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# DOES SARS-COV2 INFECTION CHANGE THE LEVEL OF FIBRINOGEN AT PREGNANCY?

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## 1. INTRODUCTION

The New Type Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV2) infection, which has been effective since January 2020 and caused a pandemic(Liu, Kuo, & Shih, 2020) continues to be a public health problem. The virus, which is transmitted through the respiratory tract, manifests itself mainly as lung disease and causes symptoms such as fever, fatigue, and shortness of breath. In addition to social effects, the effect on pregnant women, which is a special group, has gained importance due to the rapid spread of the virus around the world and its high contagiousness. Depending on the immunological and physiological changes of pregnancy on the cardiopulmonary system, more severe symptoms may develop in pregnant women after viral infections(Jamieson, Theiler, & Rasmussen, 2006).

Little is known about the effect of Covid-19 on pregnancy or the effect of pregnancy on Covid-19 infection. However, pregnant women with Covid-19 need more intensive care and oxygen demand than non-pregnant women. It has been demonstrated that the disease progresses more severely in pregnant women(Zambrano et al., 2020).

The risk of thromboembolic complications increases due to increased coagulation factors during pregnancy. It is also known that there is an increase in the total fibrinogen concentration due to these physiological changes during pregnancy(Manten et al., 2004). Inflammatory mechanisms come into play due to SARS-CoV2 infection. In this process, neutrophils, cytokines, activated platelets, microparticles, coagulation factors cause endothelial damage due to excessive thrombin formation and cytokine release. In this process, patients experience an increase in fibrinogen, excessive fibrin formation, and an increase in fibrinolysis products such as D-Dimer as a result of its fibrinolysis(Colling & Kanthi, 2020).



There have been many publications related to disseminated intravascular coagulopathy (DIC), venous thromboembolism, and fibrinogen level in the non-pregnant patient group with COVID 19, but there are not enough publications in the literature regarding pregnant women with COVID-19. The fibrinogen level increases physiologically during pregnancy and the increased tendency to thrombosis. SARS-CoV2 infection also increases the tendency to thrombosis. The interpretation of these changes in pregnant women who have a special group, Covid-19, becomes important.

## 2. MATERIAL METHOD

The study consists of pregnant women who applied to a tertiary hospital with the suspicion of SARS-CoV-2 infection between March 2020 and December 2020. The study was approved by the Hitit University Faculty of Medicine clinical research ethics committee (06.01.2021-379) and the Ministry of Health (2021-01-13T15).

During the COVID-19 pandemic, Covid PCR test and routine blood tests are taken from pregnant patients who applied to the emergency department of our hospital with the suspicion of SARS-CoV-2 infection. Fibrinogen level is also checked in routine blood tests. Pregnant women with positive Covid-19 PCR tests, and pregnant women with Covid 19 symptoms, whose PCR test is performed and whose results are reported as negative, are compared.

Evaluated patients; Age, body mass index, number of pregnancies, weeks of gestation, fibrinogen level, medical diseases were analyzed retrospectively. Those with chronic diseases, smokers, pregnant women using anticoagulants, and pregnant women in the first and third trimesters were excluded from the study.

A total of 459 pregnant women who applied to the COVID emergency department between March 2020 and December 2020 were screened, 102 of them were in the first trimester and 134 of them were in the third trimester. It was determined that 61 of 223 pregnant women did not controlled for fibrinogen level, and 10 of them used anticoagulants and smokers. A total of 152 pregnant women who were in the second trimester and met the criteria were included in the study. Flow chart of the study as shown (Figure 1).



Figure1.Study design

### 2.1 Statıstıcal Analysıs

Statistical analysis of the data was done with SPSS 21.0 Available software package. Kolmogorov-Smirnov and Shapiro Wilk tests were used to determine the normality distribution. Independent Samples T-test was used for normally distributed data. Categorical data were analyzed using Fisher's exact test and cases were expressed as percentages. Continuous variables were expressed as mean and standard deviation (SD)

A P value of <0.05 was considered statistically significant**.**

## 3 .RESULTS

A total of 152 pregnant women who were in the second trimester (14-28 weeks), did not have any chronic diseases, were not using anticoagulants, and non-smokers were included in the study. These pregnant women were divided into two groups as 31 (20.4%) Covid PCR positive and 121 (79.6%) PCR negative. The main statistical analysis of the groups is shown in Table 1.

The mean age and body mass indexes of the pregnant women were found to be similar (*P*=.265 and *P*=.792). The mean week of gestation was 26.5(6.36) in Covid PCR positives and 24.6(3.02) in negatives, no statistical difference was found (*P*=.711). There was no statistically significant difference between the groups in terms of the number of normal deliveries, the number of cesarean deliveries, and the number of abortions.

The mean fibrinogen level of Covid PCR-positive patients was found to be 461,32(68,19) mg/dl. The mean fibrinogen level of Covid PCR negative patients was found to be 431,64(119,35) mg/dl. When the two groups were compared, the fibrinogen level of Covid-positive pregnant women was statistically similar to that of covid-negative pregnant women (*P*=.073).



Table 1. Statistical Analysis Results of the Groups

BMI: Body Mass Index  Mann – Whitney U test, *P*< 0.05 was considered statistically significant.

## 4. DISCUSSION

In our study, we mainly aimed to reveal the difference between the fibrinogen level in pregnant women with Covid-19 and the fibrinogen level in healthy pregnant women. We found that the fibrinogen level of pregnant women who had Covid-19 in the second trimester was similar to the fibrinogen level of healthy pregnant women in the second trimester.

Fibrinogen, also known as factor 1 in the coagulation system, interacts with the glycoprotein IIb/IIIa found in the platelet membrane and performs platelet aggregation. With this role, it takes on the task of primary substrate. Fibrinogen, which also acts as a substrate for factor XIII and plasmin, also shows anticoagulant and antithrombin properties when thrombin production is high. Because of these effects, small changes in the plasma concentration of

fibrinogen are very important for vascular thrombosis. In a study evaluating the laboratory test results of Covid-19 patients, prolonged prothrombin and activated partial thromboplastin time, increased fibrinogen level, increased platelet count and threefold increased D-dimer level were found(Harenberg & Favaloro, 2020). In another study, it was shown that the fibrinogen level of patients who were not pregnant with Covid-19 infection increased slightly(Yang et al., 2020). In our study, we found that the change in the fibrinogen level of pregnant women who had Covid-19 was similar to these studies.

The elevated fibrinogen level due to Covid-19 infection may be a warning to the clinician for the follow-up and course of the disease. Although most of the coagulation parameters are due to Covid-19 infection change, the correlation with these parameters is different from each other in determining the severity and mortality of the disease(Tang, Li, Wang, & Sun, 2020). Although the activated partial thromboplastin time (aPTT) is generally normal in Covid 19, it can be found to be prolonged in 6% of patients(9). Although prothrombin time (PT) is also high in sepsis, it was found to be normal or close to normal in most of the Covid 19 patients, and prolonged in only 5% of them(Chen et al., 2020). Although the degree of increase in the fibrinogen level was not found to be associated with mortality, the progressive decrease in the fibrinogen level was found to be closely associated with mortality(Tang et al., 2020).



Fibrinogen also increases during pregnancy and studies are reporting that it is at a higher level, especially in the third trimester(Abbassi-Ghanavati, Greer, & Cunningham, 2009). In our study, we also showed that the fibrinogen level in pregnant women does not increase with Covid 19 infection. There is a 4-6 fold increased risk of venous thromboembolism due to hypercoagulopathy has seen in pregnancy(Sultan et al., 2012). Fibrinogen, which increases physiologically during pregnancy, increases physiologically to limit bleeding in the possible risk of bleeding. Despite this high fibrinogen level, thrombosis does not develop in all pregnant women, indicating that hyperfibrinogenemia is less likely to be prothrombotic. However, the occurrence of Covid 19 infection with pregnancy suggests that the risk of thrombosis will increase further. It has not been conclusively demonstrated that fibrinogen plays a direct and causal role in causing thrombosis in these conditions(Machlus, Cardenas, Church, & Wolberg, 2011).

It is said that fibrinogen levels can be used as a prognostic marker in pregnant women infected with Covid 19(Kadir et al., 2020). Hyperfibrinogenemia is a characteristic finding for

this patient group. As a result of a study conducted in patients who had Covid -19 and were not pregnant, it was reported that the rate of deep vein thrombosis and pulmonary embolism fluctuated between 0-54%(Kollias, Kyriakoulis, Stergiou, & Syrigos, 2020). Considering this situation, which is prone to thrombosis, the use of low molecular weight heparin for anticoagulant purposes has been recommended by the International Society for Thrombosis and Hemostasis(Thachil, Tang, & Gando, 2020). In a systematic review, the risk of bleeding associated with the use of LMWH for treatment and prophylaxis during pregnancy was <2%(Greer & Nelson-Piercy, 2005). The risk of bleeding associated with the use of LMWH for thromboprophylaxis is low, and these studies show that the use of LMWH during pregnancy may be safe.

Studies have shown that fibrinogen levels can change depending on body mass index. In a study, it was shown that fibrinogen level was correlated with body mass index, and fibrinogen level decreased in patients with weight loss(Ditschuneit, Flechtner-Mors, & Adler, 1995). The fact that the body mass index of the groups was similar in our study eliminated the change in fibrinogen level depending on the body mass index.



## 5. CONCLUSİON

It was observed that the fibrinogen level of Covid 19-PCR(+) patients, was similar to the control group. Considering the fibrinogen levels of pregnant women with Covid 19, they should be evaluated for thromboprophylaxis and their treatment should be arranged to prevent thromboembolic events.

The fact that only second-trimester patients were evaluated in the study and the tendency to thrombosis increases in the following weeks is the limitation of the study. Evaluation of pregnant women in the third trimester from this point of view and determination of their results will add additional information.

**Declaration of Competing Interest:**

The authors declare that they have no known financial or personal relationships that could have appeared to influence the work reported in this study

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| | Covid PCR (+) N= 31 (%20,4) | | Covid PCR (-) N= 121 (%79,6) | | *P* |
|---|---|---|---|---|---|
| | Min-max(Median) | Mean±SS | Min-max(Median) | Mean±SS | |
| **Age (year)** | 18-39(29) | 29,16±5,69 | 18-45(30) | 28,32±5,71 | ,265 |
| **BMI ($kg/cm^2$)** | 22,1-29,1(25,2) | 23,9±0,96 | 20,3-28,1(23,92) | 24,2±0,84 | ,792 |
| **Pregnancy Week** | 22-31(26) | 26,5±6,36 | 19-28(25) | 24,6±3,02 | ,711 |
| **Number of Vaginal Birth** | 1-2(1) | 1,5±0,70 | 0-3(1) | 1±1,06 | ,411 |
| **Number of Caesarean Sections** | 0-2(1) | 1±1,41 | 0-2(1) | 0,75±0,70 | ,780 |
| **Number of Abortions** | 0-2(0) | 1±0,7 | 0-4(1) | 1±1,14 | ,238 |
| **Fibrinogen Level* (mg/dL)** | 322-627(476) | 461,32±68,19 | 237-822(439) | 431,64±119,35 | **,073** |

*İndependent – Samples T Test

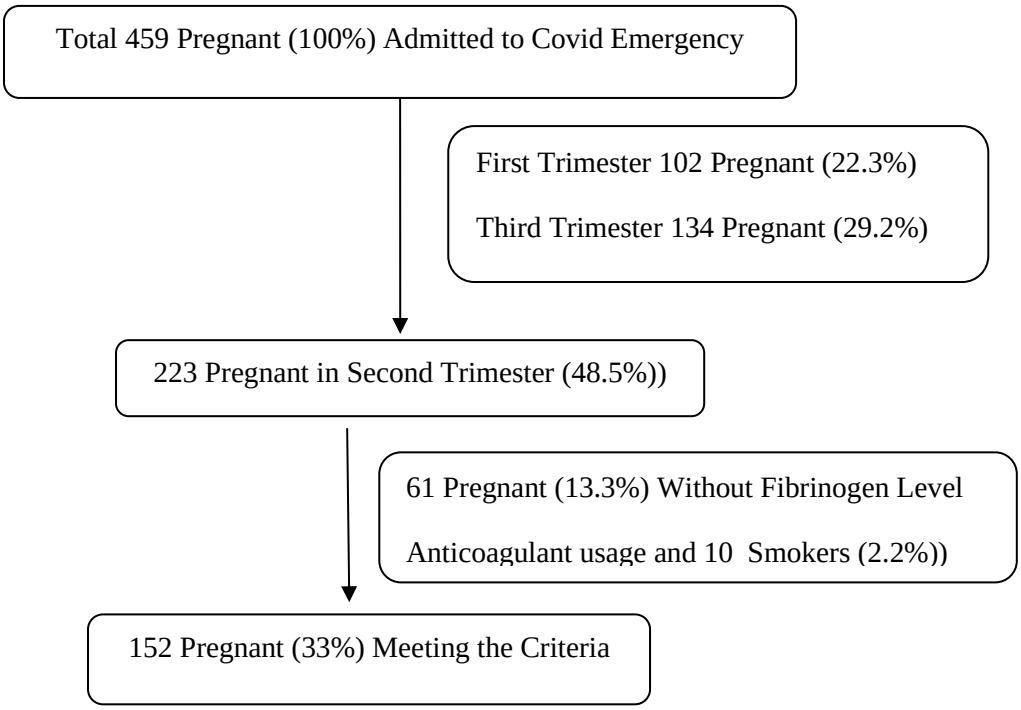


Figure1.Study design