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Adverse maternal and fetal outcomes in pregnant women recovering from asymptomatic COVID-19 and fetal Doppler ultrasound parameters

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ABSTRACT

Introduction: Coronavirus 2019 (COVID-19) is a newly emerging viral disease with multisystemic involvement. The aim of this study is to determine the changes in Doppler ultrasound (DUS) parameters, adverse maternal and fetal outcomes and maternal biochemical changes in the 3rd trimester in pregnant women who experienced COVID-19 asymptomatically in the 1st and 2nd trimesters.

Material and methods: This study is a tertiary center retrospective case-control study in which 223 pregnant women recovering from asymptomatic COVID-19 and 223 pregnant women who did not have COVID-19 were included. Medial cerebral artery (MCA) and umbilical artery (UA) vascular resistance parameters and cerebroplacental ratio (CPR) were determined by DUS for both groups. Adverse maternal outcomes (gestational diabetes mellitus [GDM], intrahepatic cholestasis of pregnancy [ICP], preeclampsia) and adverse fetal outcomes (preterm delivery, stillbirth, oligohydramnios, intrauterine growth restriction [IUGR], macrosomia and placental abnormalities) were noted in both groups. Statistical analyses were performed and $p < 0.05$ was considered significant.

Results: UA-pulsatility index (PI) ($p < 0.001$), UA-resistivity index (RI) ($p = 0.047$), UA-systolic/diastolic (S/D) ($p = 0.002$), MCA-PI ($p = 0.038$), MCA-RI ($p = 0.027$) and MCA-S/D ($p < 0.001$) values increased in the group of pregnant women recovered from asymptomatic COVID-19. When biochemical values were assessed, total bilirubin value ($p = 0.022$) and glucose value ($p < 0.001$) were significantly higher in the group of pregnant women recovered from asymptomatic COVID-19. Gestational diabetes mellitus ($p = 0.025$), ICP ($p = 0.023$), preeclampsia ($p = 0.036$), preterm delivery ($p = 0.02$), IUGR ($p < 0.001$), and oligohydramnios ($p = 0.002$) rates were higher in pregnant women recovered from asymptomatic COVID-19.

Conclusions: Even if COVID-19 has an asymptomatic course in pregnant women, it can cause maternal and fetal adverse outcomes. Changes in uteroplacental vascular structures after COVID-19 infection can be examined by Doppler ultrasonography to help prevent undesirable fetal and maternal complications.

KEY WORDS: COVID-19, fetal Doppler ultrasound, gestational diabetes, intrauterine growth restriction, preeclampsia, preterm delivery.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19), which has become the most serious global problem in a very short time, can cause acute respiratory syndrome and present with many symptoms such as fever, dry cough, myalgia, respiratory distress, severe pneumonia and multiorgan failure [1, 2]. In addition, according to the severity of the disease, pulmonary dysfunction, hemostasis

balance deterioration and thrombotic complications are observed in COVID-19 patients [3]. It has been reported that the prevalence of COVID-19 is approximately 15% in pregnant women, and the disease progresses asymptomatically in 50-90% of these women [4]. It has been reported that COVID-19 infections are more severe in the third trimester of pregnancy and may result in death [5]. In addition, the percentage of asymptomatic cases has increased with the easy access to the reverse transcriptase polymerase chain reaction (RT-PCR) test.

It is known that pregnant women are not resistant to infections due to the physical and physiological changes that occur during pregnancy, especially immunological changes and uteroplacental circulation parameters. It has been reported in various publications that there is an increase in complications such as preterm birth, intrauterine growth restriction (IUGR), preterm labor or pregnancy loss in women with COVID-19 infection [5-9].

Although it has been stated that the fetal transmission of COVID-19 may occur vertically and fetal vascular malformation may be caused in placental pathology, there are mechanisms that have not yet been clearly explained [6]. However, it can be presumed that maternal hematological changes in uteroplacental vascular structures are primarily responsible for the adverse perinatal outcomes of COVID-19 rather than vertical transmission.

Doppler ultrasonography (DUS) plays an important role in the monitoring of maternal and fetal complications. Medial cerebral artery (MCA) parameters, umbilical artery (UA) parameters and cerebroplacental ratio (CPR) values provide an effective and easy follow-up method in monitoring hematological changes [10]. It has been stated that variability in blood biochemical parameters in patients with COVID-19 affects the prognosis of the disease [11, 12]. However, there are not enough data about the change of these parameters and clinical results in pregnant women.

The aim of this study is to determine the changes in DUS parameters, adverse maternal and fetal outcomes and maternal biochemical changes in the 3rd trimester in pregnant women who experienced COVID-19 asymptomatically in the 1st and 2nd trimesters.

MATERIAL AND METHODS

This is a retrospective case-control study which analyzed the data of a total of 7612 pregnant women who applied to the obstetrics clinic in a tertiary center between January 2021 and October 2021 and underwent obstetric ultrasound and DUS examination. This study was carried out with the approval of the Ministry of Health of the Republic of Turkey and the local ethics committee and is in accordance with the Declaration of Helsinki (Bioethics Committee approval number: 2021/09-26).

STUDY POPULATION

The case group consisted of 223 pregnant women who had a positive COVID-19 RT-PCR test with samples taken from nasopharyngeal and oropharyngeal swabs in the 1st and 2nd trimesters of pregnancy, but showed an asymptomatic disease course. In order to diagnose asymptomatic COVID-19, the main criterion was the absence of findings suggestive of respiratory system disease such as cough, runny nose, and shortness of breath in patients. However, the absence of symptoms such as headache and abdominal pain was also taken into account.

The group of 223 followed-up pregnant women who did not show COVID-19 symptoms and/or had no contact history were determined as the control group. In order to create two equal groups, selection for the control group was random.

The criteria for inclusion in the case group were to be positive for the COVID-19 RT-PCR test between the 5th and 26th of pregnancy, to show an asymptomatic disease course, and not to be treated in intensive care or hospitalization.

Having gestational diabetes, preeclampsia, gestational hypertension, intrahepatic pregnancy cholestasis in a previous pregnancy, having chronic hypertension or diabetes mellitus, a history of recurrent abortion, having hypothyroidism or hyperthyroidism, and having autoimmune disease, familial or acquired thrombophilic disease were exclusion criteria for both groups.

DOPPLER ULTRASOUND IMAGING

Ultrasonographic examinations were performed with transabdominal ultrasound examination by two obstetricians with 13 and 11 years of experience and a 6-year experienced radiologist. The ultrasound device used in ultrasound examination was a Voluson S8 (GE Medical Systems, Zipf, Austria) and examinations were made with a 2-4 MHz C1-5 RS broadband convex probe. Routine ultrasonographic scans and recommendations of the International Society for Ultrasound in Obstetrics and Gynecology (ISUOG) were performed [13, 14]. The routine ultrasound evaluation stages consisted of evaluation of fetal biometry and anatomy, determination of placental location and grade, amniotic fluid amount and fetal measurements. Fetal biometry parameters included measuring biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), and femur length (FL). In addition to these measurements, estimated fetal weight measurement (EFW) was also performed.

Umbilical artery evaluation was made from the free parts of the DUS umbilical artery, and MCA evaluation was made from the peripheral part of the MCA after leaving the Willis polygon. Spectral examination results were obtained. Pulsatility index (PI), resistive index (RI),

and systolic/diastolic (S/D) values were selected to evaluate UA and MCA flow. CPR was calculated as MCA-PI/UA-PI [15, 16].

In DUS examination, MCAPI, RI and S/D values, UA-PI, RI and S/D values and CPR values were noted.

DATA COLLECTION AND CLASSIFICATION

Gestational diabetes mellitus (GDM), intrahepatic pregnancy cholestasis (ICP), preeclampsia, intrauterine growth restriction (IUGR), oligohydramnios (OH), stillbirth, and preterm birth were investigated in both groups.

The oral glucose tolerance test was performed using 75 g of oral glucose solution. GDM was diagnosed in pregnant women whose fasting plasma glucose was 92 mg/dl, 1st hour plasma glucose was 180 mg/dl, and 2-hour plasma glucose was 153 mg/dl [17]. Pregnant women with obstetric pruritus accompanied by an otherwise unexplained increase in liver function tests or bile acid concentrations and who improved dramatically after delivery were diagnosed with ICP [18]. Intrahepatic cholestasis of pregnancy is defined as: mild (peak bile acids 19-39 μmol/l), moderate (peak bile acids 40-99 μmol/l) and severe (peak bile acids 100 μmol/l or more) [18]. In the case of diastolic blood pressure of 90 mm Hg and above or systolic blood pressure above 140 mm Hg after 20 weeks in a pregnant woman without a history of hypertension, accompanied by renal failure, elevated transaminases due to liver involvement or presence of right upper quadrant pain, proteinuria, headache, mental status changes, neurological complications such as blindness, and hematological complications such as thrombocytopenia and disseminated intravascular coagulation, a preeclampsia diagnosis was made. After 20 weeks of gestation, intrauterine fetal death was diagnosed as stillbirth. Labor before the 37th gestational week was defined as preterm delivery [17]. Oligohydramnios was considered if the amniotic fluid index was < 5 or the maximum widest pocket was < 2 cm. When EFW was < 10th percentile according to the Hadlock fetal growth curve, the fetus was considered as IUGR [19]. Placental invasion anomalies (placenta increta and percreta), partial placenta previa and placenta previa totalis were determined as placental anomalies.

COLLECTION OF BIOCHEMICAL DATA

White blood cells (WBC) 10^9/l, lymphocytes 10^9/l, neutrophils 10^9/l, aspartate transaminase (AST) U/l, alanine transaminase (ALT) U/l, total bilirubin (TBil) mmol/l, albumin (ALB) g/l and glucose (Glu) mg/dl values were noted for both groups.

STATISTICAL ANALYSIS

Data analysis was performed using SPSS 22 (IBM Corp, Armonk, NY, USA). For both groups, mean, median and standard deviation (SD) values were calculated for age, gravida and parity data. Percentages between the two groups were evaluated with the χ^2 test and Fisher's exact confirmation test was performed. Relationships between adverse maternal and fetal outcomes were evaluated by logistic regression analyses. A value of $p < 0.05$ was considered statistically significant.

RESULTS

STUDY POPULATION

The mean age of the pregnant women recovered from asymptomatic COVID-19 was 26.4 ± 3.1 (17-34) and the mean age in the control group was 23.2 ± 4.7 (18-31). The clinical characteristics of both groups are given in Table 1.

STATISTICAL ANALYSIS RESULTS OF DUS PARAMETERS

In the statistical analyses performed between the DUS parameters of the pregnant women recovered from asymptomatic COVID-19 and the control group,

TABLE 1. Clinical characteristics of study group of pregnant women who were recovered from asymptomatic COVID-19 and control group

Parameter	Pregnant women recovered from asymptomatic COVID-19	Control group
Maternal age [years]	26.4 ± 3.1 (SD) (Min:17, Max: 34)	23.2 ± 4.7 (SD) (Min: 18, Max: 31)
Gravida	2.1 ± 2.81 (SD) (Min: 1, Max: 7)	2.3 ± 2.6 (SD) (Min: 1, Max: 5)
Parity	1.8 ± 2.13 (SD) (Min: 1, Max: 7)	1.4 ± 1.21 (SD) (Min: 1, Max: 5)
Abortus	0.2 (0-1)	0.3 (0-1)
GW at COVID-19 test positive		
First trimester (weeks 0-14)	9w 3d (6w 2d – 13w 6d)	
Second trimester (weeks 14-26)	19w 1d (14w 1d – 25w 3d)	
Delivery week	35w 1d (29w 1d – 38w 3d)	37w 2d (33w 1d – 41w 1d)
Vaginal delivery	174	199
Cesarean section	49	24

GW – gestational week, w – weeks, d – days, SD – standard deviation

TABLE 2. Doppler findings and biochemical values of study group of pregnant women who were recovered from asymptomatic COVID-19 and control group

Parameter	Pregnant women recovered from asymptomatic COVID-19	Control group	*p*-value
Doppler findings			
UA-PI	1.38 ± 0.05	0.97 ± 0.17	< 0.001
UA-RI	0.71 ± 0.09	0.61 ± 0.01	0.047
UA- S/D	2.73 ± 0.17	1.12 ± 0.11	0.002
MCA-PI	1.84 ± 0.21	1.15 ± 0.09	0.038
MCA-RI	0.76 ± 0.03	0.61 ± 0.02	0.027
MCA- S/D	3.86 ± 0.31	1.37 ± 0.12	< 0.001
CPR	1.2 ± 0.02	1.9 ± 0.07	< 0.001
Biochemical values			
WBC [10^9/l]	9.73 ± 3.21	9.61 ± 2.89	0.48
Lymphocytes [10^9/l]	1.63 ± 0.57	1.52 ± 1.08	0.063
Neutrophils [10^9/l]	80.17 ± 7.17	79.12 ± 8.18	0.061
AST [IU/l]	22.19 ± 23.12	15.01 ± 5.51	0.54
ALT [IU/l]	17.03 ± 22.17	17.03 ± 4.12	0.97
Total bilirubin [mmol/l]	9.33 ± 3.10	6.17 ± 3.14	0.022
Albumin [g/dl]	3.5 ± 1.07	3.2 ± 2.77	0.27
Glucose [mg/dl]	98.33 ± 22.36	77.01 ± 27.11	< 0.001

all parameters showing increased resistance in the pregnant women recovered from asymptomatic COVID-19. UA-PI ($p < 0.001$), UA-RI ($p = 0.047$), UA-S/D ($p = 0.002$), MCA-PI ($p = 0.038$), MCA-RI ($p = 0.027$) and MCA-S/D ($p < 0.001$) values increased in the group of pregnant women recovered from asymptomatic COVID-19. In addition, the CPR value was significantly lower in the group of pregnant women recovered from asymptomatic COVID-19 ($p < 0.001$) (Table 2).

RESULTS OF THE ANALYSIS OF BIOCHEMICAL DATA

In the statistical analyses performed between the group of pregnant women recovered from asymptomatic COVID-19 and control group blood values, total bilirubin value ($p = 0.022$) and glucose value ($p < 0.001$) were significantly higher in the group of pregnant women recovered from asymptomatic COVID-19. There was no significant difference in WBC, lymphocytes, neutrophils, AST, ALT and albumin values between the two groups ($p > 0.05$) (Table 3).

LOGISTIC REGRESSION ANALYSIS RESULTS FOR ADVERSE MATERNAL AND FETAL OUTCOMES

In the logistic regression analysis to investigate the incidence of adverse maternal and fetal outcomes between the pregnant women recovered from asymptomatic COVID-19 and the control group, the adverse maternal outcome – GDM ($p = 0.025$), ICP ($p = 0.023$) and preeclampsia ($p = 0.036$) – rates were higher in pregnant women recovered from asymptomatic COVID-19. In addition, the rates of preterm delivery ($p = 0.02$), IUGR ($p < 0.001$), and oligohydramnios ($p = 0.002$), which are adverse fetal outcomes, were higher in pregnant women recovered from asymptomatic COVID-19 (Table 3).

DISCUSSION

To the best of our knowledge, this is the first study with the largest population to evaluate adverse perinatal outcomes, Doppler ultrasound parameters and biochemical parameters together in pregnant women recovered from asymptomatic COVID-19. According to the results of this study, we observed that the UA-PI, MCA-PI, MCA-RI, UA-RI, MCA S/D and UA-S/D values increased and the CPR value decreased in pregnant women recovered from asymptomatic COVID-19. The incidence of GDM, IPC, preeclampsia, preterm labor and IUGR in the fetus increased in pregnant women recovered from asymptomatic COVID-19 compared to healthy pregnancies. In addition, the total bilirubin level and glucose level in the blood were increased in pregnant women recovered from asymptomatic COVID-19.

Pulsatility and resistivity indices are calculated with systolic and diastolic flow parameters to measure resistance in vascular structures with DUS examination [20, 21]. For this reason, it is thought that examination with DUS can provide information about fetal involvement in preg-

TABLE 3. Adverse maternal and fetal outcomes of pregnant women who were recovered from asymptomatic COVID-19 patients and control groups

Parameter	Pregnant women recovered from asymptomatic COVID-19	Control group	Odds ratio	95% CI	*p*-value
Adverse maternal outcomes					
GDM	31	16	2.06	1.09-3.90	0.025
ICP	17	6	2.99	1.16-7.75	0.023
Preeclampsia	27	14	2.05	1.04-4.03	0.036
Adverse fetal outcomes					
Preterm delivery	37	21	1.91	1.08-3.38	0.02
Placental anomalies	11	8	1.39	0.55-3.53	0.484
IUGR	47	19	3.008	1.70-5.31	< 0.001
Macrosomia	11	8	1.39	0.55-3.53	0.48
Oligohydramnios	44	21	2.36	1.35-4.12	0.002

GDM – gestational diabetes mellitus, ICP – intrahepatic cholestasis of pregnancy, IUGR – intrauterin growth restriction

nant women who have had COVID-19. In a study by Anuk *et al*., UA-PI and UtA PI values increased in pregnant women who had COVID-19 [22]. Ayhan *et al.* found no significant difference in DUS parameters between pregnant women who had COVID-19 and those who did not [23]. In our study, MCA and UA resistance parameters were significantly higher in pregnant women recovered from asymptomatic COVID-19.

COVID-19 is a multisystemic contagious disease, and the presence of acute inflammation in the placenta and the presence of the virus in the placental villi have been demonstrated in pregnant women infected with COVID-19 [24, 25]. In addition, studies on the placentas of pregnant women who gave birth at term have shown the presence of fetal vascular malformation with multiple thrombosis [26]. The increase in DUS resistance parameters obtained in our study suggests that pregnant women who had COVID-19, even if asymptomatically, may have shown variability due to vascular malformations caused by placental vertical transmission of COVID-19.

It has been reported that an increase in placental resistance is a risk factor for adverse perinatal outcomes such as preeclampsia, IUGR, stillbirth, and preterm labor [27, 28]. Increased resistance in DUS examination is a sign of uteroplacental insufficiency and is especially used in the follow-up of fetuses with IUGR. It has been stated that a decrease in CPR is also an indicator of IUGR. Du *et al.* in a study on adverse perinatal outcomes before and after the COVID-19 pandemic stated that the risk of maternal hypertension and IUGR increased [29, 30]. Although it has been stated in various publications that maternal comorbidity increases in pregnant women with COVID-19 infection and causes adverse perinatal outcomes, a definite explanation has not been provided yet [31]. In previous studies with more limited populations, it was reported that the incidence of preterm labor, preeclampsia, IUGR and stillbirth increased in those who had COVID-19 [7, 32, 33]. Even if there are various publications showing the vertical transmission of COVID-19 [15, 16], it is less likely that the viral load is low in asymptomatic pregnant women and thus may increase placental resistance. However, it has been reported that the COVID-19 virus is different from other viral infections in terms of binding to angiotensin converting enzyme-2 (ACE-2) receptors and reduces these receptors in the placenta [34-36]. Due to these effects, COVID-19 infection may cause pathologies such as preeclampsia with increased vascular resistance and fetal growth retardation as a result of uteroplacental insufficiency with increased placental resistance. According to the results of our study, the risk of preeclampsia, IUGR and preterm labor was observed to be increased in pregnant women who had COVID-19 asymptomatically. These findings support the above data and support the effect of COVID-19 on ACE receptors that play a role in the pathophysiology of increased placental resistance and preeclampsia, independent of vertical transmission, and the development of IUGR due to placental resistance.

Previously, various studies were conducted in which biochemical parameters were evaluated in pregnant women infected with COVID-19 [37, 38]. Total bilirubin, C-reactive protein (CRP) values, lymphocyte and neutrophil values were found to be increased compared to those who did not have COVID-19 [44]. In our study, the incidence of GDM and ICP was higher in pregnant women who had COVID-19 and an increase was observed in total bilirubin and glucose values in pregnant women who had COVID-19. This supports other publications and explains the increased frequency of GDM and ICP in our study.

Total bilirubin is a parameter that shows liver functions. This increase in total bilirubin may indicate both the deterioration in liver function and the deterioration

in liver function associated with ICP and preeclampsia. However, although the increase in AST and ALT values was higher in pregnant women who had COVID-19, there was no statistically significant difference.

The strengths of our study are that it aims to illuminate many problems by investigating adverse maternal and fetal outcomes, resistance parameters of uteroplacental vascular structures and blood biochemical parameters for pregnant women recovered from asymptomatic COVID-19, and the patient population is relatively large compared to other studies in this field.

This study has some limitations. First of all, this study is a retrospective study and may cause bias in the evaluation of these data. Secondly, since it is a single-center study, there is a homogeneous patient population. It would be appropriate to consider these before generalizing the data to the wider population.

CONCLUSIONS

As a result, although COVID-19 infection shows an asymptomatic course in pregnant women, it may cause adverse perinatal outcomes by causing changes in uteroplacental vascular structures and blood parameters. However, DUS vascular resistance parameters determined in the third trimester may be helpful in monitoring and evaluating these findings. Close follow-up of pregnant women with COVID-19 and evaluation with DUS can prevent adverse maternal and fetal outcomes.

DISCLOSURE

The authors report no conflict of interest.

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AUTHORS' CONTRIBUTIONS

EK prepared research concept and design. EK, SK collected data. EK, ME, SK analyzed data and wrote the article. EK, TE, SK critically revised the article. All authors approved the final version of publication.