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RESEARCH ARTICLE

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Comparison of VEGF-A values between pregnant women with COVID-19 and healthy pregnancies and its association with composite adverse outcomes

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Abstract

The aim is to compare VEGF-A values between pregnant women with coronavirus disease 2019 (COVID-19) and healthy controls. Furthermore, the association of inflammation parameters, disease severity, and obstetric complications with VEGF-A was investigated. This prospective case-control study was conducted on pregnant women who were admitted to Ankara City Hospital between June 14, 2020 and August 28, 2020. Pregnant women with COVID-19 ($n = 95$) were compared with a control group of healthy pregnant women ($n = 92$) with similar clinical and demographic characteristics. Demographic features, clinical characteristics, laboratory test results, VEGF-A values were compared between the groups. A correlation analysis was performed between VEGF-A levels, inflammation parameters, and clinical characteristics of the cases for pregnant women with COVID-19. VEGF-A levels were also compared between patients with composite adverse outcome and patients without any complication in the COVID-19 group. The two groups were similar except for obstetric complications ($p > .05$). The obstetric complication rate was higher in the COVID-19 group ($p = .02$). The two groups were comparable in terms of neutrophil to lymphocyte ratio and VEGF-A values. VEGF-A values were slightly different between the trimesters. A negative moderate statistically significant correlation was found between the neutrophil and VEGF-A values ($r = -0.231$, $p = .02$). VEGF-A values were similar between patients with and without composite adverse outcomes ($p > .05$). VEGF-A values were similar between pregnant women with COVID-19 and healthy controls.

KEYWORDS

adverse outcome, COVID-19, pregnancy, SARS-CoV-2, VEGF

1 | INTRODUCTION

Coronavirus disease 19 (COVID-19) is a novel viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has had a significant impact on our lives since the first day of its appearance.[1] It has spread around the world in a short period of time and caused a pandemic. Researchers all over the globe have been working on various projects to overcome this alarming situation. However, our knowledge is still very limited, and more data is necessary to establish more efficient management protocols.[2]

Pregnancy is a special condition that is associated with several adaptive physiological changes. Prominent alterations occur,

especially in the hematologic, immune, cardiovascular, and respiratory systems.[3] As COVID-19 mainly affects the above-mentioned systems, physicians have concerns related to the influence of COVID-19 on pregnant women. Although the course of the disease was generally reported to be mild in pregnant women in previous studies, COVID-19 may cause obstetric complications like miscarriage, preterm labor, pre-eclampsia, and fetal distress.[4–6] On the other hand, the underlying mechanisms behind increased obstetric complications in COVID-19 cases have not yet been revealed. Invasion of the placental villi by SARS-CoV-2, impaired coagulability, increased systemic inflammation, and decreased arterial oxygen saturation were hypothesized to be the possible pathophysiological events for poor obstetric outcomes.[7–10]

Vascular endothelial growth factors (VEGFs) are a family of growth factors that potently stimulate vasculogenesis and angiogenesis.[11] Five members of VEGFs are present in mammals with different functions: VEGF-A, placenta growth factor (PGF), VEGF-B, VEGF-C, and VEGF-D.[12] They are essential for the healthy development of the placenta and the fetus.[13–15] Moreover, their role in obstetric complications like miscarriage, fetal growth restriction, and pregnancy-induced hypertension were investigated in various studies.[16–21] Additionally, the potential role of VEGFs in the pathogenesis of COVID-19 infection has been reported in recent studies.[22–25] Considering that COVID-19 increases VEGF levels and the relationship between the same mediators and obstetric complications, VEGF levels may differ in normal and infected pregnant women. However, to the best of our knowledge, there is no study in the literature evaluating the VEGFs levels in pregnant women with COVID-19.

This study aims to compare VEGF-A values between pregnant women with COVID-19 and healthy controls. Furthermore, the association of inflammation parameters, disease severity, and obstetric complications with VEGF-A was investigated.

2 | MATERIALS AND METHODS

This prospective case-control study was conducted on pregnant women who were admitted to the Department of Obstetrics and Gynecology, Turkish Ministry of Health Ankara City Hospital between May 11, 2020 and August 30, 2020. Pregnant women with COVID-19 were compared with a control group of healthy pregnant women with similar clinical and demographic characteristics. Patients who were willing to participate and gave the required blood sample for the evaluation of the VEGF-A level were included in this study. Both the Turkish Ministry of Health and the Institutional Ethics Committee approved the study protocol (E1-20-602) and informed consent was obtained from all patients.[22–25]

The Turkish Ministry of Health Ankara City Hospital is a tertiary health-care facility that has been playing a major role in the management of COVID-19 patients since the beginning of the pandemic.[26] It has a special protocol for pregnant women with COVID-19 and all cases were followed up by a multidisciplinary team consisting of obstetricians, perinatologists, neonatologists, pulmonologists, radiologists, and infectious disease specialists. Despite being the main pandemic center, it continues to give service to both high-risk and low-risk pregnant populations with approximately 1100 deliveries per month.[26]

In the first part of the study, pregnant women with COVID-19 were compared with healthy controls in terms of demographic features, clinical characteristics, laboratory parameters, and VEGF-A values. Maternal age, body-mass index (BMI) (kg/m^2), gravidity, parity, comorbid conditions, gestational age, pregnancy status, obstetric complications, hemoglobin (Hb), hematocrit (Hct), white blood cell, platelet, lymphocyte, neutrophil counts, neutrophil to lymphocyte ratio, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), procalcitonin, interleukin 6 (IL-6), ferritin, lactate dehydrogenase (LDH), D-dimer and VEGF-A levels were compared between the groups.

Secondly, VEGF-A values were compared between pregnant women with COVID-19 and healthy controls according to pregnancy trimesters. Thereafter, a correlation analysis was performed between VEGF-A levels, inflammation parameters, and clinical characteristics of the cases for pregnant women with COVID-19. Finally, VEGF-A levels were compared between patients with composite adverse outcome and patients without any complication in the COVID-19 group. The composite adverse outcome was defined as the presence of an obstetric complication or moderate/severe COVID-19.

Real-time polymerase chain reaction (RT-PCR) assay of a nasopharyngeal and oropharyngeal specimen was used for the diagnosis of COVID-19.[27] All COVID-19 cases were managed according to the national guideline.[28] The severity of COVID-19 was determined according to the defined criteria by the Turkish Ministry of Health.[28] Blood samples were obtained from the patients along with the initial laboratory tests upon their first admission to the hospital.

VEGF-A level was measured with the Sandwich-ELISA principle at Ankara University Faculty of Medicine, Pathophysiology Laboratories. The measurements were done according to the instructions for use of the commercial kit (Elabscience, Human VEGF-A ELISA Kit).

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS.22, IBM SPSS Statistics for Windows, Version 22.0; IBM Corp.). Descriptive analyses were presented as medians and interquartile range as they were not normally distributed. The Mann–Whitney *U*-test was performed to compare the median values between the groups. Categorical variables were presented by numbers and percentages. The chi-square test was used to compare categorical variables between the groups. Correlation analysis was performed by Spearman test. A two-tailed $p < .05$ was regarded as statistically significant.

TABLE 1 Comparision of demographic features and clinical characteristics between pregnant women with COVID-19 and healthy controls

Variables	Pregnant women with COVID-19 (*n* = 95)	Healthy controls (*n* = 92)	*p* value
Maternal age (years) (median, IQR)[a]	29 (7)	28 (7.75)	.12
BMI (kg/m^2) (median, IQR)[a]	26.57 (5.54)	26.36 (6.20)	.54
Gravidity (median, IQR)[a]	2 (2)	2 (1)	.06
Parity (median, IQR)[a]	1 (2)	1 (1)	.08
Comorbidity (*n*, %)[b]	24 (25.3%)	15 (16.3%)	.13
Comorbidity type (*n*, %)[b]			.49
Obesity (*n*, %)	7 (7.4%)	10 (10.9%)	
Hypothyroidism (*n*, %)	6 (6.3%)	4 (4.3%)	
Hypertension (*n*, %)	2 (2.2%)	1 (1.1%)	
Asthma (*n*, %)	2 (2.2%)	0 (0%)	
Epilepsy (*n*, %)	1 (1.1%)	0 (0%)	
Diabetes mellitus type 2 (*n*, %)	1 (1.1%)	0 (0%)	
Ulcerative colitis (*n*, %)	1 (1.1%)	0 (0%)	
Ankylosing spondylitis (*n*, %)	1 (1.1%)	0 (0%)	
Thalassemia trait (*n*, %)	1 (1.1%)	0 (0%)	
Immune thrombocytopenic purpura (*n*, %)	1 (1.1%)	0 (0%)	
Mitral valve stenosis (*n*, %)	1 (1.1%)	0 (0%)	
Gestational age (weeks) (median, IQR)[a]	25 (22)	24 (23)	.69
Pregnancy status (*n*, %)[b]			
Miscarriage (*n*, %)	2 (2.1%)	0 (0%)	.76
On-going pregnancy (*n*, %)	74 (77.9%)	82 (89.1%)	
Delivered (*n*, %)	19 (20%)	10 (10.9%)	
Obstetric complication (*n*, %)[b]	12 (12.6%)	3 (3.2%)	.02
Obstetric complication type (*n*, %)[b]			
Pre-eclampsia (*n*, %)	3 (3.2%)	0 (0%)	.16
Preterm delivery (*n*, %)	3 (3.2%)	0 (0%)	
Miscarriage (*n*, %)	2 (2.1%)	0 (0%)	
GDM (*n*, %)	1 (1.1%)	2 (2.2%)	
ICHP (*n*, %)	1 (1.1%)	1 (1.1%)	
GHT (*n*, %)	1 (1.1%)	0 (0%)	
DVT (*n*, %)	1 (1.1%)	0 (0%)	

Abbreviations: BMI, body-mass index; COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; GDM, gestational diabetes mellitus; GHT, gestational hypertension; ICHP, Intrahepatic cholestasis of pregnancy; IQR, interquartile range.

[a]Statistical analysis was performed by Mann–Whitney *U* test.

[b]Statistical analysis was performed by chi-square test.

3 | RESULTS

There were 95 and 92 patients in the COVID-19 and control groups respectively. Thirty-two, 32, and 31 patients were in the first, second, and third trimesters of pregnancy in the COVID-19 group. On the other hand, 32, 29, and 31 patients were in the first, second, and third trimesters of pregnancy in the control group. In the COVID-19 group, 70, 23, and 2 patients had mild, moderate, and severe disease, respectively. Eighteen cases had computerized tomography findings consistent with COVID-19 and medication was necessary in 27 cases.

A comparison of demographic features and clinical characteristics between pregnant women with COVID-19 and healthy controls is shown in Table 1. Approximately a quarter of pregnant women with COVID-19 infection had comorbidities. Obesity and hypothyroidism were the leading comorbid conditions. Two pregnancies resulted in miscarriage and 19 pregnant women were delivered in the COVID-19 positive group. Pre-eclampsia and preterm delivery were the most common obstetric complications in the COVID-19 group. Two groups were similar except for obstetric complications ($p > .05$). The obstetric complication rate was higher in the COVID-19 group ($p = .02$).

A comparison of laboratory parameters and VEGF-A levels between pregnant women with COVID-19 and healthy controls is shown in Table 2. Significantly lower Hb, Hct, white blood cell, platelet, lymphocyte, and neutrophil values were found in the COVID-19 group ($p < .05$). However, ESR, CRP, procalcitonin, IL-6, ferritin, LDH, and D-dimer values were significantly lower in the control group ($p < .05$). The two groups were comparable in terms of NLR and VEGF-A values ($p > .05$).

A comparison of median VEGF-A values between pregnant women with COVID-19 and healthy controls according to pregnancy trimesters is shown in Table 3. No statistically significant difference was found between the groups ($p > .05$). VEGF-A values were slightly higher in the control group. CRP, D-dimer, and VEGF-A levels of the second trimester were significantly higher than those of the first and last trimesters in both groups.

Correlation of VEGF-A values with inflammation parameters and clinical characteristics in pregnant women with COVID-19 is shown in Table 4. A negative moderate statistically significant correlation was found between the neutrophil and VEGF-A values ($r = -.231$,

TABLE 2 Comparision of laboratory parameters and VEGF-A levels between pregnant women with COVID-19 and healthy controls

Variables	Pregnant women with COVID-19 (*n* = 95)	Healthy controls (*n* = 92)	*p* value
Hb (g/dl) (median, IQR)[a]	11.7 (1.8)	12.5 (1.5)	**.004**
Hct (%) (median, IQR)[a]	35.7 (5.25)	37.3 (4.2)	**<.001**
WBC (10^3/ml) (median, IQR)[a]	6070 (3480)	8880 (3092)	**<.001**
Platelet (10^3/ml) (median, IQR)[a]	222 (86.5)	253 (81.7)	**<.001**
Lymphocyte (10^3/ml) (median, IQR)[a]	1240 (665)	1835 (592)	**<.001**
Neutrophil (10^3/ml) (median, IQR)[a]	4250 (3185)	6265 (2862)	**<.001**
NLR (%) (median, IQR)	3.5 (3.1)	3.3 (1.8)	.55
ESR (mm/h) (median, IQR)[a]	30 (12.5)	24.5 (17.7)	**<.001**
CRP (mg/dl) (median, IQR)[a]	10.5 (15.8)	5 (5.8)	**<.001**
Procalcitonin (ng/ml) (median, IQR)[a]	0.07 (0.02)	0.03 (0.01)	**<.001**
IL-6 (pg/ml) (median, IQR)[a]	6.5 (7.6)	3.6 (1.2)	**<.001**
Ferritin (ng/ml) (median, IQR)[a]	19 (28)	12.5 (12)	**<.001**
LDH (U/l) (median, IQR)[a]	201 (50)	183.5 (62.7)	**.013**
D-dimer (mcg/ml) (median, IQR)	1.2 (1.1)	0.6 (0.5)	**<.001**
VEGF-A (pg/ml) (median, IQR)[a]	151 (60)	155 (30)	.59

Abbreviations: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hb, hemoglobin; Hct, hematocrit; IL-6, interleukin 6; DH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; VEGF-A, vascular endothelial growth factor A; WBC, white blood cell.

[a]Statistical analysis was performed by Mann–Whitney *U* test.

p = .02). However, no other significant correlation was present for the remaining parameters.

A comparison of VEGF-A levels between patients with composite adverse outcomes and patients without any complication in

TABLE 3 Comparison of median VEGF-A values between pregnant women with COVID-19 and healthy controls according to pregnancy trimesters

	First trimester VEGF-A (pg/ml)[a,b]	Second trimester VEGF-A (pg/ml)[a,b]	Third trimester VEGF-A (pg/ml)[a,b]
Pregnant women with COVID-19	145 (210)[a]	159.5 (40)[a]	140 (60)[a]
	93.06[b]	109.42[b]	72.74[b]
Healthy controls	149 (40)[a]	165 (40)[a]	149 (50)[a]
	92.77[b]	122.28[b]	75.13[b]
p value	0.79[a]	0.21[a]	0.62[a]
	0.02[c]		0.015[c]

Abbreviation: COVID-19, coronavirus disease 2019; VEGF-A, Vascular endothelial growth factor A.

[a]Median and interquartile range.

[b]Mean rank values were used, statistical analysis was performed by Mann–Whitney *U*-test.

[c]Mean rank values of first and second, second and third trimester were significantly different.

TABLE 4 Correlation of VEGF-A values with inflammation parameters and clinical characteristics in pregnant women with COVID-19

Parameter	*r* value[a]	*p* value[a]
Lymphocyte	.008	.93
Neutrophil	−.231	**.02**
NLR	−.154	.13
ESR	−.049	.63
CRP	−.033	.75
Procalcitonin	−.045	.66
IL-6	−.040	.70
Ferritin	−.079	.44
LDH	−.019	.85
D-dimer	−.162	.11
COVID-19 status	−.164	.12
Obstetric complications	−.158	.13

Abbreviations: COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IL-6, interleukin 6; LDH, lactate dehydrogenase; NLR, neutrophil to lymphocyte ratio; VEGF-A, vascular endothelial growth factor A.

[a]Correlation analysis was performed by Spearman test.

TABLE 5 Comparison of VEGF-A levels between patients with composite adverse outcome and patients without any complication in the pregnant women with COVID-19 group

	Patients with composite adverse outcome (n = 30)	Patients without any complication (n = 65)	p value
VEGF-A level (pg/ml) (median, IQR)	150.5 (30)	149 (100)	0.93

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; VEGF-A, vascular endothelial growth factor A.

pregnant women with the COVID-19 group is shown in Table 5. The two groups were similar in terms of VEGF-A values (p = .93). Patients with asthma had slightly higher VEGF-A values (0.38 ± 0.27).

4 | DISCUSSION

Cytokine storm, altered immune response, impaired coagulation, and low blood oxygen levels are the major pathologic events behind the complications of COVID-19.[7–10] In severe cases, this cascade of events leads to vascular injury and hypoperfusion. Excessive maternal immune response, formation of microthrombi in the vascular structures of the placenta and decreased oxygenation in the maternal–fetal interface are all associated with adverse pregnancy outcomes.[29,30] COVID-19 infection may adversely affect pregnancy as the growing fetus needs appropriate perfusion and oxygenation. It has been reported that COVID-19 infection was associated with various obstetric complications like miscarriage, preterm labor, preeclampsia, and fetal distress.[4–6] However, how the SARS-CoV-2 virus affects the placenta and fetus remains vague. Impaired placentation and occlusion of placental vessels by thrombus seem to be two possible pathological events behind obstetric complications. As VEGF-A production may be induced in cells receiving insufficient oxygen, it may be hypothesized that COVID-19 infection may elevate VEGF-A levels in pregnant women with COVID-19. Furthermore, increased VEGF-A levels were reported in COVID-19 patients and antiangiogenic agents were used for therapeutic purposes. VEGF-A was also found to be associated with increased angiopoietins and vascular permeability in COVID-19 infection.[22–25]

The term placenta-mediated pregnancy complications has been used widely in the recent literature.[31–33] According to this theory, impaired placentation and injury of placental vascular structures result in poor obstetric outcomes. Destruction of cellular components of the maternal-fetal interface may lead to altered fetal perfusion and hypoxia. Moreover, cell degradation products seem to activate maternal innate and humoral immunity. This cascade of pathologic events probably results in pregnancy complications.[31–33] Altered levels of VEGFs were reported to play a role in various obstetric complications like miscarriage, fetal growth restriction, and pregnancy-induced hypertension.[16–21] Thus, COVID-19 may cause placenta-mediated pregnancy complications via VEGFs.

The findings of the present study indicated that VEGF-A values were similar between pregnant women with COVID-19 and healthy controls with similar clinical characteristics. In a similar manner, inflammatory marker responses show differences between trimesters. Interestingly; the second trimester has the highest acute phase responses (D-dimer, CRP, etc) and VEGF-A levels. Moreover, VEGF-A values remained comparable between the groups at different trimesters of pregnancy. No significant correlation was found for VEGF-A values with inflammation parameters and clinical characteristics in pregnant women with COVID-19 except for a negative moderate statistically significant correlation with the neutrophil count. CRP, IL-6, and D-dimer concentrations have a negative correlation with lymphocyte count.

Additionally, VEGF-A values except lung diseases were similar between patients with composite adverse outcome and patients without any complication in pregnant women with COVID-19. However, VEGF-A values were slightly higher in patients with asthma. These results were inconsistent with the previous theories. However, this is a preliminary study and more data is necessary to make more precisive inferences.

In our opinion, the findings of the present study may lead to the development of new studies focusing on two main possible targets for the clinicians. Firstly, if the findings of future studies indicate a significant difference between COVID-19 positive and negative pregnant women with regard to VEGF-A values, this mediator may be used as an ancillary test for the prediction of disease prognosis. Secondly, medications affecting the levels and functions of VEGF-A may be used for therapeutic purposes.

The strengths of the present study were the novelty, the high number of study parameters, and the prospective design in each trimester. However, the lack of information related to the final outcomes of ongoing pregnancies and a low number of severe cases were the main limitations.

In conclusion, although VEGF-A values change with trimester; they were similar between pregnant women with COVID-19 and healthy controls. Furthermore, VEGF-A was not associated with disease severity and obstetric complications.

CONFLICT OF INTERESTS

The authors state that they have no conflict of interest in this study.

AUTHOR CONTRIBUTIONS

Nuray Yazihan: *study design*, *statistical analysis*, *manuscript writing*. Atakan Tanacan: *study design*, *statistical analysis*, *manuscript writing*. Seyit Ahmet Erol: *data collection*, *manuscript writing*. Ali Taner Anuk: *data collection*, *manuscript writing*. Selcan Sinaci: *data collection*, *review of the literature*. Derya Biriken: *statistical analysis*, *manuscript writing*. Huseyin

Levent Keskin: *critical review, study design*. Ozlem Moraloglu Tekin: *supervision, manuscript writing*. Dilek Sahin: *supervision, manuscript writing*.

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