accompanied by decreased lymphocyte count in one case [18]. It has been reported in many studies that increased NLR during SARS - Cov - 2 infection is associated with poor prognosis [19–22]. In our study, although there was a slight increase in the inpatient group compared to the control group, no significant increase was observed in NLR rates. This increase was more pronounced in the group of patients with Covid -19 infection whose pregnancy ended with miscarriage even if the difference did not reach a statistically significant level.

Erol Koç et al. evaluated hematological parameters and pregnancy outcomes in pregnant women with Covid-19 infection. While there was no difference between obstetric and neonatal outcomes, NLR was found to be high, and plateletcrit was found to be low in Covid-19 infection group [23].

It has been shown that the lymphocyte count and NLR ratio at the time of admission are related to the severity of the disease [24, 25]. While no difference was observed in NLR rates in our study group, it was observed that lymphopenia became more pronounced with disease severity.

As in a very recently published study, there was no significant difference in NLR rates in the Covid-19 group as in our study, but PLR was found to be significantly higher in the Covid-19 infection group [26].

In a multicenter study, the frequency of abortion in the patient group diagnosed with Covid-19 was reported as 2.3% [27]. Whereas in a prospective study, the frequency of spontaneous abortion was reported as 6.1% [28]. In our study, miscarriage rate in the Covid-19 infection group was 14.2%. Based on the limited studies in the literature, it can be stated that Covid -19 infection does not increase the risk of miscarriage [29].

Mostly late 2nd trimester and 3rd trimester pregnant women were included in the studies evaluating the effect of Covid-19 infection on maternal and neonatal outcome. The current study differs from previous studies in the literature by evaluating the effect of Covid-19 infection directly on the risk of miscarriage.

There are many limitations of our study. Regarding the severity of the disease, there was no hospital record of the symptoms and vital signs of the patients who were admitted to the hospital due to Covid-19 infection. Also, the number of patients in our study is not such that a general conclusion can be drawn about the impact on the miscarriage rate of Covid-19 infection.

Conclusion

Increased PLR, lymphopenia and low PCT values were observed in pregnant women who had Covid-19 infection under 20 weeks of gestation. It has also been demonstrated in this study that Covid-19 infection observed in early pregnancy causes a slight increase in miscarriage rates. However, there is a need for more comprehensive studies evaluating the relationship between Covid-19 infection in early pregnancy and the risk of miscarriage.

Declarations

Author contributions

Z Atak: Project development, data collection, data analysis, manuscript writing.

SR Ocakoglu: Data collection and statistical analysis, critical revision of the manuscript,

OO Uyaniklar: Manuscript editing and data collection, supervision.

E Ustunyurt: Manuscript editing, supervision.

All authors contributed to the final revision of the manuscript.

Disclosure of interests

No conflict of interest for any of the authors.

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Statement of Ethics

This study was approved by the Bursa City Hospital Clinical Research Ethics Committee (Approval number: 2021-11/1).

Consent for publication

All authors agree to contribute to this journal.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figures

Figure 1

Flowchart of patient selection