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Comparison of placental elasticity in normal and pre-eclamptic pregnant women by acoustic radiation force impulse elastosonography

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Abstract

Aim: The aim of this research was to study and compare placental elasticity with acoustic radiation force impulse (ARFI) elastography in pre-eclamptic and normal pregnancies.

Methods: A total of 107 singleton pregnancies in the third trimester (38 healthy control subjects, 34 patients with gestational hypertension, and 35 pre-eclampsia patients) were included in the study. ARFI elastography was used to determine the placental elasticity in the three predetermined regions of the placenta (the fetal edge, maternal edge, and central part of the placenta). The obstetrical data regarding grayscale and Doppler ultrasonography and perinatal outcomes were reviewed. A mean placental shear wave velocity cut-off value that predicts the presence of pre-eclampsia was determined.

Results: The shear wave elasticity values in the pre-eclampsia group in all three regions were significantly higher than in the gestational hypertension and healthy control groups ($P = 0.001$). The most significant difference was found in the peripheral edge of the placenta from the fetal surface in the pre-eclampsia group ($P = 0.001$).

Conclusion: The stiffness of the placenta determined by the ARFI technique is significantly higher in pre-eclampsia patients. ARFI elastography of the placenta might be used as a non-invasive and easy method in the diagnosis and evaluation of pre-eclampsia as a supplement to the already existing methods.

Key words: acoustic radiation force impulse, elastosonography, placental elasticity, placental function, pre-eclampsia.

Introduction

Hypertensive disorders of pregnancy are the leading cause of maternal–fetal morbidity and mortality. Pre-eclampsia (PE) affects 3–8% of nulliparous women.[1] It is a well-established fact that placental dysfunction is one of the main causes of PE. Pathologic examinations of placentas from hypertensive pregnant women revealed that placental abnormalities, such as infarction, inflammation, and fibrosis, are the frequently seen architecture in placental tissues of these patients.[2] These changes lead to poor placentation, which is the first step in the development of pre-eclampsia. It has been shown that there is a significant difference in the density of placental villus arrangement between normotensive and pre-eclamptic placentas.[3] This may have an effect on the stiffness and elasticity of the placenta. Doppler wave flow analysis of uterine arteries in the second trimester has established the relation between high resistance waveforms and PE.[4]

Elasticity of soft tissues is measured to investigate the differential diagnosis of many diseases, such as inflammation, fibrosis, and normal or tumoral tissues.[5,6] Elastography is a non-invasive, easy to use and rapid

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ultrasonographic new method for evaluating the elastic properties of tissue. Real-time elastosonography is used for the differential diagnosis of benign and malignant masses of the thyroid, prostate, and parotid glands as well as for the assessment of liver fibrosis.[5,6] Also, there are recently published articles on the applications for this method in obstetric and gynecology practices.[7,8] There are numerous types of sonoelastography classified as strain elastography, acoustic radiation force impulse (ARFI) elastography, shear wave elastography, and transient elastography. ARFI is a relatively new method that uses a short acoustic push pulse in the target tissue, which causes a tissue displacement of approximately 1–20 μm. The displacement creates a lateral shear wave that propagates through the tissue during recoil and it gets elasticity information from the axis of the pushing beam. Faster shear wave speeds and smaller displacements result from stiffer tissues. In a few studies, strain elastography and shear wave elastography of the placenta showed that stiffness of the placenta is significantly higher in patients with pre-eclampsia.[9,10] As far as we know from the published research, only one report by Sugitani *et al.* has studied the placentas of pre-eclamptic women using the ARFI method, but this was an *ex vivo* study.[11]

To the best of our knowledge, our study is the first reported *in vivo* study in which the ARFI elastosonography method is used in the evaluation of placental elasticity. The aim of this study was to determine whether the placental elasticity measured with the ARFI elastosonography method differs between normal pregnancy and pregnancy complicated by hypertensive disorders in the third trimester.[11]

Methods

This study was conducted at the Departments of Obstetrics–Gynecology and Radiology, Yuzuncu Yil University, Dursun Odabas Medical Center between June and November 2015. We obtained institutional review board and ethical committee approved of the study (reference no. 02, 11 June 2015). The study was designed in accordance with the Declaration of Helsinki. Written informed consent was obtained from each subject, following a detailed explanation of the objectives and protocol of the study. The study population included 107 pregnant women between 28 and 40 weeks of gestation who were admitted to the perinatal division of our hospital's obstetric clinic. The subjects were divided into three groups according to obstetric hypertensive complications. Of the 107 patients, 38 were normal (control group), defined as no maternal or fetal complications, 34 were pregnant women with gestational hypertension, and 35 were pregnant women with pre-eclampsia. The subjects were of similar ethnic and socioeconomic backgrounds. Patients with a history of miscarriage and accompanying diseases, pregnant women who had placental hematoma or extensive calcification, multiple gestations, and those with posterior placental location were excluded from the study. All ARFI examinations were performed during the afternoon. The patients with eclampsia, those hospitalized at night, and those with severe hypertension that required medications at any time before elastography were excluded from the study.

The demographic characteristics, and detailed medical and obstetric data charts were examined and obtained on admission of the patients. The perinatal outcomes, including gestational weeks at delivery, birthweight, and Apgar scores at 1 and 5 min, were collected. Pre-eclampsia was diagnosed and classified according to the criteria determined by the bulletin of the American College of Obstetricians and Gynecologists and the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy.[12] Pre-eclampsia was diagnosed when a blood pressure $>$ 140/90 mmHg and a proteinuria- 300 mg/24 h were observed at least twice, more than 6 h apart after 20 weeks of pregnancy. On admission, the pre-eclamptic patients were examined by grayscale ultrasonography for routine obstetric care and ARFI elastography of the placenta and then hospitalized. In case of severe pre-eclampsia patients, only patients who were admitted during the afternoon were included and underwent ARFI elastography and then, immediately, MgSO4 was given and labor induction was offered to the patients according to the severity of pre-eclampsia. Mild pre-eclampsia patients were followed up regularly. The control group comprised of pregnant women who had clinically normal pregnancies with normal fetal anatomy and normal obstetric outcomes without any perinatal complications.

Imaging equipment

All patients were examined with 2-D grayscale and Doppler ultrasonography using a convex 2–8-MHz multifrequency transducer with Voluson E6 (GE Healthcare, Ref.: 1 099 848-W4). The gestational age was determined according to the last menstrual period or to the crown–rump length on the first trimester ultrasonographic examination. After examination of obstetric ultrasonography, including fetal biometry, amniotic fluid index, and fetal anatomy, and Doppler examination of both uterine arteries in which we measured the presence of diastolic notch, resistivity index and pulsatility index, the patients were transferred to the Radiology Department for evaluation of placental elasticity by ARFI elastosonography. The authors from the Radiology Department in our study who performed the ARFI technique were scheduled to be available during the afternoon in our hospital, so all of the ARFI measurements were performed during the afternoon.

All ARFI examinations were performed with a 4–9-MHz 9 L4 linear transducer with Virtual Touch IQ option (Siemens ACUSON S2000, Siemens Healthcare). The standardization of the ARFI elastosonography technique was obtained by examining five healthy pregnant women before starting the study. The radiologist who performed the ARFI had at least 10 years' experience with the grayscale ultrasound and 5 years' with elastosonography and was blinded to the patient histories for the control and pre-eclamptic groups and the obstetric ultrasonography and Doppler findings. The procedure of the ARFI examination of the placenta was as follows: The patient was lying in the supine position and the placental echogenicity and homogenicity were evaluated by the grayscale ultrasound before starting the elastosonography. The patient was instructed to stop breathing, coughing or any movement during the elasticity measurement. Attention was given to the ultrasound gel thickness between the skin and probe. The placenta was evaluated and divided into three equal parts as the fetal edge (inner 1/3 of placenta), maternal edge (outer 1/3) and the central part (central 1/3 of placenta). Three measurements were taken in each of the three regions of the placenta and the mean of these three measurements was obtained as the value of the shear wave velocity (SWV) in m/s for each region. The mean of these nine measurements was also calculated and accepted as the mean placental elasticity value (Fig. 1).

Statistical analysis

Descriptive statistics for studied variables (characteristics) are presented as mean, standard deviation (SD), minimum and maximum values. Continuous variables were compared among the three groups using the one-way analysis of variance test and Duncan's test was performed to determine which group differed significantly from which other groups. A χ^2-test was used to examine the association between categorical variables. For discrimination of the control and patient groups, cut-off values of shear wave elasticity were determined by receiver–operator curve analysis. The sensitivity, specificity, positive and negative predictive values were calculated. Statistical significance levels were considered as 5%. SPSS version 20.0 was used for all statistical computations.

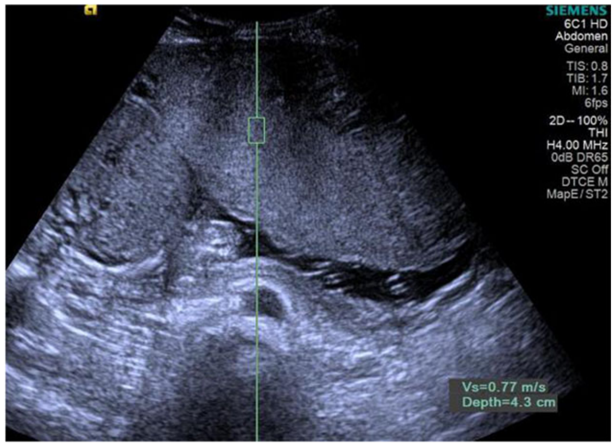

Figure 1 Measurement of shear wave velocity of central parenchyma of placenta using the acoustic radiation force impulse (ARFI) technique and the virtual touch quantification option.

Results

The present study included 107 singleton pregnant patients. These participants were divided into three groups: control (n = 38), gestational hypertension (n = 34), and pre-eclampsia (n = 35). The three groups exhibited no significant differences with respect to the age, gravidity, parity, or gestational age at sampling. Table 1 shows a comparison of demographic variables of the three groups. The pregnant women diagnosed with pre-eclampsia had significantly higher body mass index, systolic blood pressure, diastolic blood pressure, proteinuria, liver function tests (aspartate aminotransferase and alanine aminotransferase) than the control and gestational hypertension groups ($P < 0.05$). However, women with gestational hypertension had significantly higher systolic and diastolic blood pressure than the control group, whereas the other parameters, including liver function tests, proteinuria, hemoglobin, hematocrit and platelet levels, did not show any difference ($P > 0.05$).

When analyzing the perinatal outcomes of the three groups as shown in Table 2, the pre-eclampsia group delivered earlier than the control and gestational hypertension groups ($P < 0.05$). The pre-eclampsia group had

Table 1 Demographic variables among the control, gestational hypertension and pre-eclampsia groups

	Control (n = 38)	Gestational hypertension (n = 34)	Pre-eclampsia (n = 35)	P
Age (years)	26.66 ± 5.03	27.03 ± 6.58	27.51 ± 5.83	0.07
Gravida n, mean ± SD	2.29 ± 1.56	2.79 ± 2.07	3.46 ± 2.37	0.051
Parity n, mean ± SD	1.13 ± 1.55	1.56 ± 1.8	2.17 ± 1.61	0.06
BMI kg/m^2, mean ± SD	28.78 ± 3.51	29.17 ± 4.80	32.34 ± 5.72	**0.003**
Gestational age at sampling (weeks)	34.34 ± 2.43	34.35 ± 2.31	33.14 ± 3.88	0.146
Systolic blood pressure mmHg, mean ± SD	103.95 ± 7.54	142.06 ± 9.46	154.57 ± 12.91	**0.001**
Diastolic blood pressure	65.79 ± 6.42	89.41 ± 7.76	100.0 ± 5.94	**0.001**
Proteinuria mg/day, mean ± SD	102.26 ± 175.24	190.65 ± 95.61	1785.23 ± 2021.45	**0.001**
AST IU/L, mean ± SD	17.18 ± 7.28	19.29 ± 7.29	43.17 ± 66.92	**0.009**
ALT IU/L, mean ± SD	13.08 ± 3.92	14.79 ± 9.0	33.31 ± 46.50	**0.003**
Hematocrit %, mean ± SD	35.17 ± 3.44	35.09 ± 3.85	36.18 ± 5.55	0.505
Hemoglobin g/dl, mean ± SD	11.61 ± 1.16	11.53 ± 1.36	12.09 ± 1.97	0.256
Platelet count/mm^3, mean ± SD	235.89 ± 59.3	231.35 ± 60.79	202.43 ± 83.66	0.088

$P < 0.05$ indicates statistical significance.ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index.

Table 2 Obstetric and perinatal outcomes of the control, gestational hypertension and pre-eclampsia groups

	Control	Gestational hypertension	Pre-eclampsia	P
Gestational weeks at delivery	38.37 ± 1.13	37.5 ± 2.49	35.03 ± 4.15	0.001
Birthweight (g ± SD)	3143.42 ± 377.73	2978.82 ± 600.8	2537.43 ± 1096.22	0.003
1-min Apgar score	8.40 ± 1.08	6.65 ± 1.23	5.29 ± 2.12	0.002
5-min Apgar score	8.42 ± 1.22	8.38 ± 1.1	6.88 ± 2.32	0.001
Number of 1-min Apgar scores ≤ 6	1 (2.6%)	5 (14.7%)	10 (28.5%)	0.001
Delivery type, *n* (%)				0.003
• **Vaginal delivery**	28 (73.6%)	22 (64.7%)	19 (54.2%)	
• **Cesarean section**	10 (26.3%)	12 (35.2%)	16 (45.7%)	
Preterm birth, *n* (%)	6 (15.7%)	6 (17.6%)	14 (40%)	0.040
Intrauterine fetal demise, *n* (%)	1 (2.6%)	1 (2.6%)	4 (11.4%)	0.026
Admission to the neonatal intensive care unit, *n* (%)	3 (7.8%)	3 (8.8%)	18 (51.4%)	0.010

$P < 0.05$ indicates statistical significance.SD, standard deviation.

lower Apgar scores at 1 and 5 min than the other two groups ($P < 0.05$). Cesarean births were significantly more prevalent in the pre-eclampsia group ($P = 0.003$). Of the 35 women in the pre-eclampsia group, 40% (14/35) had preterm deliveries, which was defined as delivery before 37 completed weeks. Intrauterine fetal demise was found to be statistically higher in the pre-eclampsia group than in the other two groups ($P < 0.05$). Among these cases, one had severe hypertension and placental abruption. The other three cases had early onset severe intrauterine growth retardation and pre-eclampsia (one with 28/24-week, one with 29/26-week and one with 30/26-week growth retardation) and all of these patients were advised to terminate the pregnancy; however, none of them accepted this advice due to religious and cultural concerns. On the follow-up, these fetuses eventually died. The pre-eclampsia group had significantly higher admission to the neonatal intensive care unit ($P < 0.05$).

Table 3 presents the right and left uterine artery Doppler findings and a diastolic notch was present in 48.5% (17/35) of the pre-eclampsia cases, 5.8% (2/34) of the gestational hypertension cases and none of the healthy controls. The mean ± SD of the resistivity index and pulsatility index of the right and left uterine arteries in the pre-eclampsia group were found to be significantly higher than the other two groups with respect to the relevant indices ($P = 0.001$). Table 3 shows the ARFI elastosonography scores for the three groups. Elasticity values were evaluated and determined in the three different areas of the placentas in the three study groups: the peripheral edge of the placenta from the maternal

Table 3 Doppler ultrasound and ARFI elastography data for the the control, gestational hypertension and pre-eclampsia groups

	Control	Gestational hypertension	Pre-eclampsia	*P*
Right uterine artery PI	0.78 ± 0.22	0.90 ± 0.35	1.43 ± 0.61	0.001
Right uterine artery RI	0.50 ± 0.12	0.52 ± 0.12	0.66 ± 0.16	0.001
Left uterine artery PI	0.86 ± 0.26	0.87 ± 0.25	1.46 ± 0.48	0.001
Left uterine artery RI	0.52 ± 0.10	0.52 ± .012	0.67 ± 0.12	0.001
Placental maternal edge elasticity, SWV (m/s)	0.91 ± 0.26	1.24 ± 0.39	1.85 ± 0.73	0.001
Placental central part elasticity, SWV (m/s)	0.92 ± 0.29	1.27 ± 0.55	1.83 ± 0.96	0.001
Placental fetal edge elasticity, SWV (m/s)	0.94 ± 0.27	1.31 ± 0.55	2.10 ± 0.81	0.001
Mean elasticity, SWV (m/s)	0.91 ± 0.2	1.27 ± 0.36	1.93 ± 0.62	0.001

$P < 0.05$ indicates statistical significance.ARFI, acoustic radiation force impulse; PI, pulsatility index; RI, resistivity index; SWV, shear wave velocity.

surface, the peripheral edge of the placenta from the fetal surface, and the central part of the placenta. The total mean of the SWV values of all three different areas was significantly higher in the pre-eclampsia group than in the gestational hypertension and control groups ($P = 0.001$). Each elasticity value for the fetal edge, maternal edge, and central part of the placenta was statistically significantly higher in the pre-eclamptic group than the other two groups ($P = 0.001$). Again, the gestational hypertension group had significantly higher SWV values in the three different predetermined areas than the control group. The most significant difference in SWV value was observed in the pre-eclamptic group at the peripheral edge of the placenta from the fetal surface where it is near to the umbilical cord insertion (the mean SWV value at the fetal surface was 2.10 ± 0.81, 1.31 ± 0.56, and 0.94 ± 0.27 in the pre-eclamptic, gestational hypertension and control groups, respectively; $P = 0.001$).

Discussion

Our study findings showed that the placental stiffness determined by the ARFI elastosonography technique was found to be significantly higher in pre-eclampsia patients than in pregnant women with gestational hypertension and healthy controls. For more than a decade, in clinical practice, the measurement of elasticity in parenchymal organs has been used to diagnose, screen, or follow-up patients with liver fibrosis, thyroid diseases, parotid glands, and inflammatory pancreatic diseases.[13] There are different types of elastosonography methods that measure the tissue displacement and the elasticity stiffness of tissues. These are real-time elastography, shear wave elastography, transient elastography, and ARFI elastography, which have different imaging quantity, strain pattern, and measurement of the time of arrival of shear waves.[14] The ARFI technique is a non-invasive and easy method for evaluation of tissue elasticity, which generates a shear wave that propagates in the tissue and obtains elasticity information quantitatively from the axis of the pushing beam. There are a few studies that measure placental elasticity in which strain elastography and shear wave elastography have been used.[9,10] Sugitani *et al.* were the first researchers to evaluate placental tissue with ARFI elastography. They stated that ARFI poses no potential thermal or chemical risk to the placenta and that pregnant women with fetal growth restriction have significantly higher placental stiffness than healthy controls; however, their study was an *ex vivo* tissue study.[11] They recommended an *in vivo* investigation of placental elasticity using ARFI imaging for future studies. So, to our knowledge, our study is the first to use the ARFI technique for evaluation of placental elasticity in hypertensive pregnant women, including pre-eclamptic and gestational hypertensive patients.

The exact pathophysiological mechanism of pre-eclampsia is still unknown. The current theory that attempts to explain pre-eclampsia is the two-staged model.[15] The first stage is thought to derive from poor placentation and defective trophoblastic invasion. Thus, these factors lead to the second stage, which involves endothelial cell injury, chronic inflammation, and altered vascular integrity. Vinnars *et al.*[16] reported that pre-eclamptic pregnancies had placental infarcts, sclerotic changes in arteries, and intervillous thrombosis on pathologic examination. Thus, it can be speculated that pre-eclamptic patients may have a more compact and stiffer placenta than pregnancies in which placental hemodynamics are normal. Therefore, the evaluation of placental elasticity and stiffness with elastosonography methods will be very rational from the aspect of placental tissue changes in pre-eclampsia.

The early prediction of the development of pre-eclampsia is a crucial issue and very important to decrease maternal–fetal morbidity and mortality. Thus, there are many clinical screening tests to predict the development of pre-eclampsia; however, none of these methods are clinically useful and can be used exactly for the diagnosis of pre-eclampsia. Some of these methods include the evaluation of uterine artery Doppler velocimetry and some serum biomarkers, like uric acid, urinary kallikrein, and anticardiolipin antibodies.[17] A limited number of studies have evaluated the elasticity of the placenta to diagnose or predict the development of pre-eclampsia using different methods of elastosonography. Li *et al.*[18] studied the elasticity of the placenta with real-time shear wave elasticity imaging technology and reported that this technique could provide morphological evidence of placental function, which may emerge as a new clinical assessment approach. Afterwards, Kilic *et al.* evaluated the utility of shear wave elastography for assessing the placenta in pre-eclamptic patients and found that pre-eclamptic patients had a significantly higher stiffness in the placenta. They stated that shear wave elastography could be an assistive diagnostic technique for placenta evaluation in pre-eclampsia.[10] Cimsit *et al.*[9] used strain elastography for assessment of placental elasticity in pre-eclamptic patients and reported that placental elastography in the second trimester of pregnancy differs between normal pregnancies and pre-eclamptic patients. To our knowledge, the ARFI technique has not yet been used in the *in vivo* evaluation of placental elasticity. Sugitani *et al.* carried out an *ex vivo* study and evaluated placental elasticity after delivery with the ARFI method and found that *ex vivo* placentas from the fetal growth restriction group were significantly firmer than those from the normal group.[11] They also recommended additional investigation into the utility of the ARFI method for the evaluation of placental function *in vivo*. Thus, our study is the first to evaluate placental function using the ARFI method in pre-eclamptic and normotensive pregnant women. We found that each elasticity value of the three different parts of the placenta was significantly higher in pre-eclamptic patients than in the normotensive and gestational hypertensive women. Our result is inconsistent with earlier studies in which the most significant difference in the SWV value was observed at the peripheral edge of the placenta from the fetal surface. However, earlier studies observed that the central placental area facing the fetus had the most significant difference in mean stiffness value.[10,11]

The placental morphology and location or any pathology like hemangioma, bleeding can be evaluated by the conventional B-mode ultrasonography but not the function. It has been reported that the development of anchoring villi and tertiary villous formation in placental basal plate is inversely correlated with the proportions of fibrin deposition.[19] Also, trophoblastic vasculopathy or ischemia may lead to fibrin deposition and excessive syncytial knots, which would increase the placental stiffness detected by ARFI elastosonography. This theory is consistent with our data; we found significantly higher stiffness values in the pre-eclampsia group than in the pregnancies with normal placentation.

An important issue is the safety of Doppler ultrasonography for pregnant women who undergo repeated obstetric examinations. The safety and teratogenous effects of ultrasonography have been studied and clarified by many researchers for decades.[20] The ultrasound frequency, focusing, and time of exposure affect the mechanical and thermal indices of Doppler ultrasonography. Elastosonography techniques have similar safety considerations to conventional ultrasonography imaging modes. Kiliç *et al.* reported that the thermal index is advised to be no more than 15 min and this covers the safety limits of our study.[10] Beside this, Sugitani *et al.* studied the biological effects of ARFI on term delivered placentas and did not observe any thermal or structural changes.[11] Herman *et al.* reported that any temperature increase generated by the ARFI with pulse bursts might still be within the safe limit determined by the US Food and Drug Administration.[21] Furthermore, in our study, we performed elastosonography only for the placenta and the wave path was just from the probe to the placenta. The fetus was not within the direction of waveform paths of the ARFI elastography. The fetus was examined with 2-D grayscale and Doppler ultrasonography as a routine procedure before ARFI elastosonography was carried out. Although the safety issue of the ARFI technique was not primarily evaluated in our study, we can state that all our ARFI examinations were within the safety time limit.

The strengths of our study were that the radiologist who performed the ARFI measurements was experienced and the appropriate number of patients was included. Also, all patients were within the third trimester, so as to eliminate possible bias related to the changes in placental growth from the second to the third trimester. Furthermore, all ARFI measurements were performed during the afternoon. Our study had some limitations, for example, we did not compare and evaluate the relation between severity of pre-eclampsia and the placental elasticity. Also, the pathologic examination of the placentas *ex vivo* might have provided some valuable information about placental elasticity and thus an objective comparison of elastosonography and stiffness in normal and pre-eclamptic pregnancies.

In conclusion, our study demonstrated that ARFI imaging of the placenta during the third trimester showed differences in elasticity between normal and pre-eclamptic pregnancies. This is the first report on the *in vivo* examination of placental elasticity in pre-eclampsia using the ARFI technique. The elasticity changes showed stiffer placentas in pre-eclampsia patients, thus ARFI might be a useful tool for evaluation of the placenta in pre-eclamptic patients as an easy and non-invasive method. Further studies involving earlier gestational periods and larger sample groups of pre-eclampsia are needed to confirm the usefulness of ARFI elastography of the placenta for prediction of pre-eclampsia.

Authorship contributions

E. Karaman: Manuscript writing/editing, data collection, project development. H. Arslan: project development, data collection. O. Çetin: Data collection. H. G. Şahin: Data collection, data analysis. A. Bora: final reduction, manuscript editing. A. Yavuz: Data collection. S. Elasan: Data collection, statistical analysis. İ. Akbudak: Data collection.

Disclosure

The authors declare that they have no conflicts of interest.

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