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CLINICAL ARTICLE

Diagnosis of pre-eclampsia and assessment of severity through examination of the placenta with acoustic radiation force impulse elastography

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ABSTRACT

Objective: To assess the value of placental shear wave velocity (SWV) measurement by acoustic radiation force impulse (ARFI) imaging for the diagnosis of pre-eclampsia and to determine the relationship between the SWV and the severity of pre-eclampsia. *Methods:* A prospective study was performed at a center in Turkey between August 2014 and March 2015. The study included consecutive pregnant women in the second or third trimester diagnosed with pre-eclampsia and healthy pregnant women without pre-eclampsia of similar ages. Patients with pre-eclampsia were divided into two groups (severe or mild disease) on the basis of revised American College of Obstetricians and Gynecologists criteria. All patients underwent ARFI, and the SWV was measured at several placental locations. *Results:* Overall, 86 women were enrolled (42 with pre-eclampsia, 44 controls). Minimum, maximum, and mean SWV values were significantly higher in the pre-eclampsia group than in the control group ($P < 0.001$ for all). These values were also significantly higher among patients with severe pre-eclampsia than among patients with mild pre-eclampsia ($P < 0.001$ for all). *Conclusion:* Measurement of the placental SWV with ARFI imaging is a useful additional method for the diagnosis of pre-eclampsia and for determination of the disease severity.

1. Introduction

Pre-eclampsia is a pregnancy complication that is characterized by incipient hypertension, proteinuria, and vascular dysfunction [1]. It is a major maternal, fetal, and newborn morbidity and mortality factor [2]. The condition affects 5%–10% of all pregnancies, and clinically arises after the 20th week of pregnancy [3,4]. Pre-eclampsia can cause serious maternal complications, such as HELLP syndrome (hemolysis, elevated liver enzyme levels, and low platelet level), eclampsia, disseminated intravascular coagulopathy, liver and kidney failure, hypertensive encephalopathy, and pulmonary edema [5,6]. Furthermore, pre-eclampsia causes fetal complications, such as premature birth, intrauterine growth restriction, hematological and neurological problems, and bronchopulmonary dysplasia [7]. For these reasons, it is very important to include the diagnosis and follow-up of pre-eclampsia in pregnancy tracking.

Multiple serum markers (e.g. serum β-human chorionic gonadotropin and pregnancy-associated plasma protein A) combined with Doppler ultrasonography to evaluate the blood flow velocity in the maternal uterine artery have shown promise in the identification of patients at increased risk of pre-eclampsia [8,9]. However, these tests might not be sufficiently accurate in identifying patients at risk or those who already have this complication [10].

Acoustic radiation force impulse (ARFI) imaging, a new technology based on ultrasonography, is a noninvasive imaging method that evaluates the stiffness of soft tissue. The advantages of ARFI elastography include the repeatability of objective measurements, low operator dependence, and the ability to evaluate tissue stiffness and gather qualitative and quantitative information without the need for external compression [11].

Although certain factors—e.g. multifetal pregnancy, advanced age, obesity, diabetes, kidney disease, and a history of hypertension—are known to increase the risk for pre-eclampsia, the pathogenic mechanism of pre-eclampsia is still unclear. Multiple processes—e.g. impaired implantation, systemic inflammation, endothelial dysfunction, and tissue destruction resulting from recurrent ischemia reperfusion—could be responsible for the development of pre-eclampsia [12]. The primary cause in the pathophysiology of pre-eclampsia is abnormal placentation. Failure of spiral artery remodeling and trophoblast invasion can be observed at the end of the first trimester and the beginning of the second trimester [13]. There can also be pathologic changes such as

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fibrin deposition around the placental villi, phenotypic immaturity of the trophoblastic tissue, calcifications, and premature aging of the placenta [14]. The effects of these histopathologic changes on the stiffness of placental tissue can be evaluated with ARFI elastography, and the quantification of placental stiffness might help to determine the prognosis of pre-eclampsia.

Previous studies [15,16] have compared ARFI parameters in normal and pre-eclamptic pregnancies, but the relationship between placental elastography and the severity of pre-eclampsia has not yet been evaluated. The present study aimed to assess the value of the measurement of placental shear wave velocity (SWV) by ARFI for the diagnosis of pre-eclampsia and to evaluate the relationship between the SWV and the severity of pre-eclampsia.

2. Materials and methods

A prospective study was performed between August 1, 2014, and March 31, 2015. Consecutive women with a singleton pregnancy in the second or third trimester diagnosed with pre-eclampsia were enrolled on admission to the obstetrics emergency clinic of Dicle University Medical Faculty, Diyarbakır, Turkey. Consecutive women of similar ages without pre-eclampsia or another pathology who attended the obstetrics clinic at the study center were enrolled into a control group. The pregnancy duration was determined from the menstrual history and confirmed by ultrasonography. The exclusion criteria were: posterior placental position; the region of interest in the placenta placed deeper than 8 cm; placental anomalies including abnormal placental penetration or adherence, abnormal development of the placenta, placental hematoma, and placental calcification; structural fetal abnormalities such as heart defects, omphalocele, ventriculomegaly, and limb abnormalities; severe anemia (hemoglobin concentration <60 g/L); and gestational diabetes. The study was approved by the ethics committee of the study institution. Written informed consent was obtained from all patients.

The diagnosis of pre-eclampsia was made according to the 2013 criteria of the American College of Obstetricians and Gynecologists [17]: blood pressure higher than 140/90 mm Hg and proteinuria (protein >0.3 g/L or urine dipstick reading of ≥1+) after the 20th week of pregnancy, or signs of end-organ dysfunction (thrombocytopenia [platelet count $<100 \times 10^9$ per L], impaired liver function [serum transaminases at least twice the normal concentration], progressive renal insufficiency [serum creatinine >97.24 μmol/L or doubling of baseline value], pulmonary edema, or new-onset cerebral or visual disturbances). The patients with pre-eclampsia were divided into two subgroups—mild pre-eclampsia and severe pre-eclampsia—according to the 2013 criteria [17]. Patients who had a systolic blood pressure of 140–159 mm Hg and/or a diastolic blood pressure of 90–109 mm Hg and proteinuria after the 20th week of pregnancy were defined as having mild pre-eclampsia. Patients with a systolic blood pressure of more than 160 mm Hg, a diastolic blood pressure of more than 110 mm Hg, and/or signs/symptoms of end-organ injury were defined as having severe pre-eclampsia [17]. The women in the control group were normotensive and did not have proteinuria.

B-mode and Doppler ultrasonography was performed as a routine prenatal examination for all women. All study participants also underwent ARFI imaging for measurement of the SWV. All ultrasonography and ARFI elastography examinations were performed by the same radiologist (B.A.), who had 15 years of experience with obstetric and Doppler ultrasonography and 3 years of experience with elastography. The B-mode and Doppler investigations and the SWV measurements were performed using a 4C1 convex probe (2.0–4.5 MHz) with an Acuson S2000 system (Siemens Healthcare, Mountain View, CA, USA). The placental thickness was measured using B-mode ultrasonography at the thickest portion of the placenta in the longitudinal direction. The Doppler velocimetry results from the two uterine arteries and from the umbilical artery were used to calculate the respective pulsatility and resistive indices, with the pulsatility index calculated as the systolic velocity minus the diastolic velocity, divided by the mean velocity, and the resistive index calculated as the systolic velocity minus the diastolic velocity, divided by the systolic velocity. Virtual Touch (Siemens Healthcare, Mountain View, CA, USA) tissue quantification was used to measure the SWV in a region of interest (size 10 × 6 mm) in the placenta (Fig. 1). The SWV measurements were taken while the patient was holding her breath and the fetus was not moving. Seven measurements were taken from different parts of the placenta and the mean SWV value was calculated and recorded.

The data were analyzed using SPSS version 18.0 (SPSS Inc, Chicago, IL, USA). The Mann–Whitney *U* test was used to compare the data between two groups. Relationships between numerical variables were quantified by estimating Spearman rank correlation coefficients (ρ values). A receiver operating characteristic curve was used to compare the diagnostic performance of the diagnostic tests. $P < 0.05$ was considered statistically significant.

3. Results

A total of 86 women were enrolled: 42 with pre-eclampsia and 44 without the disorder. Although pregnancy duration varied from 23 to 37 weeks, there was no statistically significant difference in age or pregnancy duration between the pre-eclampsia and control groups (Table 1) and between patients with mild versus severe pre-eclampsia (Table 2). The mean thickness of the placenta was also similar between all groups (Table 1, Table 2). The resistive and pulsatility indices of the uterine and umbilical arteries were significantly higher in the pre-eclampsia group than in the control group (Table 1).

The minimum, maximum, and mean SWV values in the pre-eclampsia group were significantly higher than the corresponding values in the control group (Table 1). Moreover, the minimum, maximum, and mean SWV values in the group with severe pre-eclampsia were significantly higher than those in the group with mild pre-eclampsia (Table 2).

Spearman correlation analysis revealed that there was no correlation between the pregnancy duration and the SWV value (minimum SWV, $\rho = 0.114$ [$P = 0.9$]; maximum SWV, $\rho = 0.161$ [$P = 0.6$]; mean SWV, $\rho = 0.160$ [$P = 0.6$]).

The receiver operating characteristic analysis (Fig. 2) showed that a minimum SWV of 0.95 m/s had a sensitivity of 90.9% and a specificity of 47.0% for the diagnosis of pre-eclampsia; the area under the receiver operating characteristic curve was 0.864. A maximum SWV of 1.74 m/s had a sensitivity of 90.9%, a specificity of 66.7%, and an area under the curve of 0.883. Finally, a mean SWV of 1.46 m/s had a sensitivity of 90.9%, a specificity of 5.0%, and an area under the curve of 0.994.

4. Discussion

In the present study, the placental SWV in pregnant women with pre-eclampsia was significantly higher than that in women with a normal pregnancy. These findings are in agreement with the results from previous studies [15–17] comparing the placental SWV between women with pre-eclampsia and control individuals. Ohmaru et al. [18] reported a mean SWV value of 1.60 ± 0.45 m/s in women pre-eclampsia, compared with a median value of 1.39 m/s (interquartile range 1.32–1.53 m/s) in the present study.

It is important to distinguish between mild and severe pre-eclampsia because this can affect the clinical treatment approach. In the present study, there was a significant association between the SWV value and the severity of pre-eclampsia. Pre-eclampsia-related pathologic changes such as necrosis, infarction, and ischemic changes in the placenta could lead to increased placental stiffness. However, Sugitani et al. [19] did not detect a significant difference in the placental SWV of women with pre-eclampsia and those with a normal pregnancy in an ex vivo placental ARFI imaging study. Their findings indicate that the placental SWV in women with pre-eclampsia might be affected by factors other than pathologic changes. Ohmaru et al. [18] reported

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