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Comparison of hematological parameters and perinatal outcomes between COVID-19 pregnancies and healthy pregnancy cohort

https://doi.org/10.1515/jpm-2020-0403
Received August 22, 2020; accepted November 13, 2020; published online November 30, 2020

Abstract

Objectives: To evaluate the relationship between Coronavirus Disease 2019 (COVID-19) in pregnancy and adverse perinatal outcomes. The secondary aim is to analyze the diagnostic value of hematologic parameters in COVID-19 complicated pregnancies.

Methods: The current study is conducted in a high volume tertiary obstetrics center burdened by COVID-19 pandemics, in Turkey. In this cohort study, perinatal outcomes and complete blood count indices performed at the time of admission of 39 pregnancies (Study group) complicated by COVID-19 were compared with 69 uncomplicated pregnancies (Control group).

Results: There was no significant difference between the obstetric and neonatal outcomes of pregnancies with COVID-19 compared to data of healthy pregnancies, except the increased C-section rate (p=0.026). Monocyte count, red cell distribution width (RDW), neutrophil/lymphocyte ratio (NLR), and monocyte/lymphocyte ratio (MLR) were significantly increased (p<0.0001, p=0.009, p=0.043, p<0.0001, respectively) whereas the MPV and plateletcrit were significantly decreased (p=0.001, p=0.008) in pregnants with COVID-19. ROC analysis revealed that the optimal cut-off value for MLR was 0.354 which indicated 96.7% specificity and 59.5% sensitivity in diagnosis of pregnant women with COVID-19. A strong positive correlation was found between the MLR and the presence of cough symptom (r=41.4, p=<0.0001).

Conclusions: The study revealed that, pregnancies complicated by COVID-19 is not related with adverse perinatal outcomes. MLR may serve as a supportive diagnostic parameter together with the Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) in assessment of COVID-19 in pregnant cohort.

Keywords: blood cell count; COVID-19; pregnancy outcome; pregnancy.

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Introduction

The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) is a novel RNA virus that belongs to coronaviridae family. It is the cause of Coronavirus Disease 2019 (COVID-19) pandemics which was first clearly identified in Wuhan, China in December 2019. World Health Organization (WHO) [1] reported approximately 22,536,300 confirmed COVID-19 cases and 789,200 deaths from COVID-19 worldwide, by 22 August. The number of cases is increasing steadily, and the studies gain acceleration to evaluate the mechanism and clinical course of the disease as well as to develop the treatment modalities.

Complete blood count parameters are routinely evaluated cost-effective markers in diagnosis and clinical follow-up of infectious diseases. In previous studies, authors [2–5] have shown that mean platelet volume (MPV), platelet-lymphocyte ratio (PLR), and neutrophil-lymphocyte ratio (NLR) which could be easily calculated through the hematologic parameters, had a significant role in evaluation of disease progression in some infections. Some authors [6–8] also revealed that lymphocyte count, PLR, monocyte/lymphocyte ratio (MLR), and NLR are valuable parameters and predictive for disease progression in COVID-19. However, the pregnancy has some unique immune mechanisms [9] which may also result in altered immune responses to infectious conditions.

The current study aims to evaluate the relationship between COVID-19 in pregnancy and adverse perinatal outcomes. The secondary aim is to analyze the diagnostic value of hematologic parameters in COVID-19 complicated pregnancies.

Materials and methods

Patient characteristics and data collection

The current study included 39 pregnant women with clinical diagnosis of COVID-19 on the obstetric isolation unite and 69 pregnant women without COVID-19 who delivered between March 20 and July 25, 2020, in Ankara City Hospital Obstetrics Unit, Turkey. In this cohort study, perinatal outcomes and complete blood count indices performed at the time of admission of 39 pregnancies (Study group) complicated by COVID-19 were compared with 69 uncomplicated pregnancies (Control group). Study composed of the pregnant cohort with spontaneous and singleton pregnancies, who all delivered via vaginal route or C-section during the defined period of pandemics. The data of the relevant pregnant women were collected who has positive or negative Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) test results for SARS-CoV-2 within three days before delivery. The study protocol was approved by the Institutional Review Board of Ankara City Hospital (#E1-20-672).

The Study group included pregnant women with clinically confirmed COVID-19. The diagnosis of COVID-19 was established according to WHO guidance [10]. Participants who did not give birth within three days of positive RT-PCR test for SARS-CoV-2 were excluded from the study cohort. Control group consisted of healthy pregnant women in the same number and same gestational week with the Study group. The pregnant women in the Control group were recruited from healthy pregnancies at regular antenatal follow up in our hospital who consecutively applied and delivered in our clinic through the same period with the Study group participants and who has negative RT-PCR test for SARS-CoV-2 within three days before delivery.

Pregnancies complicated by chronic maternal diseases (rheumatological diseases, renal failure, vascular malformations, hypertension, cardiac disease, diabetes mellitus, obesity, hypo-hyperthyroidy, congenital hematological disorders), acute inflammatory conditions (acute pancreatitis, acute appendicitis), pregnancy complications (gestational diabetes, preterm premature rupture of membranes, preeclampsia), multiple pregnancies and pregnant women using anticoagulant medication were excluded from the current study.

Obstetric and demographic properties, clinical findings of COVID-19, complete blood count results and birth characteristics were recorded on patient charts for each individual patient. Adverse perinatal outcomes were referred to gestational week at birth, birth weight, APGAR score in first and fifth minutes, need for emergency C-section, need for Neonatal Intensive Care Unit (NICU) and delayed discharge from NICU, neonatal death or maternal exitus.

Biochemical analyses

The complete blood count parameters were recorded from routinely performed hematologic analyses which were concurrently studied with positive RT-PCR testing of nasopharyngeal swab sampling. Positive results for SARS-CoV-2 RNA on real-time reverse transcription polymerase chain reaction (RT-PCR) were defined as clinically confirmed infection. As mentioned above, just before delivery, the hematologic parameters of the pregnants were recorded. These parameters were hemoglobin, hematocrit, red cell distribution width (RDW), neutrophil and lymphocyte count, platelet count (PLT), monocyte count, platelet distribution width (PDW), MPV, plateletcrit (PCT), NLR, monocyte/lymphocyte ratio (MLR), PLR, MPV/PLT ratio, and PLT/MPV ratio. NLR, MLR, PLR and MPV/PLT were calculated by dividing the absolute neutrophil, monocyte, and platelet counts by the absolute lymphocyte counts. Hematologic parameters were examined from were maternal peripheral venous blood samples taken from the antecubital vein. The blood samples were drawn into sterile tubes including ethylenediaminetetraacetate (EDTA) just after the admission of patients to clinic before receiving any medication. All measurements were performed 30 min after blood collection by using the Beckman Coulter Automated Blood Count Analyzer (BECKMAN COULTER Inc.,U.S.A.).

Statistical analyses

Statistical analyses were performed by using the SPSS for Windows 22.0 (SPSS Inc.IL, USA) software package. Normality of the data was tested via Shapiro-Wilk test. Independent Samples T-test was used for normally distributed variables and the data were presented as Mean±SD. χ^2-Test and Mann–Whitney U test were used if the variables were not normally distributed and the data were presented as n (%) and Median (Min–Max), respectively. With the Confidence Interval (CI) of 95%, a p-value of less than 0.05 was considered as statistically significant. Correlations between variables were assessed by using Spearman's Correlation Analysis. Receiver Operating Characteristic (ROC) Curves was used to analyze the accuracy of the various diagnostic tests.

Power analysis was performed by using G-power software (G-power v3.1.9.2, Universitat Kiel, Kiel, Germany). Difference between two independent means (two groups) power analysis demonstrated that this study achieved a power of 0.89 and 0.98 with a 5% level of significance. This analysis was performed between 39 pregnant women with COVID-19 and the 69 healthy controls by using comparison of the MPV and MLR values, respectively.

Results

A total of 39 pregnant women with confirmed COVID-19 were admitted to the obstetric isolation unite in our clinic. Among them, 10 pregnant women with clinical diagnosis of COVID-19 delivered by vaginal route. Age ranged from 18–42 years. Gravidity ranged from 1–4, parity at the time of admission ranged from 0–3, and gestational age ranged from 26+2 weeks/d to 40+2 weeks according to the last menstrual period (LMP) (Table 1).

A total of 28 C-sections were performed in the Study group. The indications were emergency C-section (fetal distress, cephalopelvic disproportion) in eight cases (28.6%), large for gestational age in four cases (14.3%) and elective C-section due to previous C-section in 16 cases (57.1%). In Control group, totally 36 C-sections were performed. The indications were emergency C-section (fetal distress, cephalopelvic disproportion) in 11 cases (30.6%), large for gestational age in three cases (8.4%) and elective

Table 1: Demographic and clinical characteristics.

Variables	Pregnant women with COVID-19 (n=39)	Control group (n=69)	p-Value
Age, years (Mean±SD)[a]	27.5±4.9	27.8±6.01	0.78
Gravidity, n (Mean±SD)[a]	2.03±0.9	2.09±0.93	0.74
Parity at time of admission, n (Mean±SD)[a]	1.26±0.9	1.19±0.8	0.7
Gestational age at delivery, weeks (Mean±SD)[a]	35.6±3.6	35.2±4.09	0.49
BMI (Mean±SD)[a]	26.8±3.98	26.4±4.3	0.89
Smoking yes/no, n (%)[b]	5/34 (12.8%/87.2)	17/52 (24.6%/75.4)	0.21

p-value <0.05 is considered as statistically significant; [a]Independent Samples T-test was used in statistical analyses; [b]Chi-Square test was used in statistical analyses; BMI, Body mass index; SD, Standard deviation.

C-section due to previous C-section in 22 cases (61%). C-section was significantly increased in pregnant women with COVID-19 (p=0.026). However, there was no significant difference between the two groups in terms of emergency C-section rate (p=0.86) (Table 2). The gestational week at birth, birth weight, APGAR score in first and fifth minutes, need for NICU rate and delayed discharged from NICU rate were not significantly different between the two groups. Neonatal death or maternal exitus was not observed.

None of the newborns were detected as SARS-CoV-2 positive in RT-PCR which was performed at the first and third day after delivery. None of the pregnant women wished skin-to-skin contact breastfeeding. The breast milk was transported to all of the isolated newborns due to the maternal COVID-19 by suctioning the milk via a maternal milking device.

Clinical parameters were presented in Table 3. None of the pregnant women with COVID-19 had severe disease symptoms. In total of 39 pregnant women with positive RT-PCR results for SARS-CoV-2; 24 (61.5%) patients were hospitalized with cough symptom, 6 (15.3%) cases were hospitalized with fever more than 38.2 Celsius degrees (°C), 4 (10.4%) patients were hospitalized with fatigue, and 5 (12.8%) patients were hospitalized with RT-PCR positivity for SARS-CoV-2 in asymptomatic screening indicated for close contact history.

MLR was significantly increased in pregnants with COVID-19 (p<0.0001) (Table 4). A significant positive linear

Table 2: Obstetric and neonatal outcomes of the two groups.

Variables	Pregnant women with COVID-19 (n=39)	Control group (n=69)	p-Value
Birth Weight, g (Mean±SD)[a]	2987±727	2703±804	0.85
Birth length, cm (Mean±SD)[a]	48.9±3.2	47.3±4.8	0.98
APGAR score 1 min, (Mean±SD)[a]	6.81±1.6	6.86±1.15	0.88
APGAR score 5 min, (Mean±SD)[a]	8.55±1.76	8.84±1.32	0.36
APGAR score 1 min <7 n (%)[b]	11/28 (28.2/71.8)	22/47 (31.9/68.1)	0.69
APGAR score 5 min <7 n (%)[b]	4/35 (10.3/89.7)	5/64 (7.2/92.8)	0.72
Mode of delivery vaginal route/C-section n (%)[b]	11/28 (28.2/71.8)	33/36 (47.8/52.2)	0.026*
Indication for C-section emergency/elective n (%)[b]	8/20 (28.6/71.4)	11/25 (30.6/69.4)	0.86
Gender of the baby male/female n (%)[b]	21/18 (53.8/46.2)	40/29 (58/42)	0.69
NICU yes/no n (%)[b]	17/22 (43.6/56.4)	27/42 (39.1/60.9)	0.68
Delayed discharge from NICU >10 days n (%)[b]	2/37 (5.1/94.9)	6/63 (8.7/92.6)	0.71

*p-value <0.05 is considered as statistically significant; [a]Independent Samples T-test was used in statistical analyses; [b]Chi-Square test was used in statistical analyses; NICU, Neonatal intensive care unit; SD, Standard deviation; APGAR, Appearance, Pulse, Grimace, Activity and Respiration.

Table 3: Clinical parameters in terms of the vital signs of the patients.

Variables	Pregnant women with COVID-19 (n=39)	Control group (n=69)	p-Value
Systolic blood pressure, mm/Hg (Mean±SD)[a]	109±8.1	116.6±13.7	0.11
Diastolic blood pressure, mm/Hg (Mean±SD)[a]	66.8±7.6	72.3±8.04	0.001*
Oxygen saturation by pulse oximeter, [Median (Max–Min)][b]	97(95–99)	99(98–100)	0.001*
Arterial pulse, pulse/min [Median (Max–Min)][b]	86(78–148)	80(78–88)	0.34
Body temperature, °C [Median (Max–Min)][b]	36.7(36–39)	6.3(36–37)	0.016*

*p-value <0.05 is considered as statistically significant; [a]Independent Samples T-test was used in statistical analyses; [b]Mann-Whitney U test was used in statistical analyses; Min-Max, Minimum-Maximum; DS, Standard deviation.

correlation was observed between the presence of cough symptom and the monocyte count at the time of clinical diagnosis for COVID-19 (r=29.6, p=0.002). There was a significant positive linear correlation between the MLR and the presence of cough symptom (r=41.4, p≤0.0001). In addition, a significant negative correlation was found between the MPV value and the presence of cough symptom (r=–31.4, p=0.001). There was no significant correlation between the presence of fever and the MLR (p=0.28).

RT-PCR was used as the gold standard comparator for the analysis of hematological parameters that could be used as supportive tests in the diagnosis of COVID-19. A Receiver Operating Characteristic (ROC) Curve Analysis was constructed to select the optimal predictive cut-off value of the hematologic parameters in COVID-19. ROC analysis revealed that the optimal cut-off value for MLR was 0.354 which indicated a very high specificity (96.7%) and 59.5% sensitivity in diagnosis of pregnant women with COVID-19. Besides, the optimal cut-off value for monocytes was 0.4 which indicated a very high sensitivity (89.5%) and 64% specificity in diagnosis of pregnant women with COVID-19 (Table 5) (Figure 1).

Discussion

There is increasing number of studies to report the course of COVID-19 in pregnant cohort. The current study aimed to elucidate the changes in hematologic parameters in response to SARS-CoV-2 infection and whether there was an increase in adverse perinatal outcomes such as increased NICU admission and lower APGAR scores in

Table 4: Comparisons of leukocytic and thrombocytic indices in all patients between two groups.

Variables, (Mean±SD)[a]	Pregnant women with COVID-19 (n=39)	Control group (n=69)	Statistics	
			Z	p-Value
Leukocyte count, ×109/L	9.734±351	8.087±1.57	−1.470	0.14
Neutrophil count, ×109/L	8.004±3.09	7.820±3.49	−0.576	0.56
Lymphocyte count, ×109/L	1.187±5.16	1.382±5.92	−1.615	0.10
Monocyte count, ×109/L	0.49±0.25	0.27±0.13	−4.974	<0.0001*
Hemoglobin, g/dl	11.1±2.16	13.2±1.45	−0.950	0.34
Hematocrit	33.5±3.94	34.9±2.57	−1.363	0.17
MCV, fL	82.1±5.78	84.5±4.56	−1.506	0.13
RDW	15.02±2.6	14.3±2.7	−2.598	0.009*
PLT, ×109/L	207±71	231±72.3	−1.705	0.088
MPV, fL	8.4±1.5	9.3±1.17	−3.341	0.001*
PCT	0.17±0.06	0.22±0.10	−2.666	0.008*
PDW, fL	15.4±2.9	15.76±2.61	−0.640	0.52
PLR	202.2±106	191.3±82.4	−0.329	0.74
NLR	6.46±3.5	5.12±2.75	−2.028	0.043*
MLR	0.044±0.02	0.021±0.008	−5.879	<0.0001*
PLT/MPV ratio	28.4±25.5	25.2±8.5	−0.160	0.87
MPV/PLT ratio	0.047±0.027	0.045±0.018	−0.249	0.80

*p-value <0.05 is considered as statistically significant; [a]Independent Samples T-test was used in statistical analyses; MCV, Mean corpuscular volume; RDW, Red cell distribution width; PLT, Platelet count; PCT, Plateletcrit; MPV, Mean platelet volume; PDW, Platelet distribution width; PLR, Platelet/Lymphocyte ratio; NLR, Neutrophil/Lymphocyte ratio; MLR, Monocyte/Lymphocyte ratio; SD, Standard deviation.

Table 5: Receiver operating characteristic (ROC) analysis results.

Variables	AUC	95% CI	p-Value	Optimal cut-off value	Sensitivity, (%)	Specificity, (%)
Monocytes	0.841	0.757–0.923	0.000*	0.40	89.5%	64%
MPV	0.725	0.622–0.827	0.000*	8.45	51.4%	78.3%
NLR	0.614	0.499–0.730	0.049*	6.23	45.9%	75.4%
MLR	0.863	0.783–0.943	0.000*	0.354	59.5%	96.7%

*p-value <0.05 is considered as statistically significant; MPV, Mean platelet volume; NLR, Neutrophil/lymphocyte ratio; MLR, Monocyte/lymphocyte ratio; AUC, Area under curve; CI, Confidence interval.

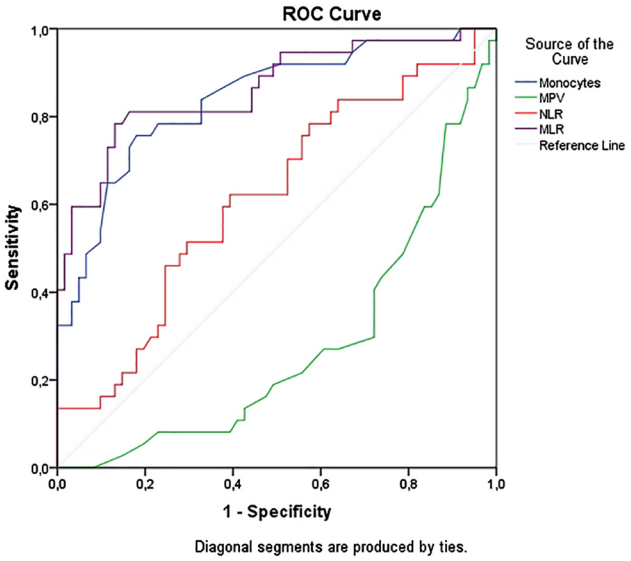

Figure 1: Diagnostic values of hematologic parameters in predicting COVID-19 in pregnancy, receiver operating characteristic (ROC) curve analysis.

COVID-19. To the best of our knowledge this is the first study in the literature distinguishing and evaluating the impact of COVID-19 on perinatal outcomes and hematologic parameters in a well-defined pregnant cohort, through a case-control manner.

Pregnancy leads to some alterations in T helper (Th1) and T helper 2 (Th2) responses through some unique mechanisms. This adaptive modulation shifts the immune response towards the anti-inflammatory side which contributes to enhance the expression of HLA-G to protect the conceptus from unfavorable immune attack [9] which may also decrease immune response against viral infections. On the other hand, authors reported that [11, 12] the severity of Th1 response has been found as associated with disease severity and increased mortality in COVID-19 patients.

Several authors reported [13–16] a mild disease course in COVID-19 during pregnancy. Consistent with the literature the current study revealed a mild course of COVID-19 in pregnancy and did not show a significant difference in terms of obstetric outcomes between the pregnant women with or without COVID-19. A significant increase in C-section rate was observed as delivery route of pregnant women with COVID-19. The increased C-section ratio may be due to the lack of consensus about the delivery management in SARS-CoV-2 positive cases, especially at the beginning of the pandemics which meanwhile the data collection of the study was started. Guan et al. [17] mentioned that some clinical characteristics of pregnant women as younger age and female gender may also contribute to the mild disease. Pregnants with the accompanying comorbidities except COVID-19 were excluded from the study cohort that may also prevent the development of adverse perinatal outcomes.

The possibility of vertical transmission of SARS-CoV-2 is one of the topics that previous studies concentrated on. In a systematic review, Huntley et al. [18] reported that even in the SARS-CoV-2 positive neonates suspicious for the vertical transmission, the route of infection could not be established. Consistently, current study did not support vertical transmission.

Increase in NLR is a rapid response to any stressing condition including systemic inflammation and infectious diseases due to an increase in neutrophil count and/or a decrease in lymphocyte count. The current study revealed a significant increase in NLR in pregnant women with COVID-19 despite no significant difference in lymphocyte count. Some authors also [17, 19] reported significant lymphopenia besides a significantly increased NLR in COVID-19 patients. However, Yang et al. [20] reported NLR as an independent predictor of poor outcomes. Peng et al. [8] also shown that NLR may be related with the disease progression, in a multicenter cross sectional study. However, they did not present NLR as a valuable diagnostic parameter. In addition, Liu et al. [21] revealed that NLR did not support or increased the diagnostic value of chest Computed Tomography (CT) in COVID-19. The current study also did not show a high sensitivity or specificity for NLR in diagnosis of COVID-19 in pregnant cohort.

Definitive diagnosis of SARS-CoV-2 infection is established by RT-PCR. On the other hand, an inexpensive and feasible parameter should contribute additional benefit

besides the RT-PCR in diagnosis and clinical evaluation of COVID-19. Chest CT imaging is a widely used valuable tool in diagnosis and follow-up of COVID-19. However, CT imaging is not accepted as safe in course of pregnancy. The current study revealed that MLR has a high specificity in diagnosis of COVID-19 in pregnant cohort. Stimulation of bone marrow with some pro-inflammatory cytokines as IL-2 and IFN-γ results in activation of monocytes [12] which may explain the increase in MLR. McClain et al. [22] reported that increased MLR has been associated with the diagnosis and disease progression in influenza A. Park et al. [23] found increased MLR has diagnostic and prognostic value in Middle East Respiratory Syndrome (MERS-CoV). Supporting the data, Yang et al. [6] reported that as a hematologic parameter only MLR showed a significant positive correlation with disease progression in chest CT scans in COVID-19 patients. Peng et al. [8] also found that MLR had a higher diagnostic value than neutrophils, lymphocytes, monocytes, platelets, NLR, and PLR in differentiating COVID-19 patients from healthy subjects.

Current study revealed a significant decrease in MPV and PCT, despite normal PLT in pregnant women with COVID-19. PCT is calculated by using PLT and MPV through an automated laboratory machine measurement. Regardless of the previous data, authors argued that [24] lack of standardization in measurement of MPV and PCT decreases the acceptability of these markers as diagnostic and prognostic parameters. Some studies presented that decrease in MPV and PCT is associated with sepsis, viral diseases, and inflammatory conditions. Renshaw et al. [3] showed a significant correlation with the decreased MPV and increased bronchoscopy rate in children with respiratory syncytial virus infection. Fei et al. [5] found that MPV has been associated with diagnosis and disease progression in influenza A. However, the authors indicated that the mechanisms by which MPV decreases in these infections were not clearly understood. The current study also revealed a significant decrease in RDW in COVID-19 pregnancies. However, authors [20, 25–27] presented conflicting data on diagnostic and prognostic value of RDW and PLR in COVID-19.

Guan et al. [17] reported the most common symptoms as cough and fever in COVID-19. In current study, the most common symptom was observed as cough in pregnant women with COVID-19. None of the pregnant women needed ICU or progressed to severe disease of which criteria defined according to WHO [10] guidance. However, a linear correlation was found between cough symptom and MLR in pregnant women with COVID-19, which can be interpreted as MLR may be a significant parameter in clinical follow-up of COVID-19 in pregnant women. Yang et al. [20] reported the fever as a prevailing symptom for COVID-19. However, WHO guidelines [10] referred that fever is detected a nearly 40% of the COVID-19 patients at admission. Fever exceeding 38.2 °C was not very common in our study group and may be associated with the absence of lymphopenia.

The current study presented the data of a high volume tertiary obstetrics center burdened by COVID-19 pandemics. This was also an advantage to reach meticulously recorded patient data and sufficient number of patients which determined the power of the study. However, the single centered and limited time period were the limitations of this study. None of the patients had severe disease course, therefore, the role of hematologic parameters in disease progression could not be assessed. Related with the nature of the study design which aimed to include the pregnant women with currently confirmed diagnosis for COVID-19, all of the pregnant women infected with SARS-CoV-2 in any day during the course of pregnancy were not included.

Conclusions

The study revealed that, pregnancies complicated by COVID-19 is not related with adverse perinatal outcomes. Even though, the C-section rate was significantly increased in women with COVID-19, the emergency C-section rate was similar with the controls. MLR may serve as a supportive diagnostic parameter together with the Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) in assessment of COVID-19 in pregnant cohort.

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The study protocol was approved by the Institutional Review Board of Ankara City Hospital (#E1-20-672).

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