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Characterizing placental stiffness using ultrasound shear–wave elastography in healthy and preeclamptic pregnancies

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Abstract

Purpose—To measure the stiffness of the placenta in healthy and preeclamptic patients in the second and third trimesters of pregnancy using ultrasound shear-wave elastography (SWE). We also aimed to evaluate the effect of age, gestational age, gravidity, parity and body mass index (BMI) on placental stiffness and a possible correlation of stiffness with perinatal outcomes.

Methods—In a case–control study, we recruited a total of 47 singleton pregnancies in the second and third trimesters of which 24 were healthy and 23 were diagnosed with preeclampsia. In vivo placental stiffness was measured once at the time of recruitment for each patient. Pregnancies with posterior placentas, multiple gestation, gestational hypertension, chronic hypertension, diabetes, autoimmune disease, fetal growth restriction and congenital anomalies were excluded.

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Author contributions

MS: protocol/project development, data collection or management, data analysis, manuscript writing/editing; CYK and AE: protocol/project development, data analysis, manuscript writing/editing; MJ: data analysis; CTR and JPF: Protocol/project development; SNI, MHF and PCWK: protocol/project development, manuscript review.

This work was presented as an abstract at the 2018 Society for Maternal Fetal Medicine Meeting, January 29–February 3 2018, Dallas, TX.

Conflict of interest The authors declare no conflict of interest.

Ethics approval This study was approved by the Institutional Review Board (MedStar Health Research Institute IRB# 2015–130).

Consent to participate Written informed consent was obtained from all patients who participated in the study.

Results—The mean placental stiffness was significantly higher in preeclamptic pregnancies compared to controls in the third trimester (difference of means = 16.8; 95% CI (9.0, 24.5); $P < 0.001$). There were no significant differences in placental stiffness between the two groups in the second trimester or between the severe preeclampsia and preeclampsia without severe features groups (difference of means = 9.86; 95% CI (−5.95, 25.7); $P \geq 0.05$). Peripheral regions of the placenta were significantly stiffer than central regions in the preeclamptic group (difference of means = 10.67; 95% CI (0.07, 21.27); $P < 0.05$), which was not observed in the control group (difference of means = 0.55; 95% CI (−5.25, 6.35); $P > 0.05$). We did not identify a correlation of placental stiffness with gestational age, maternal age, gravidity or parity. However, there was a statistically significant correlation with BMI ($P < 0.05$). In addition, pregnancies with higher placental stiffness during the 2nd and 3rd trimesters had significantly reduced birth weight (2890 ± 176 vs. 2420 ± 219 g) and earlier GA (37.8 ± 0.84 vs. 34.3 ± 0.98 weeks) at delivery ($P < 0.05$).

Conclusion—Compared to healthy pregnancies, placentas of preeclamptic pregnancies are stiffer and more heterogeneous. Placental stiffness is not affected by gestational age or the severity of preeclampsia but there is a correlation with higher BMI and poor perinatal outcomes.

Keywords

Preeclampsia; Placenta; Ultrasound; Shear-wave elastography; In vivo

Introduction

Ultrasound-based shear-wave elastography (SWE) is a noninvasive technique capable of quantifying tissue stiffness [1, 2]. SWE works on the principle of producing shear waves by a focused ultrasound push beam, followed by rapid imaging of these shear waves. The velocity of the shear-wave propagation in the placenta is converted to tissue stiffness in Young's modulus measured in kilopascals (kPa). SWE is not operator dependent and has been used to image liver lesions, benign and malignant breast masses, thyroid nodules, as well as the musculoskeletal system [3–5]. In addition, with the use of SWE techniques, cervical stiffness has been measured as a possible predictive marker for successful induction of labor or preterm delivery [6–8].

Despite the widespread applications of SWE, few studies have evaluated placental stiffness in pregnancy complications such as preeclampsia. Preeclampsia (PE) is a leading cause of maternal and perinatal morbidity and mortality, affecting 3–8% of all pregnancies [9–13]. Globally, ten million women develop PE each year, with about 76,000 pregnant women and 500,000 infants dying from PE and related hypertensive disorders [14]. According to the American College of Obstetricians and Gynecologists, the principal diagnosis of PE is the onset of hypertension with signs of end-organ damage such as proteinuria, thrombocytopenia, renal insufficiency, impaired liver function or pulmonary edema at or beyond 20 weeks gestation [15, 16]. Abnormal uterine artery Doppler velocimetry is observed in most cases of early-onset preeclampsia. Decreased end-diastolic velocity and presence of an early diastolic notch are signs of increased resistance and predict the onset of preeclampsia [17].

Our hypothesis is that placental stiffness differs between healthy and preeclamptic pregnancies and varies by gestational age and severity of preeclampsia. This was based on the clinical observation of "poor" quality, smaller and stiffer placentas after delivery of preeclamptic patients as well as evidence of altered placental pathology in preeclampsia [11]. The goal of our study was to assess placental stiffness in normal and preeclamptic pregnancies as well as changes in stiffness by gestational age in the two groups. We sought to evaluate the effect of maternal age, gravidity, parity, BMI and area of interrogation within the placenta on stiffness measurements. We also aimed to compare placental stiffness in patients with varying severity of PE. In addition, we assessed a possible correlation of placental stiffness with adverse perinatal outcomes.

Methods

Patient recruitment

This study was approved by the Institutional Review Board (MedStar Health Research Institute IRB# 2015–130). Written informed consent was obtained from all patients who participated in the study. Healthy and preeclamptic patients in the second (> 20˙weeks of gestation for preeclamptic patients) and third trimesters of pregnancy that presented for obstetrical care were recruited prospectively between January 1, 2017 and June 30, 2017. Placental SWE measurements were performed once for each patient at the time of recruitment. Patients with posterior placentas, multiple gestation, gestational hypertension, chronic hypertension, diabetes, autoimmune disease, fetal growth restriction and fetal congenital anomalies were excluded. Demographic characteristics, detailed medical and obstetrical data, and prenatal care charts were examined. PE was diagnosed according to the established criteria of the American College of Obstetricians and Gynecologists [17].

Patients included in the study received prenatal care at a single institution where the research study was performed. Routine first trimester uterine artery Dopplers for the prediction of preeclampsia is not performed in our institution. SWE measurements were obtained upon diagnosis of preeclampsia in the outpatient or inpatient setting. The research team made every possible effort to obtain the SWE measurements as soon as possible after the initial diagnosis and before any treatment was initiated in an attempt to eliminate possible confounders, but this was not possible with all patients. All patients received routine care for the management of preeclampsia based on established protocols and the clinical expertise of the supervising obstetrician. This included expectant management, treatment of hypertensive emergencies with antihypertensive medications, use of magnesium sulfate for seizure prophylaxis or delivery when that was deemed necessary. Information regarding the use of aspirin for preeclampsia prevention was not available for all patients.

Ultrasound imaging and data collection

Ultrasound imaging throughout this study was performed by the same obstetrician using a curvilinear transducer with a bandwidth of 1–6MHz and 192 elements (XC6–1, Supersonic Aixplorer, Supersonic Imagine, Aix-en-Provence, France). Blinding of the obstetrician performing the measurements as to the diagnosis of preeclampsia was not always possible.

All patients were asked to lie in the supine position, breathe lightly and refrain from moving. B-mode imaging was initially used to image and locate the placenta and the fetus. Placental morphology, thickness and subcutaneous tissue thickness were recorded. The imaging plane was adjusted based on the location of the placenta.

The ultrasound transducer was held gently on the surface of the skin and excessive compression was avoided. Patients with placentas with anterior and fundal components were imaged. In patients with posterior-fundal placentas, only the fundal component was used for measurements to avoid ultrasound push beam transmission through the fetus. Thermal and mechanical indices were recorded for all scans. The ultrasound system overlays SWE data on b-mode images in real time (Fig. 1). An adjustable rectangular box can be placed at any location of the b-mode image to measure tissue stiffness. Push beams are generated within this box and SWE data are obtained. SWE box displays placental stiffness on a chromatic scale ranging from blue to red (less to more stiffness), indicating the shear intensity in real time (measured in Young's modulus).

In every patient, the SWE box was placed entirely within the placenta and was never allowed to go through the fetus. We ensured that the size of the SWE box was as large as anatomically possible to increase the sampling area while reducing the bias from selectively sampling small areas of the placenta. Sample collection was standardized. Each placenta was sampled six times, with three samples obtained from the central area (identified as the area of highest placental thickness) and three from the periphery (within 3 cm of the placental edge). Whenever deemed necessary, we revisited prior anatomical locations to recollect data. The acquisition box was at least 3 cm in each diameter to ensure adequate sampling size. The SWE box was placed at each location of the placenta for no longer than 15 s. There was at least a 30 s gap in data collection between each anatomical location. The total scanning time for each patient did not exceed 10 min. Ultrasound software allows users to draw a free hand region of interest (ROI) over the SWE image to measure the mean and variance in Young's modulus (Fig.1). All measurements from each location were averaged to obtain mean stiffness values from the central and peripheral areas.

Statistical analysis

All statistical analysis was performed using Minitab (Minitab, Inc, State College, Pennsylvania, USA). Student's *t* test was used to perform pairwise comparisons. χ^2 test was used to test association between categorical variables. Multiple regression analysis was used to assess the relationship between placental stiffness and preeclampsia adjusting for common socio-demographic factors. Differences between peripheral and central placental stiffness by group were also evaluated to assess the heterogeneity of placental stiffness within the placenta. Receiver operating characteristic (ROC) curves were plotted to evaluate the performance of placental stiffness to differentiate between normal and PE groups; the optimized cutoff value was determined by the Youden index (J). Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated.

Results

Study population

A total of 47 women with singleton pregnancies in the second and third trimesters were recruited. A flow diagram of patient eligibility and recruitment is shown in Fig. 2. Among these participants, 24 were controls and 23 were affected by PE. The study recruited 11 patients with mild and 12 with severe preeclampsia. There were no significant differences in the maternal age (normal = 28.9 ± 1.4 years, PE = 30.9 ± 1.6 years; $P \geq 0.05$), parity, gestational age, BMI, race, smoking or alcohol use between the groups (Table 1).

Preeclamptic placentas were significantly stiffer than normal placentas

Mean placental stiffness was significantly higher in PE pregnancies than in normal controls (difference of means = 14.6; 95% CI (7.68, 21.5); $P < 0.05$); (Tables 2 and 3 and Figs. 3 and 4). PE placentas were significantly stiffer than normal placentas in the third trimester, but the difference in stiffness did not reach statistical significance in the second trimester (Table 3; $P \geq 0.05$). There were no significant differences in placental stiffness between severe PE and PE without severe features (Table 3; $P \geq 0.05$). Using a multivariate regression model, the presence of preeclampsia was the most significant predictor of placental stiffness to reach statistical significance ($P = 0.0003$). BMI was the only other statistically significant predictor of the model ($P = 0.0026$) with stiffness decreasing with higher BMI (inverse correlation), while other covariates such as age and gestational age did not reach statistical significance (Table 4).

In terms of regional differences in placental stiffness, analysis of covariance (ANCOVA) adjusted for common socio-demographic factors revealed that the periphery of the placenta was, on average, significantly stiffer than the central area in PE pregnancies (31.9 ± 4.1 kPa vs. 21.9 ± 3.04 kPa, respectively; adjusted difference of means = 10.67; 95% CI (0.07, 21.27); $P < 0.05$; Fig. 5a, Table 5). In contrast, there were no significant differences in placental stiffness between the central and peripheral regions in the control group (11.1 ± 1.81 kPa vs. 11.2 ± 2.1 kPa, respectively; adjusted difference of means = 0.55; 95% CI (−5.25, 6.35); $P \geq 0.05$; Fig. 5b, Table 5). These findings show that the mean placental stiffness was not only higher in PE placentas, but also the stiffness distribution within different placental regions was more heterogeneous.

Determining a placental stiffness cutpoint indicative of PE

To determine a cutpoint of placental stiffness indicative of the presence of PE, we constructed a receiver operating characteristic (ROC) curve (Fig. 6). The area under the curve (AUC) of the ROC curve was 0.82 and the optimized cutoff value of placental stiffness value for the presence of PE was 16.3 kPa, optimized using the Youden's J statistic. Using the optimized cutoff value for placental stiffness, the positive predictive value, negative predictive value, sensitivity and specificity for the presence of preeclampsia were 0.81, 0.76, 0.75 and 0.83, respectively.

Correlation between placental stiffness and perinatal outcomes

We grouped the study population based on the optimized cutoff value for placental stiffness (e.g. Group A = placental stiffness < 16.3 kPa; Group B = placental stiffness > 16.3; Table 6) and evaluated their respective pregnancy and neonatal outcomes. We found Group B had significantly lower birth weight and GA at the time of delivery (2420 ± 219 g and 34.3 ± 0.98 weeks, respectively) than Group A (2890 ± 176 g and 37.8 ± 0.84 weeks, respectively). Group B was also more likely to be associated with minimal or absent fetal heart rate variability during the last four hours before delivery. No correlation was found with severe variable or repetitive late decelerations during the same time period. In addition, newborns from Group B had lower Apgar scores and higher rates of NICU admission and intubation, although these differences did not reach statistical significance.

Discussion

In this study, we determined that the mean placental stiffness was significantly higher in PE pregnancies than controls, and is not affected by maternal age, GA, gravidity or parity. BMI was the only other variable shown to effect stiffness significantly. Previous studies have linked tissue stiffness to the quantity of type I collagen in the extracellular matrix (ECM) [18]. Cellular remodeling of the ECM in response to mechanical or biochemical factors leads to increases in the amount of type I collagen and fibrosis, which as a result modulates the mechanical properties of the tissue [18]. In normal pregnancy, placentation occurs by trophoblast invasion of the maternal spiral arteries to create a low resistance, high-flow maternal uteroplacental circulation [9, 11]. In PE, trophoblast invasion of the maternal spiral arteries is thought to be impaired and, as a result, placental perfusion is reduced which creates a hypoxic environment in the placenta [9, 19]. Hypoxia stimulates collagen deposition, vascular fibrin deposition, and fibrosis, which together can lead to higher tissue stiffness [20]. PE placentas exhibit injuries such as placental vascular lesions and fibrosis [21, 22], vesicular and perivillous fibrin deposition [23], syncytial knots and microcalcifications [23], findings that could explain the increased placental stiffness seen in PE.

The placental stiffness values and the relative homogeneity in stiffness of normal placentas in our study were similar to those previously reported in the literature [24, 25]. Like prior studies, we also report that there was significant variance in placental stiffness between central and peripheral areas of the placenta in PE patients. However, in contrast to prior studies [24], peripheral areas of the placenta were found to have higher stiffness values. The absence of a statistically significant difference in stiffness between the preeclampsia with and without severe features groups could represent a lack of direct correlation between placental ultra-structural changes and clinical severity of preeclampsia. A post hoc power calculation demonstrated that our study only had a 53.2% power to differentiate between the two groups with an alpha of 0.05. Of interest was the increased incidence of adverse perinatal outcomes in patients with increased placental stiffness. These results could be confounded by the increased likelihood of fetal growth restriction and iatrogenic preterm delivery in preeclamptic pregnancies.

Safety considerations are of paramount importance when a new diagnostic modality is introduced in clinical practice. Potential adverse effects stemming from ultrasound beam exposure on fetal and maternal safety have been substantially studied during pregnancy. Mechanical and global maximum intensity are limited by the US Food and Drug administration (FDA) to 1.9 and 720 mW/cm^2. Routine ultrasound scans including pulsed wave Doppler and b-mode imaging as well as SWE have been shown to not exceed these limits and not adversely affect the fetus or the mother [26, 27]. The mechanical intensity of SWE in our study was maintained to less than 1.6mW/cm^2 at all times, which is similar to a regular diagnostic b-mode scan. The SWE scans did not exceed 15 s per acquisition at each anatomical location and completely avoided the fetus. In addition, we ensured that SWE push beams were exclusively within the placenta and did not propagate or focus on the fetus.

This study had several strengths. PE placentas were characterized by significant variance in stiffness. To eliminate sampling bias, we maintained a large SWE acquisition area and sampled both central and peripheral areas of the placenta. In addition, this is the first study to examine the association between placental stiffness and maternal age, gestational age, BMI and perinatal outcomes. Our study was limited by the fact that all sonograms were performed by one expert obstetrician. However, the measurements of tissue stiffness with SWE are not operator dependent and we obtained multiple measurements to minimize intraob-server variability. We were also not able to obtain pathology specimens of the examined placentas. Due to the limited number of studies on placental elastography, it is not known whether increased stiffness is only seen in preeclampsia or could be present with other causes of placental insufficiency such as diabetes, chronic hypertension or intrauterine growth restriction. Interestingly, recent reports identified increased placental stiffness in patients with gestational diabetes and intrauterine growth restriction [28, 29]. A limitation of placental elastography is that appropriate operator training in image acquisition as well as additional equipment is required in order to obtain accurate and reproducible measurements.

In conclusion, we have demonstrated that placental stiffness is increased in pregnancies with preeclampsia and is not affected by gestational age or maternal age. It is also more likely to be associated with poor perinatal outcomes such as lower birth weight and earlier GA at delivery. Further research would be needed to evaluate the utility of placental SWE as a biomarker of placental insufficiency in patients with preeclampsia.

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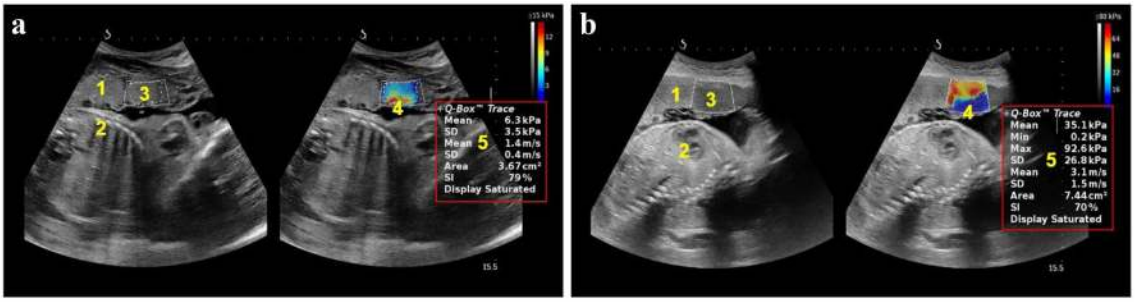

Fig. 1.

B-mode images of SWE date acquisition in **a** healthy and **b** preeclamptic pregnancies. (1—Placenta, 2—fetus, 3—SWE data acquisition box, 4—chromatic scale of placental stiffness in kPa, 5—Q-box of measurements from the interrogated area)

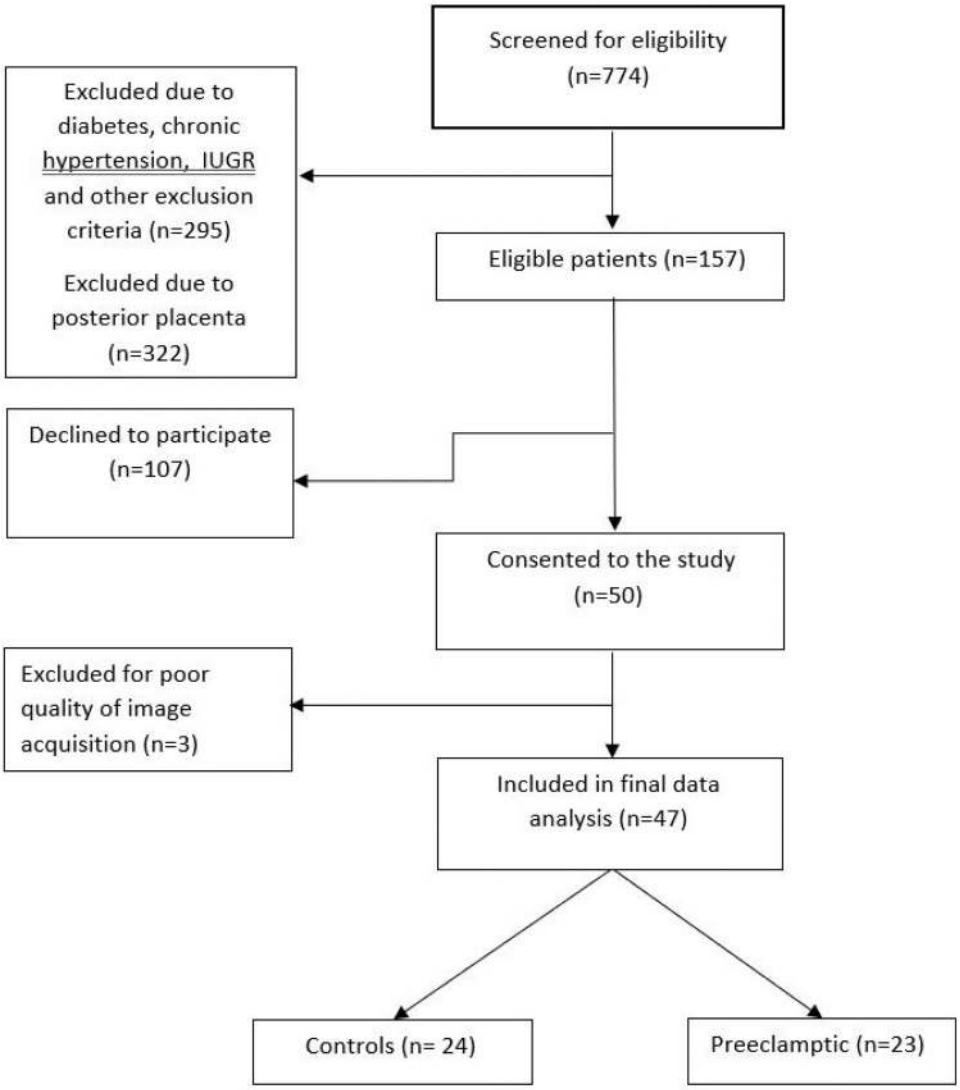

Fig. 2.
Flow diagram of patient recruitment at each stage of the study

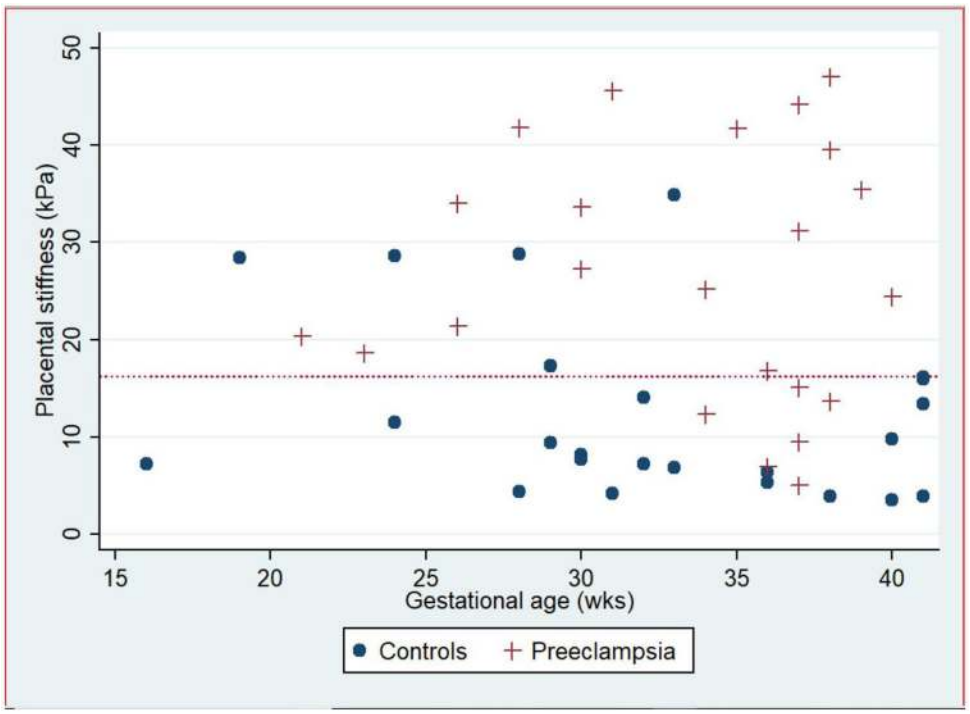

Fig. 3.

Placental stiffness measurement distribution at different gestational ages in the control and PE groups. Dotted line represents the optimal cut point (16.3 kPa) for the presence of preeclampsia determined by the ROC curve

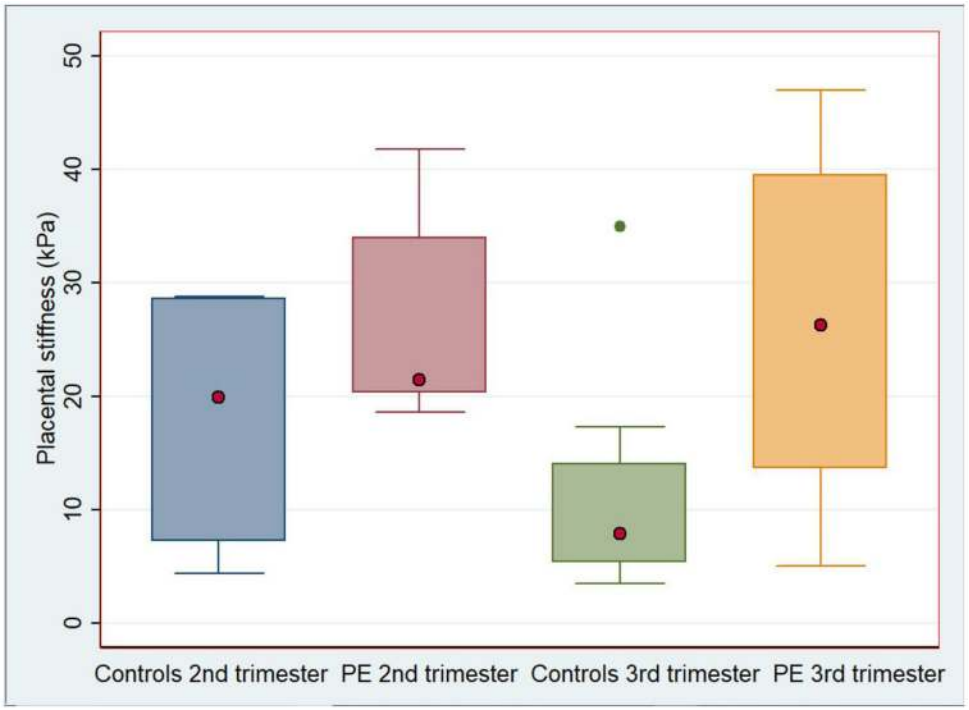

Fig. 4.

Box and whisker plots of placental stiffness in different trimesters and disease states.PE placentas were significantly stiffer than those of controls in the third trimester ($P < 0.05$).Dots represent median values for each group

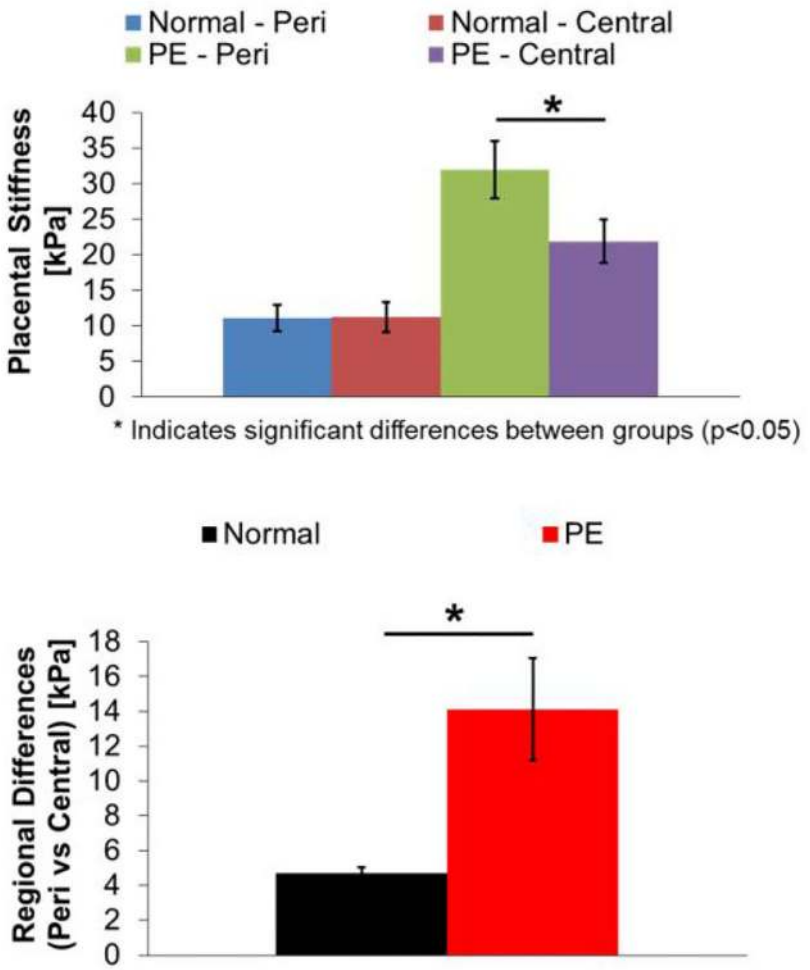

Fig. 5.

Heterogeneity of placental stiffness between peripheral and central location of the placenta. **a** There were no statistically significant differences in averaged placental stiffness between the central and peripheral regions in the control group. In contrast, the periphery of the placentas was significantly stiffer than that of the central region in PE patients ($P < 0.05$). **b** We found significant regional differences, while controlling for GA and maternal ages, between the control and PE groups. *Indicates statistically significant differences between groups ($P < 0.05$) and error bars in **(a)** and **(b)** are standard error of mean

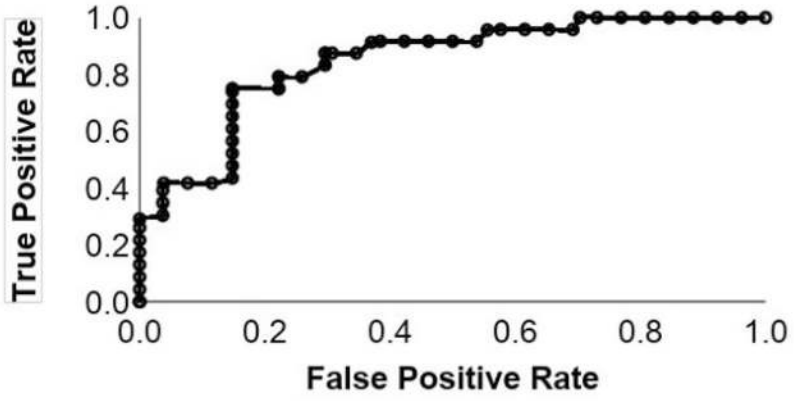

Fig. 6.

ROC curve calculating the optimized cutoff value of placental stiffness to indicate the presence of PE

Table 1

Demographics of the study population

	Controls (*n* = 24)	**PE (*n* = 23)**	***P* value**
Maternal age (years)	28.9 ± 1.4	30.9 ± 1.6	0.25
Parity (%)			0.76
Nullipara	12 (50)	13 (56)	
Multipara	12 (50)	10 (44)	
Gestational age (GA) at recruitment (weeks)	29.2 ± 1.9	33.5 ± 1	0.49
Body mass index (BMI)	32.5 ± 1.4	34.7 ± 1.6	0.45
Obesity (%)	16 (66)	15 (65)	0.75
Race (%)			0.75
African-American	82	76	
Caucasian	8	12	
Asian	5	0	
Other	5	12	
Smoker (%)			0.52
Yes	5	0	
Former	14	11	
No	81	89	
Alcohol usage (%)	5	0	0.31

Errors are expressed as standard error of mean

Table 2

Mean placental stiffness in the control and PE groups at different trimesters of pregnancy

	Placental stiffness (kPa)	
	2nd trimester	**3rd trimester**
Controls ($n = 24$)	18.16 ± 11.6 ($n = 6$)	10.45 ± 7.6 ($n = 18$)
PE ($n = 23$)	27.23 ± 10.1 ($n = 5$)	26.36 ± 14.1 ($n = 18$)

Table 3

t test for differences of means

Comparison	Difference of means	95% Confidence Interval	*P* value
Control vs PE (2nd + 3rd trimester)	14.6	(7.68, 21.5)	< 0.001 *
Control vs PE (2nd trimester)	9.07	(− 6.03, 24.1)	0.2
Control vs PE (3rd trimester)	16.8	(9.0, 24.5)	< 0.001 *
PE without severe features vs severe PE	9.9	(− 5.95, 25.7)	0.208

There were significant differences of mean stiffness between PE and control group during the third trimester and combined ($P > 0.05$). Between severe PE and PE without severe features, there were no significant differences in placental stiffness ($P > 0.05$)

*Significant differences between groups ($P < 0.05$)

Table 4

Effect of preeclampsia and common socio-demographic factors on placental stiffness measured by SWE calculated with multiple regression analysis

	Coefficient	Standard error	*P* Value	95% CI
Preeclampsia	13.7	3.17	0.0003 *	(7.27, 20.1)
BMI	0.52	0.22	0.026 *	(0.06, 0.98)
Maternal age	− 0.009	0.25	0.969	(− 0.52, 0.1)
Parity	− 2.89	3.18	0.368	(− 9.33, 3.54)
Gestational age (at examination)	− 0.28	0.25	0.269	(− 0.80, 0.23)

* Significant differences between groups ($P < 0.05$)

Table 5

ANCOVA for differences of mean between central and peripheral placental regions in the control and PE groups

Comparison groups	Difference of means	95% Confidence Interval	Adjusted *P* value
Control group—peripheral vs central	0.55	(− 5.25, 6.35)	0.848
PE group—peripheral vs central	10.67	(0.07, 21.27)	0.049 *

* Significant differences between groups ($P < 0.05$)

Table 6

Neonatal outcomes using optimized cutoff value of placental stiffness

	Group A: placental stiffness < 16.3 kPa	Group B: placental stiffness > 16.3 kPa	*P* value
Birth weight (grams)	2890 ± 176	2420 ± 219	0.047 *
GA at delivery (weeks)	37.8 ± 0.84	34.3 ± 0.98	0.028 *
Low Apgar score (< 7)—1 min (% of group)	8.3	13.6	0.564
Low Apgar score (< 7) 5 mins (% of group)	8.3	4.54	0.603
Cord blood pH—arterial	7.21 ± 0.02	7.21 ± 0.01	0.403
Cord Blood pH—venous	7.29 ± 0.01	7.26 ± 0.01	0.076
NICU admission rate (% of group)	30	47	0.148
Intubation rate (% of group)	12	16	0.362
Minimal/no variability (% of group)	18	52	0.019 *
Late/severe variable decelerations (% of group)	41	36	0.789

Errors were expressed as standard error of mean

* Significant differences between groups ($P < 0.05$) using Student's *t* test