Özgün Araştırma / Original Article

Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology - Obstetrics and Neonatology

DOI: 10.38136/jgon.1345235

Evaluation of first trimester uterine artery resistance and placental volume in patients who had coronavirus disease-19 Before pregnancy

Gebelikten önce COVID-19 geçirenlerde ilk trimester uterine arter direnci, plasental volüm ve gebelik sonuçlarının incelenmesi

MEHMET ÖZER [1] Orcid ID: 0000-0003-0683-0710
PINAR TUĞÇE ÖZER [2] Orcid ID: 0000-0002-3571-8894
ALPER İLERİ [3] Orcid ID: 0000-0002-4713-5805
SERCAN KANTARCI [4] Orcid ID: 0000-0001-5608-060X
HALİL GÜRSOY PALA [5] Orcid ID: 0000-0003-1569-4474

[1] University of Health Sciences, Department of Obstetrics and Gynecology, Division of Perinatology, Tepecik Training and Research Hospital Izmir, TURKEY

[1] Kemalpasa State Hospital, Department of Obstetrics and Gynecology, İzmir, TURKEY

[1] University of Health Sciences, Department of Obstetrics and Gynecology, Tepecik Training and Research Hospital Izmir, TURKEY

[1] Department of Obstetrics and Gynecology, Aydin Provincial Health Directorate Gynecology and Pediatrics Hospital, TURKEY

[1] Department of Obstetrics and Gynecology, Division of Perinatology, Ekol Private Hospital, Izmir, TURKEY

ÖZ

Amaç: Gebelikte geçirilen koronavirüs hastalığı 2019 (COVID-19) vasküler hasar yaratarak ve uterin kanlanmayı etkliyerek gebelik sonuçlarını kötüleştirdiğine dair çalışmalar mevcuttur. Bu çalışmada Covid-19 geçirdikten sonra gebe kalanlarda ilk trimester plasenta gelişimini ve gebelik sonuçlarını değerlendirerek ve Covid-19 etkisinin kalıcılığını araştırdık.

Gereçler ve Yöntem: Bu prospektif çalışma, gebeliğinden bir yıl öncesine kadar Covid-19 maruziyeti olan gebeler ile sağlıklı gebe kontrol grubundaki plasental hacim ve uterin arter Doppler akım ölçümleri arasındaki farklılıkları değerlendirmektedir.

Bulgular: Yaş, doğum oranı ve vücut kitle indeksi gibi demografik özelliklerin, 50 hasta ve 50 kontrol üzerinde yapılan bu çalışmada benzer olduğu görüldü. Oligohidramniyoz, prematürite, preeklampsi ve intrauterin büyüme geriliği gibi çeşitli sonuçlar incelendiğinde; bu verilerde istatistiksel olarak anlamlı olmayan hafif varyasyonlar dikkat çekti. Doğum ağırlığı ve 1. dakika Apgar skoru gibi parametreler iki grup arasında benzerlik gösterirken, plasental hacim ve uterin arter Doppler sonuçlarında anlamlı farklılıklar saptanmadı.

Sonuç: Yapılan çalışmada, gruplar arasında plasental veya Doppler ölçümlerinde herhangi bir farklılık bulunmamıştır. Bugüne kadar yapılan çalışmalar genellikle gebelikte geçirilen Covid -19'un gebelikteki etkisi üzerine gerçekleştirilmiştir. Bu çalışma ise gebelik öncesi geçirilen Covid-19'un gebelikteki etkisinin belirlenmesine yardımcı olmuştur.

ABSTRACT

Aim: There are studies showing that acquiring coronavirus disease 2019 (COVID-19) while pregnant might cause vascular damage, affect uterine blood circulation, and worsen pregnancy outcomes. In this study, we looked at the first-trimester placental development and pregnancy outcomes in people who conceived after getting better from Covid-19. We also looked into the durability of the Covid-19's effects on pregnancy.

Matherials and Methods: This prospective case-control study investigates placental volume and uterine artery Doppler flow differences in pregnant women with Covid-19 exposure within a year prior to pregnancy versus healthy pregnant controls.

Results: In a study involving 50 patients and 50 controls, it was discovered that demographic traits like age, birth rate, and body mass index were comparable. There were statistically insignificant slight differences in these results when different outcomes, including as oligohydramnios, preterm, preeclampsia, and intrauterine growth retardation, were studied. While birth weight revealed similarity between the two groups, placental volume and uterine artery Doppler results did not reveal any appreciable variations.

Conclusion: No distinction between the groups' placental or Doppler readings was found in the investigation that was completed. This work has helped identify the impacts of Covid-19 contracted prior to pregnancy on gestation, whereas previous study has mainly focused on the impact of Covid-19 infected during pregnancy.

Keywords: Intrauterine growth retardation, placental volume, preeclampsia, uterine artery Doppler

Sorumlu Yazar/ Corresponding Author: Mehmet ÖZER
Adres: University of Health Sciences, Department of Obstetrics and Gynecology, Division ofPerinatology, Tepecik Training and Research Hospital Izmir, TURKEY
E-mail: memozer1@hotmail.com

Başvuru tarihi: 17.08.2023
Kabul tarihi: 20.08.2023

INTRODUCTION

Placental volume is a structure that grows as a result of increased vascularity with the effect of hormones secreted by the placenta during pregnancy. Placental volume plays an important role in fetal development and varies in the prenatal period (1). Ultrasonographic methods are the most common technique used to measure placental volume. This method can be performed at any time of pregnancy and can measure placental volüme (2). Placental volume can be calculated by creating a three-dimensional image, or placental thickness, width, and length can be measured using a two-dimensional image. Evaluation of placental volume plays an important role in determining complications in pregnancy (3). Placental volume may be decreased in cases such as placenta previa, placental abruption, and growth restriction. On the other hand, placental volume may increase in gestational diabetes and twin pregnancies. Ultrasonographic evaluation of placental volume plays an important role in pregnancy follow-up and provides information about the health of the fetus (4,5). The effect of coronavirus disease 2019 (Covid-19) infection on placental volume is not fully known. However, some studies show that Covid-19 infection may cause a decrease in placental volume in late pregnancy (6). There are not enough studies yet on whether having Covid-19 has any effect on uterine artery pulsatility index (PI) dopplers. However, Covid-19 infection, like other viral infections, can cause vascular damage and therefore affect blood flow in the uterine arteries (7).

Covid-19 can create detrimental effects on the placenta, potentially leading to malperfusion and resulting in adverse outcomes (8). Understanding the long-term effects of these impacts and how they affect subsequent pregnancies is of significant importance. The primary objective of this study is to determine the persistence of Covid-19-induced detrimental effects on the placenta and their impact on subsequent pregnancies.

MATERIALS AND METHOD

Study Design and Patients' Selection

Our study was designed as a prospective case-control study aiming to evaluate the differences in placental volume and uterine artery Doppler flow between pregnant women who had contracted Covid-19 within the past year before pregnancy and healthy pregnant women. There is also assessed pregnancy outcomes. The study commenced after obtaining ethical committee approval (decision no.15-02-2022- 2022/02-44). The inclusion criteria for our study consisted of women who presented for the first-trimester screening test and had a gestational age of between 12 and 14 weeks of pregnancy, determined based on the last menstrual period. Only women with singleton pregnancies and no additional medical conditions were included. In the patient group, 50 pregnant women who had tested positive for Covid-19 by PCR prior to pregnancy within the last year were recruited. The control group comprised 50 pregnant women who had not previously contracted Covid-19 (no symptoms and negative PCR results). Placental volume and uterine artery Doppler measurements were conducted for each participant. Exclusion criteria encompassed multiple pregnancy, molar pregnancy, cesarean scar pregnancy, ectopic pregnancy, maternal systemic diseases, and cases of fetal demise. The findings of PCR tests were taken into consideration for the individuals hired for work, and vaccination records were not questioned.

Perinatal complications such as oligohydramnios, preeclampsia, fetal growth restriction, and preterm delivery were documented during the patients' prenatal follow-up.

Using sonographic measurements of intrauterine growth retardation (IUGR), such as fetal biparietal diameter, head circumference, abdominal circumference, and femur length, the estimated fetal weight (EFW) was characterized as falling below the 3rd percentile, accompanied by the observation of diastolic end-flow loss during Doppler examination. Furthermore, the EFW percentile was ascertained based on the 'International estimated fetal weight standards of the INTERGROWTH-21st Project' study (9).

Oligohydramnios was characterized based on the definitions provided by Rabie et al. as an amniotic fluid index (AFI) measurement below 5% or less than 5cm, along with a single deepest pocket (SDP) measurement of 2 cm or less (10).

In our study, the diagnosis of preeclampsia for our patients was based on the diagnostic criteria provided by the American College of Obstetricians and Gynecologists (ACOG) (11).

Ultrasound Measurement Techniques of The Placenta

The US measurements were conducted by a single sonographer with 10 years of experience using the Samsung Ultrasound System HS70A, a 3D ultrasound machine manufactured by Samsung Medison Company in the Republic of Korea. The 3D ultrasound probe was utilized to determine the location and maximum vertical diameter of the placenta. Subsequently, the placental contour was manually recorded in 6 consecutive images to ensure exclusion of the uterine wall. The placental volume was automatically calculated for all planes using the Virtual Organ Computer-Aided Analysis (VOCAL) technique.

Statistical Analysis

All statistical analyzes were performed using the Statistical Package for the Social Sciences (SPSS) v.23.0 for Windows (SPSS, Inc., Chicago, IL, USA). Categorical variables were presented as numbers and percentages, and continuous variables as mean, deviation, and minimum–maximum. Pearson's Chi-square test was used to compare categorical variables. For comparing continuous variables between the groups, independent Student's t-test was used for binary variables by controlling the distributions. The differences observed between the groups were summarized using a boxplot. The statistical significance level was set at P:0.05 for all the tests.

RESULTS

We aimed to prospectively compare the effect of having Covid-19 in the last 1 year on placental volume and uterine artery Doppler flows between 2 groups, 50 patients in the study group and 50 patients in the control group. The mean age was 25.3(±5.4) in the Pregnant with Previous Covid-19 group and 24.4 (±5.5) in the control group (p=0.4). When compared in terms of the number of births, the mean of the study group was 2.8(±1.2) while it was 2.9(±1.4) in the control group (p=0.7). When the body mass index was compared between the 2 groups, it was found to be 27.3(±3.8) in the study group and 27.6(±4.3) in the control group (p=0,6) (Table 1).

Table 1: Comparison of Clinical and Obstetric Outcomes

	Pregnant with Previous COVID-19 patient (n=50)	Control patient (n=50)	P Value
Age	25.3(±5.4)	24.4(±5.5)	0.4
Gravide	2.8(± 1.2)	2.9(±1.4)	0.7
Body Mass Index	27.3(±3.8)	27.6(±4.3)	0.6
Preterm Birth			
Yes	5 (%10)	4(%8)	0.77
No	45(%90)	46(%92)	
Oligohidroamniyozis			
Yes	6 (%12)	7(%14)	0.76
No	44(%88)	43(%86)	
İntra Uterin Growth Restriction			
Yes			0.5
No	7(%14)	9(%18)	
	43(%86)	41(%82)	
Preeclampsia			
Yes	3(%6)	2(%4)	0.5
No	47(%94)	46(%96)	

We compared the frequencies of intrauterine growth retardation, oligohydramnios preterm birth and preeclampsia parameters between the two groups. While oligohydramnios was seen in 6 (12%) patients in the group that had Covid-19 infection, amniotic fluid was normal in 44 (88%) patients. In the control group, while oligo was detected in 7 (14%) patients, amniotic fluid was normal in 43 (86%) patients. (p=0,76) While intrauterine growth retardation was observed in 7 (14%) patients in patients who had Covid-19, it was not detected in 43 (86%) patients. In the control group, while iugr was detected in 9 (18%) patients, it was not detected in 41 (82%) patients.(p=0,5) When the 2 groups were compared, preterm birth was seen in 5 (10%) patients in the study group, while 45 (90%) patients had term births. In the control group, 4 (8%) patients had petterm birth, while 46 (92%) patients had term births. (p=0.77) While preeclampsia was seen in 3 (6%) patients in the Pregnant with Previous Covid-19 group, it was not detected in 47 (94%) patients. In the control group, preeclampsia was observed in 2 (4%) patients (p=0.5) (Table1).

When the group with placental volume Covid-19 was compared and the control group, 60,7 ml (± 4,97) was found in the Pregnant with Previous Covid-19 group and 62,7 ml (±5,34) in the control group. No significant difference was observed between the two groups. There was no statistically significant difference between the mean uterine artery PI parameters for the 2 groups. Mean uterine artery PI was found to be 1.79 (±0.23) in the Pregnant with Previous Covid-19 group, and 1.70 (±0.14) in the control group. Birth weight was 3065 g (±901) in the Pregnant with Previous Covid-19 group and 2983 (±490) in the control group (p=0.5). There was no statistically significant difference between the 2 groups (Table2).

Table 2: Comparison of perinatal and neonatal effects of having COVID 19 infection

	Pregnant with Previous COVID-19 patient (n=50)	Control patient (n=50)	P Value
Placenta volüme(ml)	60.7 (± 4.97)	62.7 (±5.34)	0.053
Mean UA Artery PI	1.79 (±0.23)	1.70 (±0.14)	0.09
Birth Weight	3065 (±901)	2983 (±490)	0.5

DISCUSSION

Uterine artery Doppler measurement is performed to assess the blood flow in maternal uterine arteries. Normal blood perfusion in the uterus is of vital importance for supporting fetal development and placental function. Spiral arterioles that supply the intervillous space in the placenta undergo significant morphological changes to meet the increasing demands of the fetoplacental unit (12). Alterations in these changes may result from defective placentation and contribute to the development of conditions such as preeclampsia and fetal growth restriction (13).

Understanding the relationship between uterine artery blood flow and placental development is fundamental in comprehending the normal placental process and its disruption in conditions like preeclampsia and fetal growth restriction (12).

The existing literature provides diverse findings regarding the impact of Covid-19 on uterine artery Doppler parameters. A majority of these studies indicate a negative effect of the Covid-19 virus on placentation, resulting in detrimental alterations in fetal Doppler parameters (14,15). The mean uterine artery pulsatility index (PI) in the group of pregnant women with a previous Covid-19 infection was 1.79 (±0.23), demonstrating a higher value compared to the control group with a mean of 1.70 (±0.14). However, upon statistical analysis, no significant difference was found between the two groups in terms of the mean uterine artery PI.

During pregnancy, changes in the immune system such as a shift from T-helper 1 (Th1) to Th2 response, decreased natural killer (NK) cell population, and reduced plasmacytoid dendritic cells can be observed. Additionally, there is an increase in progesterone levels, which plays a regulatory role in the circulating immune system, and alterations in pattern Toll-like receptors (TLRs) may occur. These alterations can impact the immune response against viral infections during pregnancy, but further research is needed to determine their precise effects on Covid-19 (16). First-trimester miscarriages occur in approximately 10-15% of pregnancies and can stem from genetic, environmental, or multifactorial etiologies. Mid-trimester pregnancy losses, with an estimated incidence rate of 1-2%, are thought to be influenced by maternal general conditions and a heterogeneous array of causes (17).

In a study conducted by Kazemi et al. (17), it was postulated that Covid-19 cases might be associated with placental insufficiency and inflammation, potentially contributing to pregnancy losses and preterm birth. Nevertheless, Ryan et al (18). Underscored the insufficiency of evidence to establish a definitive relationship between preterm birth and Covid-19 infection, notwithstanding the occurrence of cases involving spontaneous preterm membrane rupture.

According to the cohort study conducted by Pasternak et al. in Denmark, it was observed that Covid-19 was associated with an increased frequency of preterm birth (19). However, in our study, we did not find any statistically significant difference in terms of preterm birth between the control group and the patient group, which is consistent with previous studies in the literatüre (18,20).

Evidence suggests that Covid-19 can elicit inflammation at the maternal-fetal interface, potentially disrupting placental function and contributing to fetal growth restriction (FGR) and villitis (21).

Meta-analyses examining the relationship between Covid-19 and fetal growth restriction have demonstrated an association between Covid-19 infection during pregnancy and an increased frequency of intrauterine growth retardation (17,22). In the PAN-COVID study, which involved the evaluation of 8239 patients, it was observed that women who gave birth two weeks after contracting Covid-19 exhibited a significantly higher prevalence of fetal growth restriction compared to those who gave birth within the same two-week period of infection. However, the study did not yield statistically significant findings regarding fetal growth restriction (FGR) (20).

Despite the hypothesis that SARS-CoV-2 could lead to preeclampsia by binding to angiotensin converting enzyme 2 receptors and causing disruption in the renin-angiotensin system along with vasoconstriction, the precise underlying mechanism remains incompletely understood (23). In the study conducted by Wei et al., it has been demonstrated that Covid-19 is associated with preeclampsia (24). However, our study did not provide statistically significant evidence indicating an increased incidence of preeclampsia among individuals with a history of infection prior to pregnancy.

Covid-19 infection may be associated with many pregnancy complications such as early pregnancy loss, intrauterine growth retardation, preeclampsia (25). When these pregnant women were compared with the control group, no statistically significant difference was found in terms of the frequency of oligohydramnios.

In the literature, a correlation has been established between placental volume and pregnancy complications such as growth retardation, preeclampsia, and chromosomal anomalies (26–28). Considering the detrimental impact of the Covid-19 virus on placentation, our study aimed to investigate potential disparities in placental volume between pregnant women with a history of Covid-19 infection and a control group. The placental volume was determined as 60,7 ml (± 4,97) in the patient group, while it measured 62,7 ml (±5,34) in the control group, indicating a slightly higher value in the control group. However, this difference did not reach statistical significance, suggesting that there was no significant disparity in placental volume between the two groups.

There are many publications in the literature on Covid-19 and pregnancy outcomes. However, the effects of the history of Covid-19 infection on the next pregnancy need new research. While determining the method of our study, we planned to prospectively compare pregnant women who had Covid-19 infection in the last 1 year pre-pregnancy compared to the control group in terms of pregnancy complications. We found no difference between the two groups in terms of pregnancy complications. Although the placental volume seemed to be slightly lower in the pregnant with previous Covid-19 group, no statistically significant difference was found. In our view, the results obtained from this study can enhance our limited knowledge regarding the presence of permanent damage in pregnant women who have experienced Covid-19 pre-pregnancy.

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