Placenta 128 (2022) 57–61

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com/locate/placenta

# Point shear wave velocity(pSWV) evaluation of the placenta of pregnant women who had recovered from COVID-19: A prospective cohort study from a tertiary pandemic center

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ARTICLE INFO

*Keywords:*
Elasticity
COVID-19
Placenta
Shear wave velocity
Placental stiffness

ABSTRACT

*Introduction:* To assess the placental elasticity using point shear wave velocity (pSWV) in pregnant women who had recovered from coronavirus COVID-19.

*Methods:* A total of 40 pregnant women who had recovered from moderate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and 40 healthy pregnant women were included in this study. We evaluated placental elasticity by using transabdominal pSWV method. Three measurements were made, and their average was accepted as the mean placental velocity value in each case. The results were compared between the post-COVID-19 and control groups.

*Results:* The mean pSWV values were significantly higher in the post-COVID-19 group compared to the control group, indicating that the women with a history of COVID-19 had stiffer placentas. Furthermore, the pSWV values were significantly and positively correlated with the uterine artery pulsatility index. We also found that the NICU requirement was statistically higher in the post-COVID 19 group.

*Discussion:* The pregnant women who had recovered from COVID-19 had rigid placentas than the healthy controls. The use of pSWV for the assessment of placental velocity may provide valuable information in the diagnosis and management of post-COVID-19 patients as a complementary tool to the existing ultrasonography methods.

## 1. Introduction

COVID-19 is an infectious agent with a procoagulant effect, which may lead to hypoxia in infected patients [1]. Studies show that obstetric complications, such as stillbirth and fetal distress have increased with COVID-19 [2,3]. Some studies have indicated that COVID-19 may cause maternal and fetal complications. Pathological changes in the placenta like chronic intervillositis, villitis, funisitis, and chorioamnionitis were also reported in the literature [4]. COVID-19 may lead to persistent hypoxia, which is associated with intrauterine growth restriction (IUGR), preeclampsia, and stillbirth [5].

Placenta-related pathological conditions play an important role on fetal and maternal morbidity and mortality [6]. The measurement of tissue elasticity or stiffness allows for the assessment of underlying pathologies in an organ. Elastography has been used in the field of oncology for years to differentiate cancerous tissue and surrounding normal tissue based on tissue stiffness [7]. Sonoelastography is a non-invasive technique used to quantitatively assess the elasticity of parenchymal tissue [8–11]. There are few studies in the literature evaluating the elasticity of the fetal placenta with the virtual touch tissue quantification (VTTQ) technique [12]. VTTQ, which is based on acoustic radiation force impulse (ARFI) imaging, a non-invasive method that quantitatively evaluates tissue elasticity [13]. A higher shear wave velocity (SWV) indicates a stiffer tissue. In the present study, we investigated changes in point SWV (pSWV) between patients that had recovered from COVID-19 and those without a history of COVID-19 using the VTTQ technique to measure the elasticity of the placenta. Our hypothesis was that COVID-19 affects the placenta, which may cause differences in placental elasticity.

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https://doi.org/10.1016/j.placenta.2022.08.003
Received 2 February 2022; Received in revised form 3 July 2022; Accepted 12 August 2022
Available online 23 August 2022

## 2. Material & methods

The present study was performed at the Perinatology Clinic of the Turkish Ministry of Health XXXX Hospital between July 1, 2021 and December 31, 2021. Approval for the study was obtained from the Human Ethics Committee of the XXXX Hospital (date:June 30, 2021, number:E2-21-593).). SARS-CoV-2 positive cases confirmed by real-time polymerase chain reaction (RT-PCR) in nasopharyngeal and oropharyngeal samples were included in the study group. All cases were categorized for disease severity and, managed according to TR Ministry of Health General Directorate of Public Health, COVID-19 (SARS-CoV-2 infection) Guide, Scientific Committee Reports [14]. Pregnant women in the post-COVID-19 group had moderate infection according to this guideline. Evaluation of placental elastography and other fetal parameters of the patients was performed at least one month after infection. All pregnant women have survived in the post-COVID-19 group. Forty pregnant women that had recovered from COVID-19 and 40 gestational age-matched healthy pregnant women were included in the study. The exclusion criteria were multiple gestation, fetal aneuploidy or major anomalies, chronic hypertension, gestational diabetes mellitus, and preeclampsia. Women with posteriorly located placentas were also excluded for limitations in determining elastography evaluation. Maternal obstetrical histories of all patients were recorded. In addition, fetal biometry, body mass index (BMI), thickness of placenta, gestational age based on early week ultrasound evaluation, doppler parameters (umbilical artery, uterine artery, ductus venosus, and main cerebral artery), and gestational age at the time of active infection for the post-COVID-19 group were evaluated.

### 2.1. Imaging technique

The patients were evaluated transabdominally and placental elastography images were obtained with a 3.5-MHz convex transducer (6C1-PVT-375BT) using the Logiq S8 (GE Medical Systems) device. Measurements were made while the patient was in the supine position and breathing shallowly, with less fetal movement and without applying any pressure to the skin [15]. VTTQ based on ARFI imaging is a new non-invasive method to quantitatively evaluate tissue elasticity. A short acoustic push pulse is generated with VTTQ, which results in a minute displacement of the targeted tissue, propagating a lateral SWV (m/sec) that can be measured (Fig. 1). SWV is correlated with Young's modulus, which is an index of elasticity [16]. A region of interest (ROI) with a fixed size of 10 × 10 mm was defined using a probe. Three separate measurements were taken from the fetal, maternal and mid-section where the placenta was the thickest, and the average of the three measurements of pSWV was accepted as the placental elasticity value for each patient. Regarding the depth of ROI, pSWV is not reported to be affected at a depth of <8 cm, but the emaciation of the acoustic pulse or distribution of SWV may make the measurement difficult at a depth of >8 cm [17]. Therefore, the ROI was chosen at a maximum depth of 6 cm from the subcutaneous adipose tissue in patients with anterior placenta. The histopathologic examination findings of the placenta specimens were recorded in available cases. In Turkey placental pathologic examination is performed only for limited obstetric indications due to cost-effective issues and limitations in the number of experienced pathologists. Thus, only four placenta specimens were evaluated by the expert pathologists.

### 2.2. Statistical analysis

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS v. 22, IBM, SPSS for Windows, NY: IBM Corp.). Descriptive statistics were presented as mean and standard deviation values as they were normally distributed. Student's t-test was used to compare the mean values between the study groups. Categorical variables were presented as numbers and percentages. The chi-square test was used to compare the categorical variables between the study groups. A correlation analysis was performed with the Pearson test. A two-tailed p value of <0.05 was regarded as statistically significant.

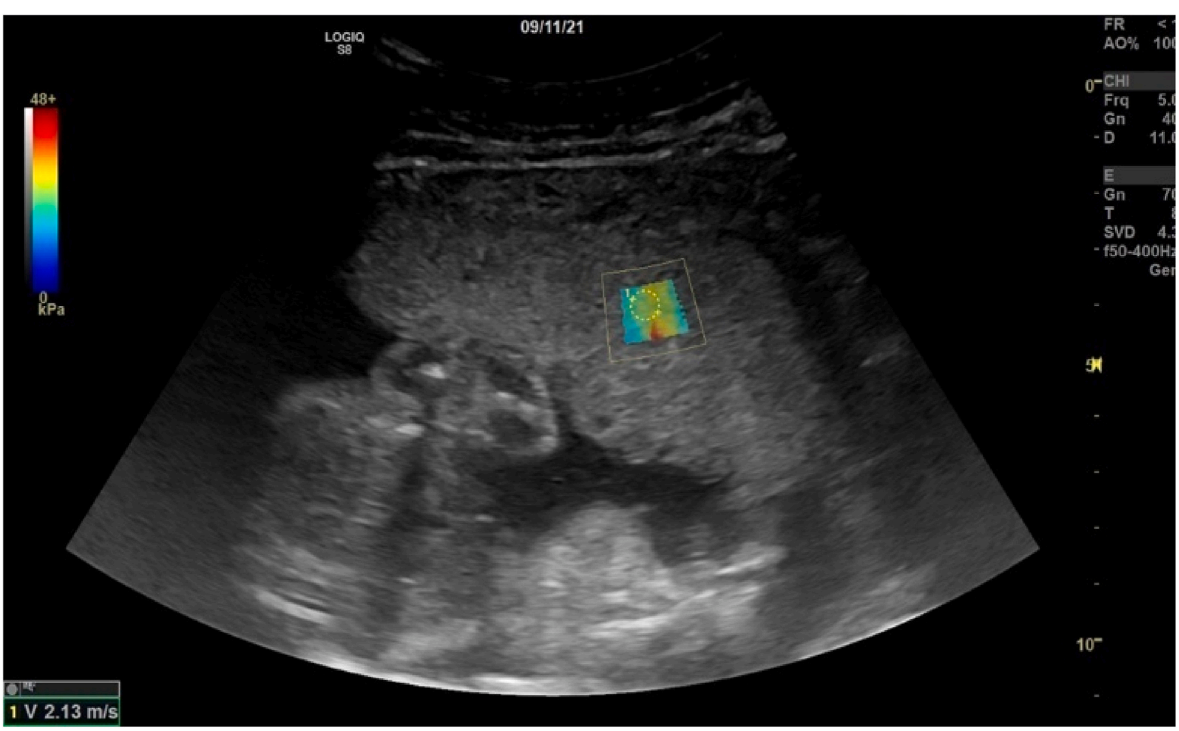


**Fig. 1.** Technique of pSWV
pSWV:point shear wave velocity.

### 2.3. Results

The study included 80 patients (age range, 18–44 years) with 40 healthy pregnant woman and 40 pregnant woman that had recovered from COVID-19. The mean age was 30.2 ± 5.6 for the control group and 28.7 ± 4.7 years for the post-COVID-19 group. The mean gravida and parity numbers were 2.6 ± 1.4 and 1.0 ± 07, respectively in the control group and 2.1 ± 134 and 0.7 ± 08, respectively in the post-COVID-19 group. There was no significant inter-group difference regarding gestational week, patient age, gravidity or parity, placental thickness, BMI, umbilical artery, ductus venosus, and middle cerebral artery pulsatility indices. However, a significant difference was observed between the groups concerning the measurement of placental SWV (m/sec), placental lacunae, and uterine artery pulsatility index. The mean placental SWV(m/sec) measurement value of the post-COVID-19 group was significantly higher than that of the control group ($p = 0.01$). The mean SWV was determined as 1.77 ± 0.25 for the control group and 1.9 ± 0.12 for the post-COVID-19 group, and the mean values of uterine artery pulsatility index were 0.77 ± 0.23 and 0.96 ± 0.25, respectively ($p = 0.01$).

The percentage of patients with placental lacunae was 2.5% (n = 1) for the control group and 77% (n = 31) for the post-COVID-19 group ($p < 0.001$) (Table 1).

There was no significant difference in the placental SWV measurements of the post-COVID-19 group according to hospitalization ($p = 0.5$), steroid use ($p = 0.98$), or receiving medical treatment ($p = 0.70$) (Table 2).

A positive and significant correlation was detected between having a history of COVID-19 and SWV ($r = 0.28$, $p = 0.01$) and presence of placental lacunae ($r = 0.28$, $p = 0.01$), while there were negative and significant correlations between BMI and SWV ($r = -0.22$, $p = 0.04$) and between gestational week and SWV ($r = -0.31$, $p = 0.004$) (Table 3).

There was no significant difference gestational week at birth ($p = 0.5$), fetal birth weight ($p = 0.6$) and fifth minute Apgar score ($p = 0.2$) between groups. In addition, first minute Apgar scores ($p = 0.019$) were lower and the NICU requirement was higher ($p = 0.006$) in the post COVİD-19 group, and it was statistically significant. (Table 4).

Histopathologic examination of the placenta could be performed only in four cases in the study group. Perivillous fibrin deposition, hemorrhagic infarction and villous degeneration were the main findings for these specimens.

**Table 1**
Maternal demografic characteristics, ultrasound parameters and placental parameters.

| Variable | Control group (n = 40) | COVID-19 group (n = 40) | p |
|---|---|---|---|
| Maternal indexes | | | |
| Maternal age (mean ± SD) | 30.2 ± 5.6 | 28.7 ± 4.7 | 0.19 |
| Gravida | 2,6 ± 1,4 | 2,1 ± 1,3 | 0.07 |
| Parity | 1 ± 0,7 | 0,7 ± 0,8 | 0.9 |
| BMI | 27,9 ± 5,07 | 28,6 ± 4,17 | 0.4 |
| Fetal indexes | | | |
| Gestational Week | 30 ± 5,1 | 30 ± 4,2 | 0.8 |
| Ultrasound indexes | | | |
| pSWV(m/sec) | 1,77 ± 0,25 | 1,9 ± 0,12 | 0.01* |
| Umb.Pİ | 0,9 ± 0,2 | 0,95 ± 0,26 | 0.5 |
| Mca Pİ | 2,04 ± 0,58 | 2,04 ± 0,53 | 0.9 |
| Ut.Pi | 0,77 ± 0,23 | 0,96 ± 0,25 | 0.01 * |
| Dv.Pi | 0,65 ± 0,17 | 0,66 ± 0,30 | 0.8 |
| Placental indeces | | | |
| Placental thickness | 39,1 ± 7,8 | 38,6 ± 7 | 0.7 |
| Placental lacunae (n, %) | 1 (2.5%) | 31 (77%) | <0.001* |

pSWV:point shear wave velocity BMI:body mass index.
Student-t test.

**Table 2**
Hospitalization and treatment to relationship of shear wave velocity.

| | pSWV(m/sec) | p |
|---|---|---|
| Medication use | | |
| Yes (n = 31) | 1,89 ± 0,12 | 0.70 |
| No (n = 9) | 1,9 ± 0,13 | |
| Steroid use | | |
| Yes(n = 8) | 1,89 ± 0,11 | 0.98 |
| No(n = 32) | 1,89 ± 0,13 | |
| Hospitalization | | |
| Yes(n = 21) | 1,9 ± 0,13 | 0.5 |
| No(n = 19) | 1,8 ± 0,12 | |

Chi-square test.

**Table 3**
Correlation of placental shear wave velocity.

| | pSWV(m/sec) | |
|---|---|---|
| | r | p |
| COVID-19 positivity | 0.28 | 0.01* |
| Placental thickness | −0.191 | 0.09 |
| BMİ | −0.22 | 0.04* |
| Gestational week | −0.31 | 0.004* |
| Placental lacunae | 0.28 | 0.01* |
| Gestasyonel week at the time of COVİD-19 infection | −0.30 | 0.05 |

Pearson correlation test.

**Table 4**
Neonatal outcomes.

| | Control group (n = 40) | COVID-19 group (n = 40) | p |
|---|---|---|---|
| Gestational week at birth | 37.5 ± 2 | 37.1 ± 2.6 | 0.5 |
| Fetal birth weight | 3019 ± 574 | 2953 ± 637 | 0.6 |
| Apgar, first-minute | 7.3 ± 0.57 | 6.9 ± 0.8 | 0.019* |
| Apgar, fifth-minute | 8.7 ± 0.6 | 8.5 ± 0.8 | 0.2 |
| NICU | | | 0.006* |
| Yes | 2 (5%) | 11 (27.5%) | |
| no | 38 (95%) | 29 (62.5%) | |

NICU: neonatal intensive care unit.

## 3. Discussion

Evaluating the structure and function of the placenta with the elastography technique may be useful in different diseases in which the placenta is affected, such as IUGR, preeclampsia, gestational diabetes mellitus (GDM), and inflammatory/infectious agents [18]. Our aim was to investigate the effect of infection on the placenta using the VTTQ technique in pregnant women who had recovered from COVID-19. In an experimental study, the effects of ARFI imaging evaluated and researchers determined the modality was safe [19]. It has been stated that the temperature increase and mechanical effect caused by vibration pulses in VTTQ are still within the safe limits determined by the American Institute of Ultrasound in Medicine [20,21]. SWV can be affected by various factors during pregnancy. Impairment of perfusion in tissues results in hypoxia, and collagen and fibrin deposition increases in the environment. These situation lead to fibrosis and tissue stiffness increases [22]. In the presence of gestational hypertension and/or intrauterine growth retardation, pathological findings showing infarction, ischemic changes, and fibrosis are frequently detected in the placenta [23–25]. Ohmaru et al. reported that increased SWV in preeclampsia might be affected by focal swelling resulting from ischemic changes, and inflammation, as well as vascular dysfunction [26]. In the current study, we found that the pSWV value of the placentas of pregnant women who had a history of COVID-19 were higher than that of the control group.

Using VTTQ, an acoustic impulse pulse is generated, which emits wave velocity. In this technique, higher pSWV rates are associated with stiffer tissues. The elasticity measurement do not significantly vary between the different regions of the placenta [27,28]. Therefore, we took the measurements from the same plane of the section where the placenta was the thickest. We found the pSWV value to be significantly higher in the post-COVID-19 group compared to the control group. Some of the hospitalized patients required steroids. We also compared the elastographic measurements of the patients with a history COVID-19 between the subgroups that did not require hospitalization, those that were hospitalized and required steroids, and those that were hospitalized but did not receive steroid treatment. This comparative analysis revealed no significant difference between the hospitalized and non-hospitalized patients or between the patients that were given steroid therapy and those that received other medical therapy. Interestingly, we found a high rate of lacunae in the placentas of patients who had recovered from COVID-19, and there was a significant positive correlation between a history of COVID-19 and presence of placental lacunae. While there was a positive correlation between an earlier gestation week at the time of active COVID-19 infection and pSWV, a negative correlation was detected between gestational week, BMI, placental thickness, and pSWV. While there was a positive correlation between an earlier gestation week at the time of active COVID-19 infection and pSWV, a negative correlation was detected between gestational week, BMI, placental thickness, and pSWV. It is physiologically expected that the more severe and longer the duration of inflammation and inflammatory cell infiltration, the greater the tissue damage. This is also confirmed by the higher pSWV values of the patients in the post-COVID-19 group of this study. In a previous study, Anuk et al. found a negative relationship between the pSWV values and the fifth-minute Apgar score [29]. We also establish a positive interrelation between the pSWV rates and uterine artery Doppler pulsatility index. There is a recent study reported that, there were not specific histological findings in most of the placentas (54.8%) of pregnant women who had COVID-19. Also, they found mild maternal vascular malperfusion (22.6%) and/or mild microscopic increased intrauterine infection (24.3%) in the study group [30]. In another study, specific histomorphological changes related to SARS CoV-2 were not recorded in placentas, but villous agglutination and subchorionic thrombus were detected more in placentas from SARS-CoV-2-positive women than in placentas from SARS-CoV-2-negative women [31]. We speculate that increased arterial resistance and placental stiffness are consequences of the same pathophysiological event in patients with a history of COVID-19. In our study, first-minute Apgar scores were found lower in the study group. In addition, NICU requirement was statistically higher in the study group. Increased placental stiffness may give valuable information for adverse perinatal outcomes.

With the constantly developing elastography technology, differences in flexibility between pathological and normal placentas are emerging. pSWV can contribute a new diagnostic technique for pregnant women with a history of COVID-19 and those with gestational diabetes, preeclampsia, placental invasion anomalies, IUGR, or other diseases that are considered to be affected by the placenta due to inflammation/fibrosis during pregnancy. To the best of our knowledge, there is no cohort study in the literature evaluating the elasticity of the placenta in patients with a history of COVID-19. Thus, this is the first report presenting the data of placental elasticity using the VTTQ technique in a cohort of patients that recovered from COVID-19 during pregnancy. The delimitations of the research include its single-center design, inclusion of only anterior placentas, relatively small number of patients. We had organised the study design according to conservative obstetric Doppler indices and the novel technique "shear wave velocity"'. However, these methods evaluated the placental blood flow only in limited aspect. Lack of information related to other novel techniques examining the arterial and venous blood flow of the placenta is a major limitation for the present study. Future studies including more vascular indexes may be favorable to obtain more precisive outcomes. Another major limitation is the lack of information related to the histopathologic findings of the placental specimens in a great number of cases.

In conclusion, increased placental elasticity during pregnancy was found to be high in the post-COVID-19 group. This situation suggests that the VTTQ technique can provide information indicating the presence of pathological findings such as infarction and fibrosis.; nevertheless, the limitation of this technique with regard to placental placement should be noted.

## Financial support statement

All authors approve the final version of the article. Our study is not financially supported.

## Authors contributions

Concept: BS, DŞ, MA, AT, ŞGA,NF, ÖK,RD
Design: BS,AT, DŞ,ÖK
Data collecting: BS,NF,RD
Experiments and procedures; BS,DŞ,AT,ŞGA
Writing of article: BS,AT,DŞ,MA.

## Research funding

None declared.

## Author contributions

All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

## Informed consent

Informed consent was obtained from all individuals included in this study.

## Ethical approval

The ethical approval is E2-21-593.

## Declaration of competing interest

Authors state no conflict of interest.

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