Effects of pro-inflammatory interleukin-6 and anti-inflammatory interleukin-10 cytokines in pregnant women diagnosed with coronavirus disease 2019

Koronavirüs hastalığı 2019 tanısı konmuş gebe kadınlarda proinflamatuar interlökin-6 ve anti-inflamatuar interlökin-10 sitokinlerinin etkileri

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Abstract

Aim: This study aims to investigate the relationship between serum interleukin (IL)-6 and IL-10 levels in coronavirus disease (COVID)-19 positive pregnant women and the course of the disease.

Methods: In our study, serum IL-6 and IL-10 levels were measured in 28 third-trimester COVID-19-positive pregnant women and 30 third-trimester healthy pregnant women. COVID-19-positive cases were classified as carriers or patients. While 13 of the pregnant women in the study group were asymptomatic or were being followed out due to mild illness; a total of 15 pregnant women, 7 of whom were in the intensive care unit (ICU), were hospitalized and treated. IL-6 and IL-10 tests of COVID-19-positive pregnant women were studied at the time of first application.

Results: Seven (25%) patients with COVID-19 required admission to an ICU. The IL-6 level was found to be significantly lower in COVID-19-negative pregnant women compared to pregnant women who were COVID-19 carriers and patients (p=0.01). The IL-10 level was found to be significantly higher in pregnant women who were negative for COVID-19 compared to pregnant women who were COVID-19 carriers (p=0.002) and patients (p=0.002).

Conclusion: Close monitoring of IL-6 and IL-10 cytokine levels is recommended to minimize the risk of adverse outcomes in pregnant women presenting with a suspected or confirmed diagnosis of COVID-19. In this way, it may be possible to distinguish moderate–mild COVID-19 from severe COVID-19 in pregnant women.

Keywords: COVID-19; interleukin-6; interleukin-10; pregnancy

Öz

Amaç: Çalışmamızda Koronavirüs Hastalığı (COVID)-19 pozitif gebelerde serum interlökin (IL)-6 ve IL-10 düzeyleri ile hastalığın seyri arasındaki ilişkinin araştırılması amaçlandı.

Yöntemler: Çalışmamızda 28 üçüncü trimester COVID-19 pozitif gebe ve 30 üçüncü trimester sağlıklı gebede serum IL-6 ve IL-10 düzeyleri ölçüldü. COVID-19 pozitif vakalar, taşıyıcı veya hasta olarak sınıflandırıldı. Çalışma grubundaki gebelerden 13'ü asemptomatik iken veya hafif hastalık nedeniyle takip edilirken; 7'si yoğun bakım ünitesinde (YBÜ) olmak üzere toplam 15 hamile kadın hastaneye kaldırılarak tedavi altına alındı. COVID-19 pozitif gebe kadınların IL-6 ve IL-10 testleri ilk uygulama sırasında çalışıldı.

Bulgular: COVID-19'lu 7 (%25) hastanın yoğun bakım ünitesine kabul edilmesi gerekti. COVID-19 negatif gebelerde IL-6 düzeyi, COVID-19 taşıyıcısı ve hasta gebelere göre anlamlı derecede düşük bulundu (p=0,01). COVID-19 negatif olan gebelerde IL-10 düzeyi, COVID-19 taşıyıcısı olan gebelere (p=0,002) ve hastalara (p=0,002) göre anlamlı derecede yüksek bulundu.

Sonuç: Şüpheli veya doğrulanmış bir COVID-19 teşhisi ile başvuran hamile kadınlarda olumsuz sonuç riskini en aza indirmek için IL-6 ve IL-10 sitokin düzeylerinin yakından izlenmesi önerilir. Bu şekilde hamile kadınlarda orta-hafif COVID-19'u şiddetli COVID-19'dan ayırt etmek mümkün olabilir.

Anahtar Sözcükler: COVID-19; gebelik; interlökin-6; interlökin-10

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INTRODUCTION

Toward the end of 2019, a new coronavirus variant was identified in Wuhan/China that caused acute respiratory distress syndrome (ARDS). The disease was named coronavirus disease 2019 (COVID-19), and, because of its rapid spread, was declared a pandemic in March 2020 (1-3). Due to pregnancy, various physiological changes in the respiratory system, immune system, and endocrine system can change the response of pregnant women to viruses (4,5). The immune system in pregnancy tends to be anti-inflammatory to protect the fetus. COVID-19 has been associated with unregulated and excessive production of pro-inflammatory chemokines and cytokines, resulting in a cytokine storm accompanying ARDS (6-8). In pregnancy, inhibition of the pro-inflammatory T helper-1 (Th-1) pathway and activation of the anti-inflammatory T helper-2 (Th-2) pathway occur thanks to placental hormones produced from the first trimester (estriol, estradiol, progesterone, hCG, prostaglandins, and corticosteroids), decidual Vitamin D, leukemic inhibitory factor, and type 2 macrophage (M2). Interleukin 10 (IL-10) and macrophage colony-stimulating factor (M-CSF) play an active role in the transition from Th-1 dominance to Th-2 dominance. M2 and trans-regulatory cells (Treg) produce vast amounts of transforming growth factor beta (TGF-b) and IL-10 to support anti-inflammatory immune responses and heal damaged tissues (9-12). In addition, increased interleukin 6 (IL-6) levels because of inflammation in patients with COVID-19 initiates coagulation activation and thrombin formation by increasing tissue factor expression from mononuclear cells (13). As a result of immune-modulating mediators and diverse anti-inflammatory endogenous ligands formed during pregnancy, COVID-19 infection is thought to follow a moderate and less mortal course, as is the case with some autoimmune diseases (14). Interestingly, there are reports that, unlike most viral infections, there is no clinical worsening of COVID-19 infection during pregnancy (15-17). The possible inhibitory effect of the natural immunosuppressive environment of pregnancy on the pro-inflammatory cytokine storm is the subject of the present study. Thus, it was planned to investigate the effects on the clinical manifestation of the disease by measuring the levels of IL-10 and IL-6, the dominant cytokines of two opposite pathways, in pregnant women infected with COVID-19.

MATERIALS AND METHODS

The present study includes 28 COVID-19 positive cases, all of whom had third-trimester singleton pregnancies, and a control group of 30 healthy third-trimester pregnant women. IL-10 and IL-6 levels were examined in the study. This research was conducted as an observational case-control study. The study was approved by the medical ethics committee of our hospital, and its design and implementation adhered to the principles of the Helsinki Convention (Health Sciences University Gazi Yasargil Training and Research Hospital Clinical Research Ethics Committee, no: 2021/739, date: 26.03.2021).

Patients were declared as COVID-19 suspects if they exhibited at least one of the primary symptoms of the disease, namely fever (>37.8 °C), shortness of breath, cough, loss of taste and smell, or diarrhea. For suspected patients, the main diagnosis was made by physical examination and vital signs, various blood tests (hemogram, biochemical tests, C-reactive protein (CRP), ferritin, procalcitonin, coagulation parameters, etc.), PCR (polymerase chain reaction) test from a nasopharyngeal swap sample, and chest X-ray and thorax tomography tests (in pregnancy chest CT can be done safely) when necessary (18). Pregnant women in the first two trimesters, multiple pregnancies, patients with concomitant diseases (i.e. diabetes, cardiovascular diseases), and those who did not accept thoracic tomography examination at hospitalization were excluded from the study.

Of the 28 pregnant women included in the study, 15 were hospitalized and 13 were followed-up outpatients. The mean age of the outpatient, hospitalized and control groups, was 25.85±3.58, 31.27±6.24, 28.10±6.27 years, and gestational weeks were 35.85±2.41, 34.27±2.09, 37.70±1.76 weeks, respectively. Seven of the hospitalized women were in requiring intensive care. The PCR test at admission was positive for all patients. A computed thorax tomography examination was performed by fitting hospitalized or followed-up women with a fetal protective lead vest. A high-resolution, thin-section (1-1.5 mm), and non-

Table 1: Comparison of age, gestational week, IL-6 and IL-10 parameters between the groups admitted to the COVID 19 negative, COVID 19 positive (carrier), COVID 19 positive (inpatient)

Parameters	n	Mean±SD	Median (min-max)	p value
Age				0.081
COVID-19 negative	30	28.10±6.27	27.00 (19.00-41.00)	
COVID-19 positive (carrier)	13	25.85±3.58	25.00 (21.00-32.00)	
COVID-19 positive (inpatient)	15	31.27±6.24	29.00 (23.00-42.00)	
Gestational week				0.121
COVID-19 negative	30	37.70±1.76	38.00 (34.00-40.00)	
COVID-19 positive (carrier)	13	37.85±2.41	37.00 (32.00-39.00)	
COVID-19 positive (inpatient)	15	37.27±2.09	37.00 (31.00-39.00)	
IL-6				0.001
COVID-19 negative	30	9.76±10.44	4.87 (2.00-41.80)	
COVID-19 positive (carrier)	13	22.60±26.21	16.30 (0.52-99.29)	
COVID-19 positive (inpatient)	15	24.35±22.78	21.09 (7.32-101.00)	
IL-10				0.001
COVID-19 negative	30	183.59±162.57	131.00 (10.70-512.00)	
COVID-19 positive (carrier)	13	41.53±38.14	36.00 (11.60-147.00)	
COVID-19 positive (inpatient)	15	50.07±49.50	36.00 (0.00-151.00)	

COVID-19: Coronavirus disease 2019, IL-6: Interleukin 6, IL-10: Interleukin 10, min: minimum, max: maximum, n: number, SD: Standard Deviation

Table 2: Comparison of age, gestational week, IL-6 and IL-10 parameters between the groups admitted to the control, normal service and intensive care unit

Parameters		n	Mean±SD	Median (min-max)	p value
Age					0.274
COVID-19 negative		30	28.10±6.27	27.00 (19.00-41.00)	
COVID-19 positive	Normal service	8	30.12±5.51	27.50 (24.00-39.00)	
	Intensive care	7	32.57±7.18	31.00 (23.00-42.00)	
Gestational week					0.229
COVID-19 negative			37.70±1.76	38.00 (34.00-40.00)	
COVID-19 positive	Normal service	8	37.37±2.20	37.00 (32.00-39.00)	
	Intensive care	7	37.14±2.12	37.00 (32.00-38.00)	
IL-6					0.003
COVID-19 negative		30	9.76±10.44	4.87 (2.00-41.80)	
COVID-19 positive	Normal service	8	19.16±10.24	19.45 (7.51-38.20)	
	Intensive care	7	30.29±31.80	21.09 (7.32-101.00)	
IL-10					0.009
COVID-19 negative		30	183.59±162.57	131.00 (10.70-512.00)	
COVID-19 positive	Normal service	8	53.36±49.29	42.60 (0.00-140.00)	
	Intensive care	7	46.32±53.41	19.70 (0.00-151.00)	

COVID-19: Coronavirus disease 2019, IL-6: Interleukin 6, IL-10: Interleukin 10, min: minimum, max: maximum, n: number, SD: Standard Deviation

contrast were used as the acquisition method. Patients who needed oxygen had severe pneumonia and might need intensive care were hospitalized and treatment was started. For the patients who were classified as uncomplicated and patients with pneumonia based on the clinical findings, thorax tomography was performed, when necessary, in line with the COVID-19 national guidelines. Pneumonia patients were divided into three groups, namely those with mild-moderate pneumonia, those with severe pneumonia, and patients in need of intensive care (Figure 1 and Figure 2). In addition to routine laboratory tests, serum IL-10 and IL-6 levels were examined in all 28 COVID-19-positive pregnant women during their first admission to the hospital. After the blood samples were taken in biochemistry tubes, they were centrifuged at 3000 rpm for 5 minutes within 15 minutes of their being taken. Serum samples were transported to the laboratory and analyzed following cold chain principles. The clinical information and the findings of laboratory and radiological examinations of the patients were obtained from the database of our hospital.

1. Uncomplicatedpatient (Figure 1)

Asymptomatic but PCR positive.

2. Patients with pneumonia(Figure 2)

2.1. Mild-moderate pneumonia

Patients with symptoms, e.g., fever, cough, respiratory rate <30/minute, SpO2 level >90% at room temperature, and bilateral diffuse (>50%) involvement in lung imaging.

2.2. Severe pneumonia

Patients with symptoms, e.g., fever, cough, tachypnea (≥30/minute), SpO2 level ≤90% at room temperature, and bilateral diffuse in lung imaging.

2.3. Patients requiring evaluation for ICU

Patients with dyspnea and respiratory distress, respiratory rate ≥30/min, partial arterial oxygen pressure/fraction of inspired oxygen (PaO2/FiO2)<300, PaO2 <70 mmHg or SpO2 <90% despite 5 L/min oxygen therapy, hypotension, troponin elevation, lactate >2 mmol, acute kidney injury, acute liver function tests, confusion, acute organ dysfunction such as acute bleeding diathesis and immunosuppression, capillary return disorder, and skin disorders such as cutis marmaratus.

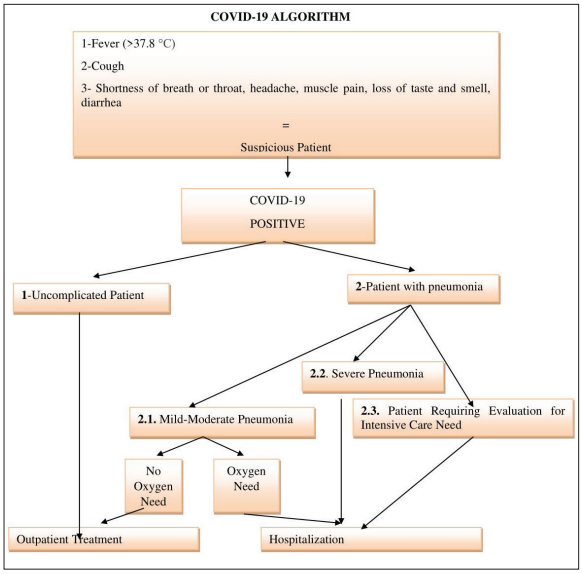

Figure I. COVID-19 algorithm.

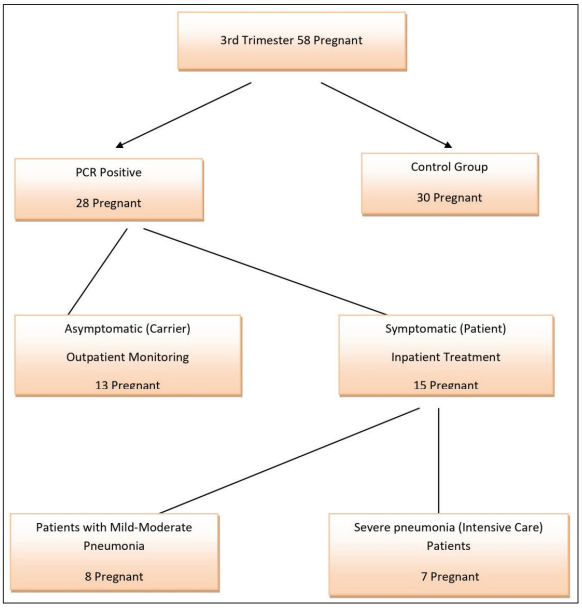

Figure 2: Grouping of cases

Statistical Analysis

The normality assumptions of the variables were examined with the Kolmogorov–Smirnov test, and the Kruskal–Wallis test was used for intergroup comparisons. In case a significant difference was obtained with the Kruskal–Wallis test, the Bonferroni-corrected

Mann–Whitney test was applied to determine which groups the difference originated from. Statistical Package for the Social Sciences package program version 23.0 (SPSS Inc., Chicago, IL, USA) program was used in all analyses, and the significance level was accepted as $p<0.05$.

RESULTS

In this study, normal pregnant women, asymptomatic COVID-19 patients, mild-moderate patients hospitalized in the normal service, and patients followed in the ICU unit were analyzed. It was determined that 46.43% (n=13) of pregnant women with COVID-19 were carriers and 53.47% (n=15) were sick. Seven of the patients were hospitalized in the ICU, and eight patients were followed up in the normal service. The IL-6 parameter was found to differ significantly between the groups (p=0.001). The Bonferroni-corrected Mann–Whitney test showed that the IL-6 value in COVID-19 negative patients was significantly lower than in the COVID-19 positive (patient) group (p=0.001) (Table 1).

The IL-10 parameter was found to differ significantly between the groups (p=0.001). The Bonferroni-corrected Mann–Whitney test, which was used to determine which groups caused the difference, showed that the IL-10 value in COVID-19 negative patients was significantly higher than in the COVID-19 positive (carrier) group (p=0.002) and the COVID-19 positive (patient) group (p=0.002) (Table 1).

COVID-19 negative pregnant women, mild-moderate COVID 19 pregnant women hospitalized in the normal service, and COVID-19 pregnant patients hospitalized in the ICU were compared. It was found that the IL-6 parameter differed significantly between the groups (p=.003). The Bonferroni-corrected Mann-Whitney test, which was performed to determine between which groups the difference originated, was significantly lower in the IL-6 value of COVID-19 negative patients compared to the COVID-19 positive normal ward (p=.008) and COVID-19 positive intensive care group (p=.004) demonstrated that (Table 2).

It was found that the IL-10 parameter differed significantly between the groups (p=.009). The Bonferroni-corrected Mann-Whitney test showed that the IL-10 value of COVID-19 negative patients was significantly higher than the COVID-19 positive intensive care group (p=.011).

DISCUSSION AND CONCLUSION

In the present study, anti-inflammatory IL-10 and pro-inflammatory IL-6 cytokine levels were compared in third-trimester pregnant women who were COVID-19 positive and negative. COVID-19 patients were classed as carriers or inpatients. Of the total, 46.43% (n=13) of the pregnant women with COVID-19 were carriers, while 53.47% (n=15) were patients; 25% (n=7) of the COVID-19 patients required admission to the ICU. In a study conducted by Samadi and Alipour with 206 COVID-19-positive pregnant women, all of whom were symptomatic, 12.8% of the patients required intensive care (19). In another study by Kim et al., 12.9% of pregnant women with COVID-19 were taken into intensive care (20). The rate of admission to the intensive care unit, which was found to be higher in the present study than in other studies, could be since all our patients were in the third trimester. As the pregnancy progresses, the need for intensive care may arise with increased immunological and physiological stress. IL-1, IL-6, IL-8, and IL-10 have been shown to be associated with COVID-19, having been found to be mediators of the cytokine storm involved in the pathogenesis of the disease. Recent studies in the literature report that IL-6 levels increase and IL-10 levels decrease during a severe course of COVID-19 (21,22). High levels of IL-6 in the blood indicate inflammation, which is characteristic of severe COVID-19 and is associated with respiratory failure (23). It has been reported that IL-6 levels are higher in COVID-19 patients requiring intensive care (24). Maternal pro-inflammatory and anti-inflammatory cytokines are tightly regulated during pregnancy (25-30). The first two trimesters of pregnancy are prone to pro-inflammation and the last trimester to anti-inflammation. While cytokines such as IL-6 are stable in the second half of pregnancy, the balance is disturbed in favor of anti-inflammatories (31). IL-6 is a pleiotropic cytokine that functions differently at various stages of pregnancy. In addition, excessive production of IL-6 may lead to undesirable pregnancy complications such as preterm birth and premature rupture

(32). In the present study, IL-6 levels were higher in mild-moderate and severe COVID-19 patients compared to healthy controls (p=0.001). Similarly, in a study by Tanacan et al., the IL-6 level was greater in pregnant women with COVID-19 than in healthy controls (33). Sherer et al. reported that IL-6 levels were similar between healthy pregnant women and pregnant women with mild to moderate COVID-19 (34). The cytokine levels such as IL-2, IL-10, and IL-12 in pregnant women with COVID-19 are greatly reduced compared to healthy pregnant women (35). In the present study, IL-10 levels were significantly lower in pregnant women with COVID-19 carriers and patients compared to healthy pregnant women (p<0.01). In a study by Tanacan et al., IL-10 levels were found to be significantly lower in pregnant women with COVID-19 than in the controls (p=0.002) (33). On the other hand, some studies have reported elevated IL-10 levels in pregnant women with COVID-19 (36). These studies have found that, as pregnancy progresses, the cytokine balance shifts towards anti-inflammatories and this leads to an increase in cytokines such as IL-10. The generally milder course of COVID-19 disease in pregnant women is answered by this increase in IL-10 levels. In the present study, it is considered that the lower IL-10 levels in pregnant women with COVID-19 are the underlying cause of impaired immune tolerance.

This study has some limitations. First, the study was designed retrospectively. In addition, the number of patients included in the study was relatively small. Finally, the effects of IL-6 and IL-10 cytokines in pregnant women with COVID-19 could be compared separately between all three trimesters. However, considering the inadequacy of studies on the subject, it is thought that the findings will guide similar and comprehensive studies to be carried out in the future. The present study shows that IL-6 levels are increased and IL-10 levels are decreased in asymptomatic and symptomatic pregnant women with COVID-19. These increases and decreases become more effective as the severity of the disease increases. Close monitoring of IL-6 and IL-10 cytokine levels is recommended to minimize the risk of adverse outcomes in pregnant women presenting with a confirmed or suspected diagnosis of COVID-19. In this way, it should be possible to distinguish moderate–mild COVID-19 from severe COVID-19 in pregnant women.

Conflict-of-interest and financial disclosure

The author declares that she has no conflict of interest to disclose. The author also declares that she did not receive any financial support for the study.

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