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Evaluation of the optic nerve using strain and shear-wave elastography in pre-eclampsia

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AIM: To investigate the utility of strain elastography and shear-wave elastography for assessing optic nerve involvement in pre-eclampsia.

MATERIAL AND METHODS: A total of 120 eyes were evaluated in 60 cases consisting of 30 participants in the pre-eclamptic and 30 participants in the non-pre-eclamptic pregnant patient group. The findings of strain and shear-wave elastography, grey-scale sonography, and optical coherence tomography were compared between the groups.

RESULTS: There was a statistically significant difference for the average shear-wave elastography values between groups (17.6±4.1 and 9.4±2 kPa, $p<0.01$). The analysis of the strain elastography types also revealed a statistically significant difference between the groups ($p<0.01$). A statistically significant difference was found for the average values of the optic nerve sheath diameter between the two groups ($p<0.05$). A statistically significant difference was found in the average value of the superior quadrant of the retina nerve fibre layer between the groups in optical coherence tomography analysis ($p=0.04$). The peripapillary choroidal thickness values of pre-eclamptic pregnant women were higher than that of non-pre-eclamptic pregnant women, but the difference was not significant ($p>0.05$).

CONCLUSION: Stiffness of the optic nerve was greater in patients with pre-eclampsia in the study. Elasticity changes in the optic nerve may be generally attributed to microvascular and biomechanical changes secondary to increased hypertension in pre-eclamptic patients. Elastography could be used as assistive diagnostic techniques to evaluate the optic nerve structure changes in pre-eclampsia.

Introduction

Pre-eclampsia is a multi-systemic, pregnancy-specific clinical syndrome characterised by the onset of hypertension and proteinuria in the second half of pregnancy.[1] A pre-eclampsia diagnosis is determined by urinary protein excretion of >300 mg/day and blood pressure >140/90 mmHg.[1,2] Pre-eclampsia can cause dysfunction and damage to many organs and systems.[3,4] It is also associated with ocular pathologies[2,3]; visual loss has been reported in 30–100% of pre-eclamptic patients and is associated with chorioretinal circulatory disorders, retinopathy, retinal oedema, optic neuropathy, central serous chorioretinopathy, and retinal detachment.[5]

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Conventional imaging techniques have been used for decades to assess eye findings in pre-eclampsia,[2,3] but they have limited resolution and measurement accuracy.[5] Grey-scale sonography is a non-invasive and easy-to-apply radiology imaging method, but it provides inadequate information about tissue structure.[6] Optical coherence tomography (OCT) is a new diagnostic ophthalmological imaging method used to evaluate the chorioretinal layer,[5] while diffusion tensor imaging is an advanced magnetic resonance imaging technique that can evaluate microstructural tissue changes.[7]

Elastography is currently less well developed than other medical imaging methods,[8] but it has nonetheless been used to evaluate changes in tissue stiffness, which are dependent on changes in the tissue structure.[9] Ultrasound (US) and magnetic resonance elastography are the most widely used elastography techniques for diagnosing tissue changes; although optical elastography is also sometimes used, it has limited penetration depth compared to both US and magnetic resonance elastography.[8]

The degree of tissue stiffness can be measured by either qualitative or quantitative sonoelastography.[10] The qualitative method uses strain elastography (SE) to measure external compression of the tissues, while the more objective quantitative method uses shear-wave elastography (SWE) to measure the velocity of waves generated by a transducer.[6,10] In this latter method, shear waves are generated using a focused acoustic radiation force from a linear US probe, thereby applying local stress and generating local displacement in the tissue.[11] The shear waves then propagate at a much slower pace through the adjacent tissues in the transverse plane, which is perpendicular to the primary wave that generates the acoustic radiation force, leading to shear displacements in the tissue.[11] As the shear waves propagate, the excitation of the fast plane wave is used to assess the tissue displacement, which is calculated using a speckle tracking algorithm, and the shear-wave speed, which is calculated using tissue displacement maps and which is commonly expressed in metres per second (m/s).[11] At each pixel, the shear-wave speed distribution is directly correlated to the shear modulus, which is calculated using a basic mathematical equation. The speed value ultimately shows the stiffness and elasticity of the tissue, as well as the pressure (kPa).[11]

To the authors' knowledge, no study to date has used elastography to evaluate the stiffness of the optic nerve tissues in pregnant women with pre-eclampsia. The purpose of the present study was therefore to determine the utility of elastography versus OCT for assessing optic nerve involvement in patients with pre-eclampsia. The present study investigated whether the elasticity of the optic nerve structure can be measured using SE and SWE elastography, and how the results compared to those of OCT, in pregnant women both with and without pre-eclampsia.

Materials and methods

Study population and exclusion criteria

This prospective, cross-sectional study was conducted with 30 pre-eclamptic and 30 non-pre-eclamptic pregnant women between March and November 2018 in the Departments of Radiology, Ophthalmology, and Obstetrics, after approval from the local ethics committee (decision 06/01 on 20 March 2018) and the study was conducted in accordance with the principles of the Declaration of Helsinki. All participants were informed of their participation in the study.

Pre-eclampsia was diagnosed according to the criteria of the National High Blood Pressure Education Program Working Group of the US National Institutes of Health.[12] All clinical evaluations of pre-eclampsia were performed by an obstetric expert. The comparison group consisted of women who were normotensive before and during pregnancy. All participants received an ophthalmological examination performed by an experienced ophthalmologist in the Ophthalmology Department. All radiological and ophthalmological examinations were performed within 24–48 hours after delivery.

Patients were excluded from the study if they had any systemic disease, including all types of hypertensive disease; if they had any clinical vascular disease, such as central retinal artery occlusion or retinal vein occlusion; if they had any disorders that could induce optic nerve damage; if they had any infections that could include optic nerve involvement; if they had had ocular surgery or trauma or any prominent orbital disease; if they had a refractive error of more than ±5D of spherical equivalent or more than ±2D of astigmatism; or if their best corrected visual acuity was less than 20/25 (as assessed using a Snellen chart). The full inclusion and exclusion criteria are shown in Fig 1.

B-mode US and elastography examination techniques

B-mode US and elastography examinations were carried out by one radiologist using a LOGIQ E9 sonographic system (GE Healthcare) with elastography software and a linear array probe of 9L, 6–15L MHz. The sonoelastography examinations were performed with each participant in a supine position, not moving, with eyes closed. A connecting gel was used between the eyelids and the probe to obtain the image. The optic nerve sheath diameter (ONSD) was measured for each eye in all participants. As shown in Fig 2, the ONSD was measured at 3 mm behind the globe, perpendicular to the longitudinal axis of the optic nerve, and the measurement was taken between the external edges of the hyperechogenic area surrounding the optic nerve.[13]

Measurements were first made using B-mode US, followed by simultaneous SE and SWE measurements. The B-mode US and elastography results were displayed simultaneously on a side-by-side split-screen display. SE images

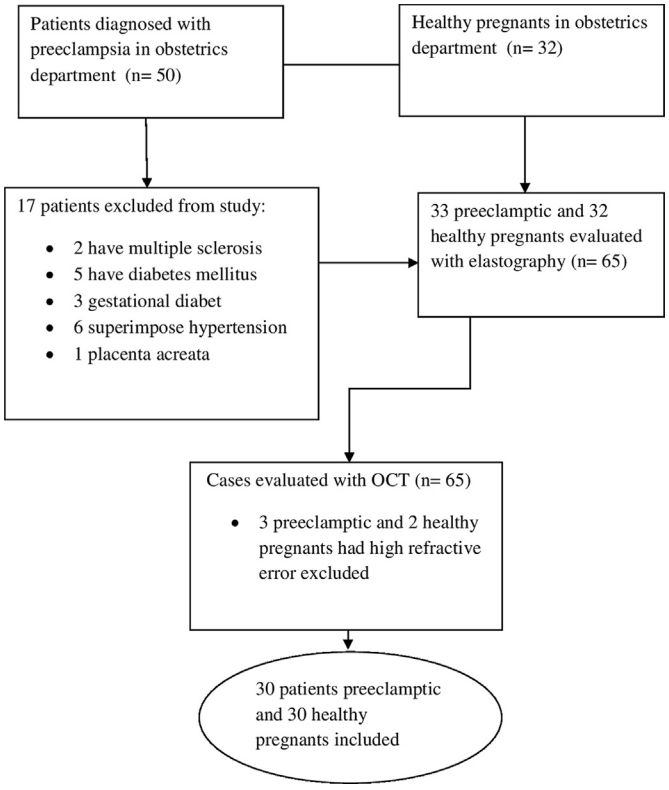

Figure 1 PRISMA study population flow diagram.

were produced using compression from a handheld transducer. The compression bar indicator, ranging from 1–7, was monitored in real-time, and image results were displayed when compression was in the optimal range of 5–7 bars. To visually present the varied levels of strain, the SE images were shown on a grey-scale background in a colour diagram ranging from red to blue, where red indicated low stiffness, green indicated intermediate stiffness, and blue indicated high stiffness.[6,10] Based on the SE colour mapping results, patients' optic nerves were classified as one of three

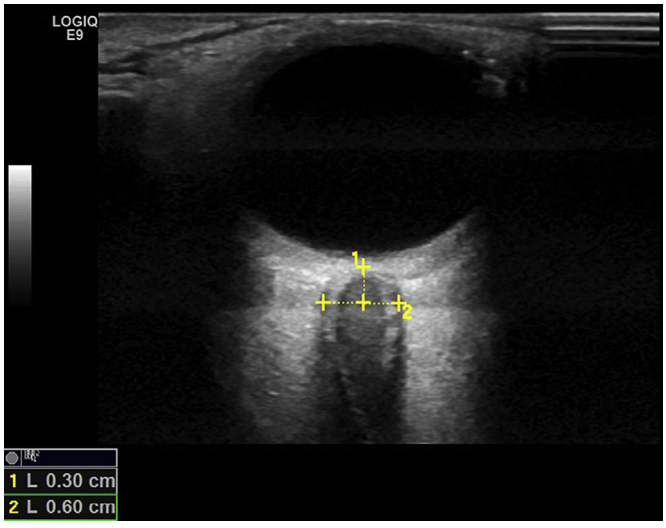

Figure 2 Grey-scale sonograms. ONSD measurement.

primary types: Type 1 was predominantly blue (hardest structure), Type 2 was predominantly blue-green (hard structure), and Type 3 was predominantly green (intermediate structure). Two subtypes (a) and (b) were also identified: (a) consisted of only related colours, and (b) included yellow and red colours[10] (Fig 3). Pattern types were determined by consensus between two radiologists, each of whom had at least 3 years of experience in elastography and 10 years of experience with conventional US.

The SWE images were acquired without compression and static images were recorded digitally on the machine for subsequent identification. A quantitative analysis of the optic nerve stiffness with SWE measured the pressure in the elasticity imaging interval (0–150 kPa). A circular region of interest (ROI) with a 2–3 mm diameter was located for each optic nerve, and the ROI quantitative values were then assessed using at least three measurements, which were then averaged for subsequent statistical analyses (Fig 4).

Ophthalmological examination technique

Spectral domain OCT (SD-OCT; Nidek RS-3000 OCT Advance; Nidek, Gamagori, Japan) was used for all ophthalmological evaluations. The examinations were performed on each patient's peripapillary area with a circular scan centred on the optic disc (3.45 mm diameter, "disc circle" option). Measurements of the peripapillary retinal nerve fibre layer (RNFL), retinal thickness, and choroidal thickness were carried out in the temporal, superior, nasal, and inferior quadrants. The average peripapillary retinal thickness and average retinal thickness in each quadrant were measured, manually changing the lower border to match the retina pigment epithelium of the same image. All parameters were automatically calculated by SD-OCT. For measurements of the peripapillary choroid thickness overall and in each quadrant, "Layer Editor" was selected from the display menu. The hyper-reflective external border of the retinal pigment epithelial layer was shown automatically, and the sclerochoroidal interface was drawn manually. The vertical distance between the two layers was measured to assess choroid thickness. The average values of each quadrant and the average values of the whole were used for statistical analysis.

Statistical analyses

Statistical analyses were performed using SPSS 20.0 software (IBM, Armonk, NY, USA). All values are expressed as mean ± standard deviation or median (range), depending on normality, as determined with the Kolmogorov–Smirnov test. After the samples' SE colour types were determined, chi-square tests were used to assess the relationships among the types.

An independent *t*-test was used to compare the ONSD, peripapillary RNFL, retinal thickness, choroidal thickness, and SWE values between the pre-eclamptic and non-pre-eclamptic pregnant women. A Pearson correlation was applied between the ONSD and SWE values, between the RNFL and SWE values, between the retinal thickness and

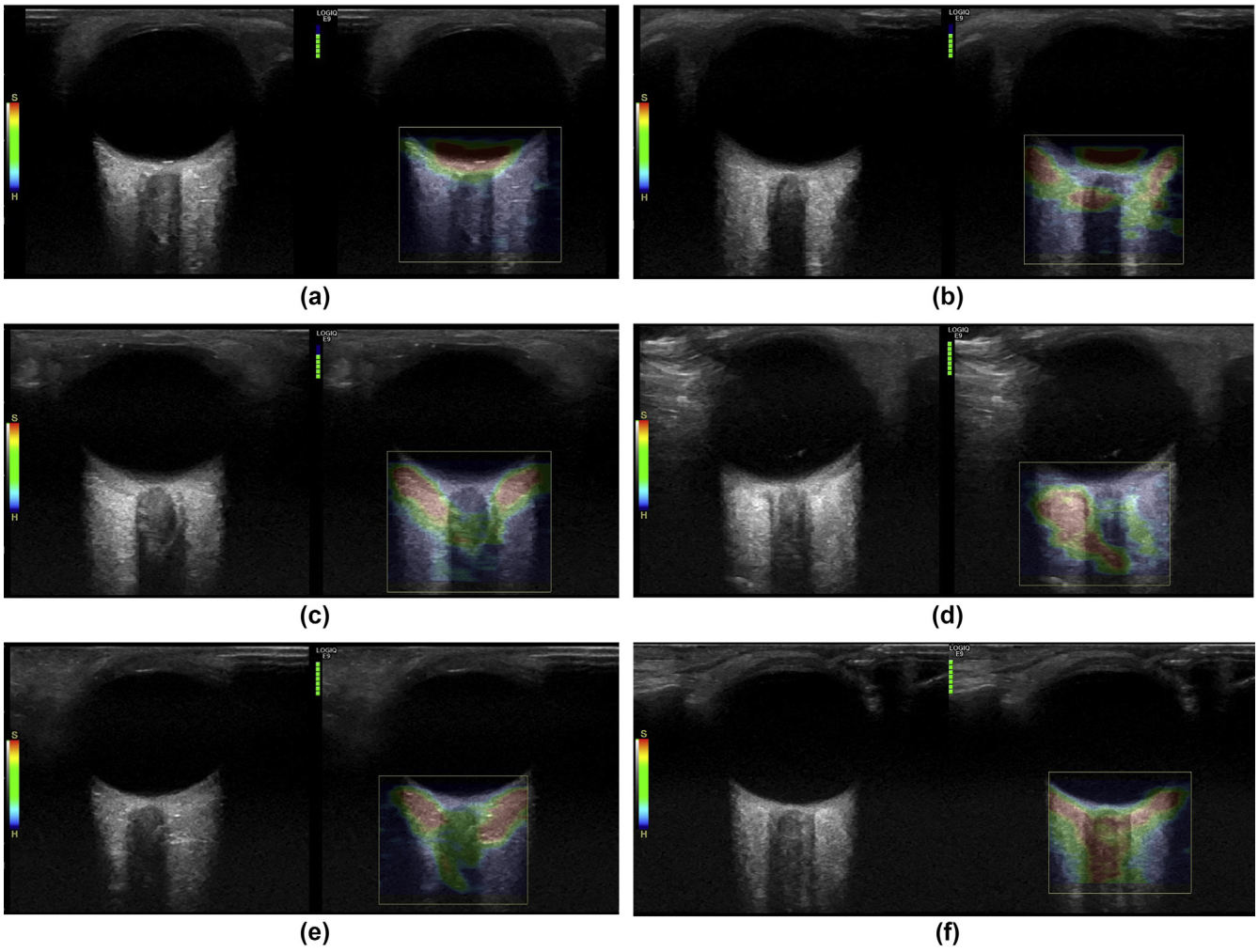

Figure 3 Grey-scale (left) and colour (right) sonograms representing different elastographic patterns of the optic nerve. (a) Type 1a in a 26-year-old patient with pre-eclampsia. (b) Type 1b in a 26-year-old patient with pre-eclampsia. (c) Type 2a in a 22-year-old patient with pre-eclampsia. (d) Type 2b in a 40-year-old patient with pre-eclampsia. (e) Type 3a in a 20-year-old healthy pregnant woman. (f) Type 3b in a 38-year-old healthy pregnant participant.

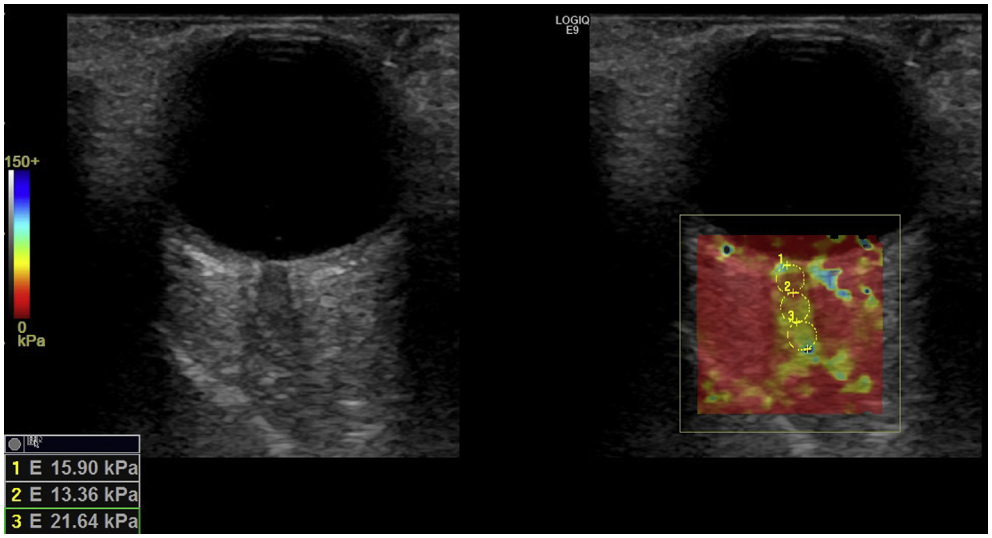

Figure 4 Grey-scale (left) and colour (right) SWE images of the optic nerve and circular ROI box examples in various cases. Elasticity measurement using SWE of the optic nerve of a 40-year-old patient with pre-eclampsia revealing a mean score of 17 kPa.

SWE values, and between the choroidal thickness and SWE values. A p-value of <0.05 was considered statistically significant.

A receiver operating characteristic (ROC) curve analysis was conducted to determine the diagnostic value of the SWE ratios. ROC curves were utilised to assess diagnostic sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), based on which an SWE cut-off point for differentiation between pre-eclamptic and healthy pregnant women was determined.

Results

A total of 120 eyes were examined bilaterally in 60 patients, including 30 pre-eclamptic women and 30 non-pre-eclamptic pregnant women. The age and gestational age parameters of the women in both groups are summarised in Table 1. The average ONSD value was 5.9±0.4 mm (range: 5.3–7) in the pre-eclamptic group and 5.6±0.3 mm (range: 4.8–6.5) in the non-pre-eclamptic pregnant group (Table 1); the difference was statistically significant ($p<0.05$).

The OCT results are presented in Table 2. A statistically significant difference was found between the average superior quadrant RNFL values of the two groups ($p=0.04$). There were no statistically significant differences in the quadrant averages or overall average for retinal thickness or choroidal thickness between the two groups ($p>0.05$). Although higher peripapillary choroidal thickness values were observed in the pre-eclamptic women than in the non-pre-eclamptic pregnant women, the differences were not significant (Table 2).

The results of the analysis of the SE elasticity types for both groups are summarised in Table 3. This analysis revealed a statistically significant difference between the two groups ($p<0.01$): the average SWE value was 17.6±4.1 kPa for the pre-eclamptic women and 9.4±2 kPa for the non-pre-eclamptic pregnant women (Table 1). No significant correlation was found between the ONSD and the SWE values, between the RNFL and the SWE values, or between the choroidal thickness and the SWE values in the pre-eclamptic women ($p>0.05$). However, a significant negative correlation was observed between the overall average peripapillary retinal thickness and SWE values among women in the pre-eclamptic group ($R=-0.311$, $p=0.02$).

The ROC analysis results of the SWE values was 0.979 (95% confidence interval=0.934–0.996, $p<0.01$). Based on the ROC curve analysis, the best cut-off value for determining pre-eclampsia was a shear value of 13 kPa, which had high sensitivity and specificity (90% and 98.3%, respectively) and high NPV and PPV (90% and 98%, respectively) The ROC analysis results are shown in Fig 5; diagnostic sensitivity, specificity, PPV, and NPV for the pre-eclamptic group are shown in Table 4.

Discussion

Pre-eclampsia is a multisystem disorder characterised by peripheral vasoconstriction and endothelial damage.[14] Multiple systems and organs, including the eye and the visual system, are susceptible to systemic pathological changes.[1,5] Pre-eclampsia can also cause major ophthalmic changes in which cortical blindness, exudative retinal detachment, and optic neuropathy are secondary to ischaemia.[5,14] Ocular involvement is common in pre-eclampsia and is correlated with foetal mortality.[15] Visual changes help indicate a need for prompt intervention as they may reflect similar ischaemic vascular changes in the placenta.[15]

The pathophysiology of pre-eclampsia is complex and is characterised by peripheral vasoconstriction and decreased arterial compliance.[1,16] The hypertension effects extend to the vasculature of the retina, choroid, and optic nerve head.[1] The decreased blood supply to the prelaminar portion of the optic nerve, and the associated retinal pathology (which can include vascular abnormalities, oedema or detachment, and acute ischaemic optic neuropathy), can result in blindness.[1] Furthermore, in pre-eclampsia, endothelial cell dysfunction and hyperpermeability are major causes of multiorgan damage, including to the ocular tissues.[17] In rare cases in pre-eclampsia, optic atrophy secondary to retinal vascular involvement may also occur.[18]

Previous studies have used radiological and ophthalmological imaging methods to evaluate ocular findings in patients with pre-eclampsia.[4,5,14,19] OCT is a non-invasive, noncontact transpupillary imaging method that was first developed in the 1990s,[20] but which has only recently become available in clinical practice.[5] SD-OCT is a more advanced technique that was approved by the United States Food and Drug Administration in 2006.[20] The OCT device used in the present study was created in 2009 with advanced imaging technology, including spectral domain technology, and a confocal scanning laser.

Elastography is a new US imaging method that measures deformative changes in soft tissues and identifies the elastic properties of both healthy and diseased soft tissues. In the

Table 1
The results of age, gestational age, optic nerve sheath diameter, shear-wave elastography between pre-eclamptic and healthy pregnant women.

Parameters	Pre-eclamptic pregnant women (n=30, 60 eyes)	Healthy pregnant women (n=30, 60 eyes)	p-Value[a]
Age mean±SD (range)	28.1± 6.5 years (20–45)	26.6±5.9 years (20–39)	>0.05
Gestational age mean±SD (range)	35.7±2.9 weeks (28–40)	38±1.1 weeks (35–41)	<0.01
ONSD mean±SD (range)	5.9±0.4 mm (5.3–7)	5.6±0.3 mm (4.8–6.5)	<0.01
SWE mean±SD (range)	17.6±4.1 kPa (9.3–30)	9.4±2 kPa (4.7–13.7)	<0.01

ONSD, optic nerve sheath diameter; SWE, shear-wave elastography.
[a] Independent t-test.

Table 2
The results of retinal nerve fibre layer thickness, retinal thickness, and choroidal thickness in OCT between pre-eclamptic and healthy pregnant women.

	Pre-eclamptic pregnant women (n=30, 60 eyes) Mean±SD (μm)	Healthy pregnant women (n=30, 60 eyes) Mean±SD (μm)	p-Value[a]
RNFL thickness			
T	67.3±10.5	67.7±13	>0.05
N	80.8±21.9	79.7±15.4	>0.05
S	131.3±23.5	140.2±23.1	0.04
I	127.5±19.2	125.7±20.1	>0.05
WA	101.7±12.8	103.3±11.6	>0.05
Retinal thickness			
T	313.6±19.3	312±16.9	
N	302.1±29.2	302.2±17.7	
S	355±29	362.3±27.5	>0.05
I	342.8±26.5	339±23.3	
WA	328.4±22.6	329±17.6	
Choroidal thickness			
T	212.3±55.1	208.7±53.8	
N	212.1±60.5	202.6±51.3	
S	198.3±45.9	196.5±51.6	>0.05
I	206.5±55	193.6±52.7	
WA	208.5±47.8	200.5±49	

RNFL, retinal nerve fibre layer; T, temporal; N, nasal; S, superior; I, inferior; WA, whole average; SD, standard deviation.
[a] Independent t-test.

Table 3
The results comparison of strain elastography findings between pre-eclamptic and healthy pregnant women.

Strain elasticity types	Pre-eclamptic pregnant women (n=30, 60 eyes) (%)	Healthy pregnant women (n=30, 60 eyes) (%)	p-Value[a]
Type 1a	5 (8.3%)	0	
Type 1b	8 (13.3%)	0	
Type 2a	15 (25%)	4 (6.7%)	<0.01
Type 2b	27 (45%)	20 (33.3%)	
Type 3a	0	5 (8.3%)	
Type 3b	5 (8.3%)	31 (51.7%)	

[a] Chi square test analysis.

past two decades, it has been used widely in clinical studies of many organs, including ocular and periocular tissues.[6,9,10,16,21–26] Recently, for example, Inal *et al.* used SE and SWE to report increased optic nerve stiffness in patients with multiple sclerosis and Behcet's disease.[6,10] Similarly, Dikici *et al.* used SWE to identify increased stiffness in the optic nerves and peripapillary structures of patients with glaucoma; they subsequently determined that glaucoma's pathophysiology may be associated with biomechanical changes and the susceptibility of ganglion cell axons due to chronic high intraocular pressure.[22] Other studies that used elastography to assess liver and placenta tissue structures in pre-eclamptic women reported a reduction in tissue elasticity dependent on similar mechanisms.[16,23–25]

The present study was the first to use SE and SWE to measure stiffness in the optic nerve structure in pre-eclamptic women. Sonographic evaluations, including ONSD measures and OCT evaluations (peripapillary RNFL, retinal thickness, and choroidal thickness) were also performed. The results indicated that the SE pattern types and SWE values of pre-eclamptic women were significantly different than those of non-pre-eclamptic pregnant women. The average superior quadrant peripapillary RNFL thickness of the pre-eclamptic women was significantly lower than that of the non-pre-eclamptic pregnant women, while the ONSD values were significantly higher in the pre-eclamptic women than in the control group The peripapillary choroidal thickness values of the pre-eclamptic women were also higher than those of non-pre-eclamptic women, but this difference was not statistically significant.

SE patterns were classified by pattern type using a method similar to the one used by Inal *et al.*[10] The Type 3 elasticity pattern was most frequent among the non-pre-eclamptic pregnant women, followed by the Type 2 elasticity pattern. In contrast, in the pre-eclamptic women, the Type 2 and Type 1 patterns were more commonly observed. The differences between the two groups was statistically significant ($p<0.01$). A quantitative analysis was also conducted using SWE and significantly difference results between the average SWE values of the two groups were detected ($p<0.01$). ROC curve analysis was also able to determine a pre-eclampsia cut-off shear value of 13 kPa, with 90% sensitivity and 98.3% specificity.

No statistically significant differences were found between the two groups in average overall values or average quadrant values for the peripapillary retinal thickness and choroidal thickness using OCT ($p>0.05$), although the peripapillary choroidal thickness values were non-significantly higher in pre-eclamptic women. Kim *et al.* also reported increased subfoveal choroidal thickness in pre-eclamptic

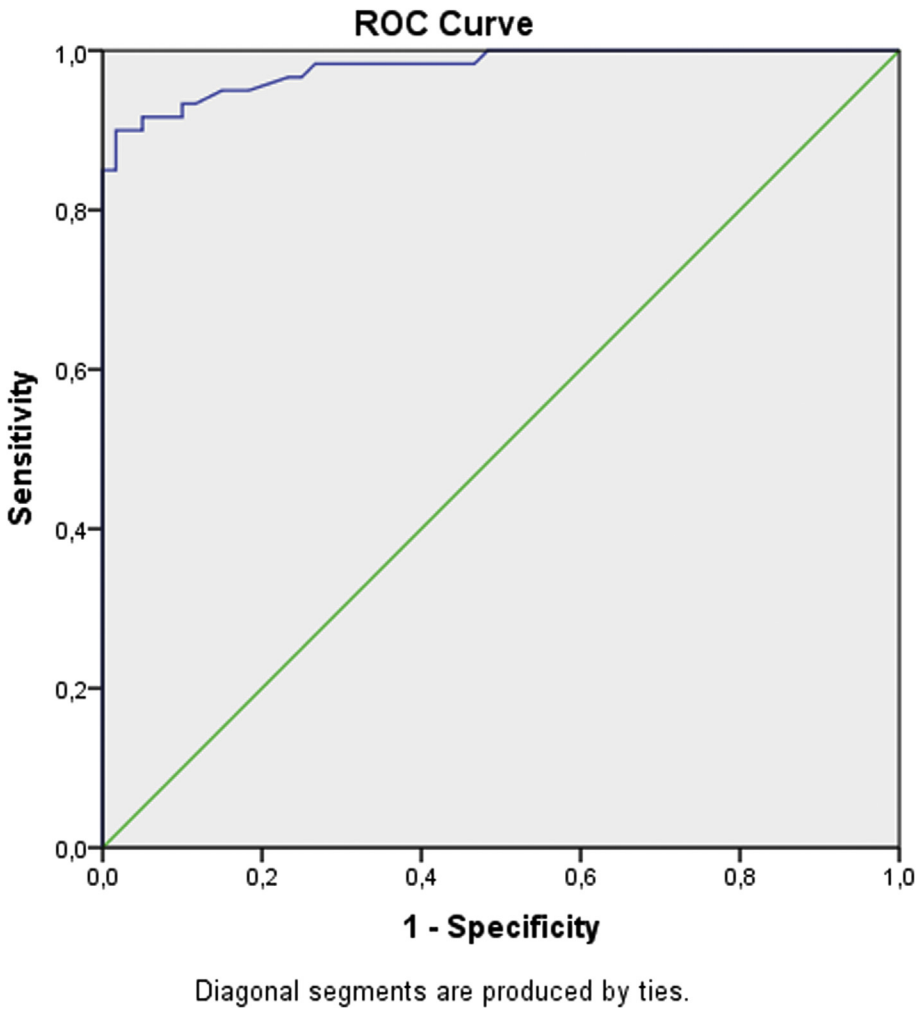

Figure 5 ROC curves of SWE values in differentiating patients with pre-eclampsia from healthy pregnant women. The blue curve represents the ROC curve, and the green line represents the diagonal line used as a reference.

Table 4
The results of sensitivity, specificity, PPV, and NPV of shear-wave elastography for pre-eclamptic pregnant women.

	Pre-eclamptic pregnant women (n=30, 60 eyes)	Healthy pregnant women (n=30, 60 eyes)	
Positive	True positive 54	False positive 1	PPV 98%
Negative	False negative 6	True negative 59	NPV 90.7%
	Sensitivity 90%	Specificity 98.3%	

PPV, positive predictive value; NPV, negative predictive value.

women, possibly related to the vascular hyperpermeability, increased body fluid, and decreased colloidal osmotic pressure associated with pre-eclampsia.[17] Evcimen *et al.*[27] similarly reported significantly increased choroidal thickness values in pre-eclamptic women, possibly as the results of interstitial oedemas.

The present results also indicated that the average RNFL thickness in the superior quadrant peripapillary was significantly lower among pre-eclamptic women (p=0.04). Arab *et al.* similarly reported decreased peripapillary RNFL thickness values in pre-eclamptic and eclamptic women, as well as in non-pre-eclamptic pregnant women in the second month of delivery; they hypothesised that the thinning of the RNFL could be due to RNFL atrophy, to resolved pregnancy-induced oedema, or to both.[3] The OCT findings in the present study are more likely explained by pre-eclampsia-related changes in the chorioretinal layer, including endothelial damage, hypoperfusion causing ischaemia, or hyperperfusion causing retinal oedemas.[28] A significant negative correlation was found between the overall average peripapillary retinal thickness values and SWE values among women in the pre-eclamptic group (R=−0.311, p=0.02).

The average ONSD value of the pre-eclamptic women in our study (5.9±0.4 mm) was significantly higher (p<0.05) than that of the non-pre-eclamptic women (5.6±0.3 mm).

This is consistent with results reported by Dubost *et al.* of significantly enlarged ONSD values in pre-eclamptic women as compared to non-pre-eclamptic pregnant women.[19] Moreover, neurological complications in pre-eclampsia are believed to be associated with increased intracranial pressure (ICP), and the optic nerve, as part of the central nervous system, is surrounded by a dural sheath and a subarachnoid space containing cerebrospinal fluid.[19] Geeraerts *et al.* further identified an ONSD cut-off value of 5.8 mm for raised ICP.[29] The increased ONSD values found in the present study may thus be an indirect sign of increased ICP in pre-eclamptic women.

Taken together, the present results suggest that increased optic nerve stiffness may be associated with changes in the optic nerve structure due to ischaemic neuropathy, optic head swelling, and endothelial cell damage of the optic nerve in pre-eclamptic women. The observed increase in SWE values among pre-eclamptic women could be caused by fibrosis and cell damage in the optic nerve structure; although it is not clear whether this is a cause or a result.

Nonetheless, the present study has a few limitations. First, ocular changes may occur even during otherwise healthy pregnancies as a result of physiological reactions to the gestational product.[30] Further research is therefore needed that includes non-pregnant participants as a control group. Second, long-term post-partum results were not available. Third, the sample size was relatively small. Fourth, no data regarding patient body mass index were recorded but could potentially be relevant. Fifth, SE is an application-dependent technique, and evaluation of strain elasticity patterns is subjective. Finally, interobserver variability could not be determined for the study.

Elastography is a new, non-invasive method to assess tissue elasticity and does not require ionising radiation. This study demonstrated the ability of SE and SWE elastography imaging to assess optic nerve stiffness in pre-eclamptic women. The results were confirmed by sonographic and OCT findings and indicated an increase in optic nerve stiffness in pre-eclamptic women, as compared to non-pre-eclamptic pregnant women. Changes in the elasticity of the optic nerve may be due to microvascular and biomechanical changes associated with pre-eclampsia. Strain and shear elastography could also be used to indirectly identify structural changes in the optic nerve before other clinical presentations of pre-eclampsia and could therefore be used as a diagnostic tool. Additional studies involving non-pregnant participants and a larger sample size are needed to further explore these results.

Conflict of interest

The authors declare no conflict of interest.

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