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Study of Use of Shear Wave Elastography in Placental Dysfunction by Comparison of Elasticity Values in Normal and Pre-eclamptic Pregnancies

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ABSTRACT

Background: It has been believed that placental stiffness varies between normal and pre-eclamptic pregnancies. In order to appreciate this difference, Share Wave Elastography (SWE) of the placenta was done to assess the degree of placental stiffness. **Objective:** The aim of the current study was to evaluate the utility of SWE in detection of pre-eclampsia and correlate the degree of placental stiffness with severity of pre-eclampsia and with perinatal outcome. **Patients and methods**: A total of 76 pregnant females in second or third trimester were enrolled in the present study. Half of them (38 females) had normal pregnancy with no history of medical disease and the second half (38 females) had pregnancy complicated by pre-eclampsia. SWE was used for all cases.

Results: In pre-eclamptic placentas, the mean stiffness values were significantly higher across all regions and layers compared to healthy controls. The central placental region showed the greatest disparity. A moderate correlation was also found between the severity of pre-eclampsia and SWE data. Maximum diagnostic accuracy was achieved with a cutoff of 18.47 kPa for the central placenta (area under the curve: 0.97; confidence interval: 0.88-1; sensitivity: 94.7%; specificity: 94.7%; PPV 92.3; and accuracy: 94.7%). Regarding other obstetric and Doppler findings there was a significant decrease in measured abdominal circumference AC and femur length FL among preeclamptic pregnancies compared with the control group, together with abnormal Doppler indices with highly statistical significant increase of resistive index of umbilical artery and significant decrease of resistive index of middle cerebral artery among pre-eclampsia patients compared to the control group. **Conclusion:** Difference in placental stiffness between healthy and pre-eclamptic pregnancies can be assessed using SWE, and it can be used for mentoring early perinatal outcome together with routine obstetric and Doppler ultrasound study.

Keywords: Shear Wave Elastography, Placental Dysfunction, Pre-eclampsia.

INTRODUCTION

Preeclampsia is a prominent cause of maternal as well as perinatal mortality and morbidity, contributing to premature birth in 5-8% of pregnancies and perinatal mortality in 1-3% of births globally [(1)].

Pre-eclampsia is characterized by abnormal development of uterine placental perfusion, an elevated inflammatory response, and endothelial dysfunction, all of which can have negative effects on the developing fetus [(2)]. The condition occurs after 20 weeks of pregnancy while fetal impairment is primarily correlated with gestational age at beginning of preeclampsia [(3-5)]. The uterine artery Is abnormal women who develop pre-eclampsia before 34 weeks of pregnancy often have abnormal Doppler readings, have babies with growth restrictions, and have a difficult pregnancy and delivery [(6)]. Disseminated coagulopathy/hemolysis elevated liver enzymes, and low platelets (HELLP) syndrome, pulmonary edema, acute renal failure, placenta abruption, and long-term cardiovascular problems are all common complications of severe pre-eclampsia in mothers [(7)]. Elasticity is the degree to which the rigidity of soft tissue fluctuates in response to the physiologic and pathologic processes [(8)].

Shear waves are generated through a focused ultrasonic push beam and then rapidly imaged, measured by Young's modulus values, expressed in kilopascals. Breast, thyroid, prostate, kidney, spleen, lymph node characterization, and liver fibrosis imaging are just some of the many applications of SWE. In our study we aimed to translate the placental shear-wave velocity into equivalent unit of stiffness (kPa) [(3)].

The diagnostic utility of this method is now being investigated by comparing the elastic characteristics of healthy and diseased tissues [(9)].

The aim of the current study was to evaluate the utility of SWE in detection of pre-eclampsia and correlate the degree of placental stiffness with severity of pre-eclampsia and with perinatal outcome.

PATIENTS AND METHODS

A total of 76 pregnant females in second or third trimester aged between 19 and 43 years old were enrolled in the present study. Half of them (38 females) had normal pregnancy with no history of medical disease and the second half (38 females) had pregnancy complicated by pre-eclampsia that are diagnosed clinically and by urine analysis then classified according to clinical severity of the disease into mild, moderate and severe degree. All cases were referred from the Obstetrics and Gynecology Department at Zagazig University Hospitals, to Radio diagnosis Department, Digital Ultrasonography Unit.

Inclusion criteria:

1. Group I: 38 females who are at least halfway through their pregnancies (not just the first trimester) and who have a healthy baby and no

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history of medical problems was served as a control group.
2. Group II: 38 females diagnosed with pre-eclampsia in their second or third trimesters of pregnancy that made up the case group.

Exclusion criteria:
1. Pregnant women with medical conditions other than preeclampsia as severe anemia (hemoglobin 6 g/ dL), diabetes or hypertension.
2. Pregnant women with obstetric disorders as previous history of miscarriage in twin pregnancy, who have polyhydramnios or oligohydramnios with band formationor who have bronchopulmonary sequestration.
3. Pregnant women with a significant structural or chromosomal abnormality, such as hydrops fetalis or Chiari malformations.
4. Pregnant women with posterior placental site or abnormal placental locations as placenta previa, placental calcifications or retroplacental hematomas.

Methods:
All patients have been subjected to the following:
1) Complete history taking: Personal history, history of present illness, clinical manifestations, family history and history of previous surgery or medication.
2) Radiological Assessment:
a. Evaluation of fetal biometric measurements, amniotic fluid, placental shape, and position using standard grayscale B-mode obstetric sonography.
b. The umbilical artery and the middle cerebral artery were evaluated using Doppler.
c. Supine placental SWE with elasticity measurements taken from 8–10 locations centrally and peripherally.
d. Recording the previous findings then comparison of the results between the two groups.
e. Preparing conclusion and recommendations.
f. Technique:

Comparisons were conducted for maternal age, gravidity, and body mass index between healthy and pre-eclamptic patients in the second and third trimesters of pregnancy (>20 weeks of gestation for pre-eclamptic patients).

To identify an association between the severity of pre-eclampsia and the measured elasticity values at both the central and peripheral placenta, a grading scale was developed to categorize the case group's cases into mild, moderate, and severe. This classification was done following certain clinical and laboratory parameters as mentioned by **and the American College of Obstetricians and Gynecologists [(10)]**.

Patient was examined using elastography while lying supine. A perpendicular view of the closest area of the placenta was obtained using sagittal imaging planes. The imaging plane for both grayscale and elastography was restricted to a shallow view in order to minimize deeper beam penetration over the fetus, and the placenta was also brought into sharper focus. In order to get rid of compression artefacts caused by the probe, a lot of transmission gel was employed. Patients were instructed to take shallow breaths and to remain still during the acquisition process. Different tests were recorded based on their thermal and mechanical indices. Following picture freezing, a circular region of interest (ROI) of varying diameters is positioned within the elastography window in a region of the placenta that does not include blood vessels. The computations were done with color photos. Using a spectrum scale, the current work assessed tissue elasticity in kilopascals (kPa), which then directed the positioning of the ROI pointer.

Ethical Consideration:
This study was ethically approved by the Institutional Review Board of the Faculty of Medicine, Zagazig University. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical Analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 27.0 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), and Kruskal-Wallis test was used for comparison between groups. Pearson's and Spearman's correlation coefficients were employed to check for statistical significance in the observed discrepancies. P value ≤ 0.05 was considered to be statistically significant.

RESULTS

There was no statistically significant difference between the two studied groups regarding age, gravidity and history of medical disorders (**Table 1**).

Table (1): Comparison between pre and control group regarding maternal age, gravidity, and history of medical disorders.

Variables	Control No= 38 (%)	Pre-eclampsia No=38 (%)	Test	P-value
Age				
19-30	27 (71.1 %)	23 (60.5 %)		
31-40	7 (18.4 %)	10 (26.3 %)	0.6	0.5
>40	4 (10.5 %)	5 (13.2 %)		
Mean ± SD	28.1 ± 5.1	29.8 ± 7.1		
(Range)	(19 - 40)	(19 - 43)		
Gravidity				
G1	9 (23.6 %)	9 (23.6 %)		
G2-3	20 (52.6 %)	19 (50 %)		
> G3	9 (23.6 %)	10 (26.3 %)	1.6	0.09
Mean ± SD	1.78 ± 1.5	2.52 ± 2.2		
(Range)	(0 - 5)	(0-7)		
History of medical disorders:				
Yes	Zero	Zero	0	1
No	38 (100%)	38 (100%)		

Table 2 shows that there was a highly statistically significant decreased birth weight, and birth age among preeclampsia patients than the control group (P=0.001**), while there was no IUFD among the studied groups.

Table (2): Comparison between pre-eclampsia patients and control group regarding perinatal outcome as birth age, birth weight and IUFD.

Variables	Control No= 38	Pre-eclampsia No= 38	Test	P-value
Birth age (weeks)				
Preterm (before 37 weeks)	No	9 (23.7%)		
Term (after 37 weeks)	38 (100%)	29 (76.3%)		
Mean (SD)	38 (SD 0.6)	36 (SD 0.89)	9.6	**0.001****
Range	(38 - 40)	(35 - 38)		
Birth weight (grams)				
Small For Age	No	7 (7.9%)		
Normal For Age	38 (100%)	31 (81.6%)		
Mean (SD)	3171 (SD 230)	2529 (SD 471)	7.5	**0.001****
Range	(2800 - 3600)	(2000 - 3200)		
IUFD	No	No	1	0.000

Table 3 shows that there was a highly statistically significant increased resistive index of the umbilical artery among pre-eclampsia patients than the control group (P=0.001**), while, the resistive index of the middle cerebral artery was a highly statistically significant decrease among pre-eclampsia patients than the control group (P=0.001**).

Table (3): Comparison between pre-eclampsia patients and control groups regarding the fetal Doppler indices.

Doppler Indices	Control No= 38 (%) Mean ± SD (Range)	Pre-eclampsia No=38 (%) Mean ± SD (Range)	T-test	P-value
Resistive index of Umbilical Artery (RI of UA)	0.55 ± 0.06 (0.5 - 0.7)	0.67 ± 0.11 (0.5 - 0.9)	6.1	**0.001****
Resistive index of Middle Cerebral Artery (RI of MCA)	0.81 ± 0.05 (0.7 - 0.9)	0.72 ± 0.04 (0.6 - 0.8)	7.9	**0.001****

Table 4 shows that there was a highly statistically significant increased both central and peripheral placental **SWE** values among pre-eclampsia patients than the control group (P=0.001**), with the central placental elastography values being higher than the values measured at the periphery of the placenta.

Table (4): Comparing of placental Shear Wave Elastography (SWE) values between pre-eclampsia patients and control groups.

Shear Wave Elastography	Control (No= 38)	Pre-eclampsia (No=38)	Test	P-value
Central Placental Mean ± SD Median (Range)	 11.07 ± 4.5 9.4 (6.08 - 28.38)	 27.1 ± 22.7 22.4 (7.15 - 128.9)	 MW = 6.1	 **0.001****
Peripheral Placental Mean ± SD Median (Range)	 9.38 ± 3.05 8.2 (6.23 - 18.8)	 20.7 ± 14.2 17.87 (6.4 - 96.3)	 MW = 6.5	 **0.001****

Table 5 shows that there was a statistically significant increase in central placental SWE values among severe than moderate than mild pre-eclampsia patients (P=0.00039*). Regarding peripheral placental SWE, it also show increased among severe than moderate or mild pre-eclampsia patients but this difference wasn't significant.

Table (5): The relation between the severity of Pre-eclampsia and placental Shear Wave Elastography (SWE) values.

Shear Wave Elastography	Pre-eclampsia			Test KW	P-value
	Mild No=19 (50%) Mean ± SD (Range)	**Moderate No = 12 (31.5%)** Mean ± SD (Range)	**Severe No = 7 (18.4%)** Mean ± SD (Range)		
The central placental	18.6±18.7 (7.1-40.8)	32.4± 15.9 (10.3-80.8)	46.6 ± 38.1 (15.5-128)	H statistics= 15.6928	**0.00039***
The peripheral placental	16.8± 8.6 (6.4-35.5)	16.4 ±13.7 (8.8-52.7)	29.8± 22.1 (9.8-96.3)	H statistics= 9.7274	0.00772

Table 6 shows that there was a highly statistically significant positive correlation between the central placental SWE and changes in fetal Doppler indices as resistive index of both the umbilical artery and the middle cerebral artery among pre-eclampsia patients (P=0.001**). Oppositely the central placental SWE was statistically significant negatively correlated with expected fetal body weight, birth age, and birth weight.

Table (6): The correlation between the central placental shear wave elastography values and other variables among the pre-eclampsia patients.

Variables	Pre-eclampsia group		
	The central placental Shear Wave Elastography		
	R	**P-value**	**Significance**
➢ **Age** **Maternal factors:**	0.1	0.5	NS
➢ **BMI**	0.1	0.4	NS
➢ **Gravidity & parity**	0.1	0.15	NS
Doppler Indices: ➢ RI of UA	0.5	0.001**	HS
➢ **RI of MCA**	0.7	0.001**	HS
Perinatal Outcome: ➢ **Expected fetal body weight (grams)**	-0.4	0.02*	S
➢ **Birth age (Weeks)**	-0.39	0.03*	S
➢ **Birth weight (grams)**	-0.4	0.02*	S
The peripheral place stiffness	0.38	**0.01***	S

Table 7 shows that there is a statistically significant positive correlation between peripheral and central SWE among pre-eclampsia patients (P=0.01*). Otherwise, there was no statistically significant correlation between peripheral SWE and other variables among pre-eclampsia patients

Table (7): The correlation between The Peripheral placental Shear Wave Elastography values and other variables among the pre-eclampsia patients.

Variables		Pre-eclampsia group		
		The Peripheral placental Shear Wave Elastography		
		R	P-value	Significance
➢ Age	**Maternal factors :**	0.01	0.9	NS
➢ BMI		0.02	0.8	NS
➢ Gravidity & parity		0.005	0.15	NS
➢	**Doppler Indices: RI of UA**	0.005	0.9	NS
➢ RI of MCA		0.1	0.4	NS
➢	**Perinatal outcome : (Expected fetal body weight grams)**	0.06	0.7	NS
➢ Birth age(Weeks)		0.1	0.6	NS
➢ Birth weight (grams)		0.1	0.5	NS
	The central placental stiffness	0.38	**0.01***	SIG

Both the central and peripheral placental Shear Wave Elastography had high sensitivity (94.7% and 88.6%), specificity (92.3% and 82.9%), predictive value positive (92.1% and 81.6%), predictive value negative (94.7% and 89.5%) and accuracy (97.4% and 85.6%) (**Figure 1**).

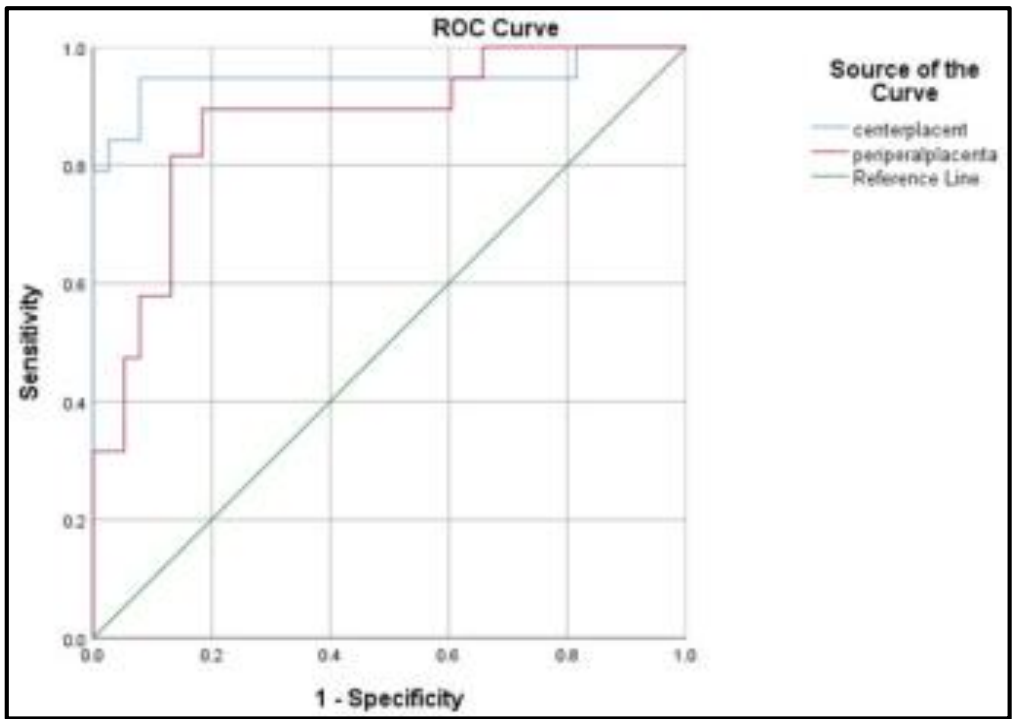


Figure (1): ROC curve for the diagnostic ability of the central and peripheral placental shear wave elastography to determine placental stiffness among pre-eclampsia patients from healthy controls.

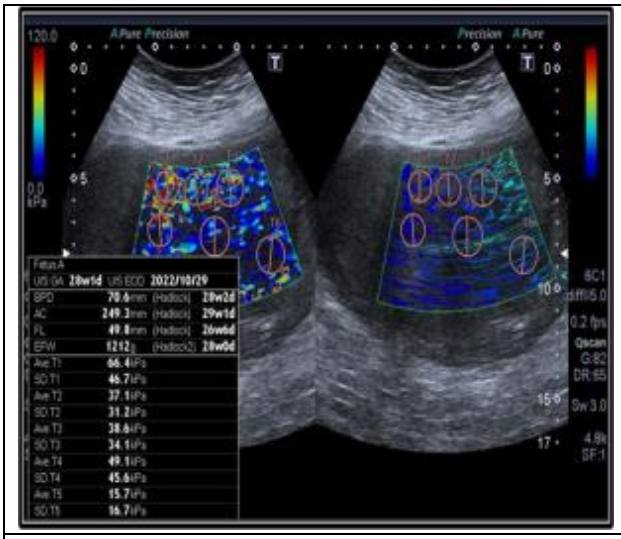
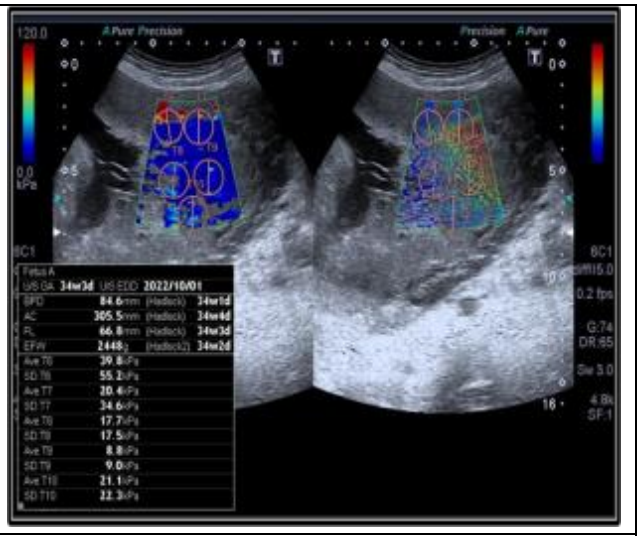
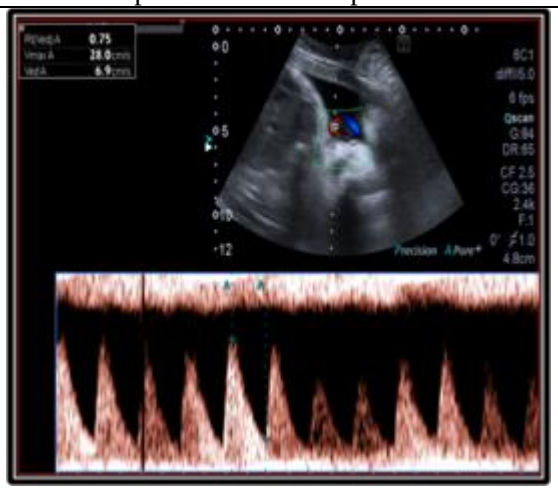
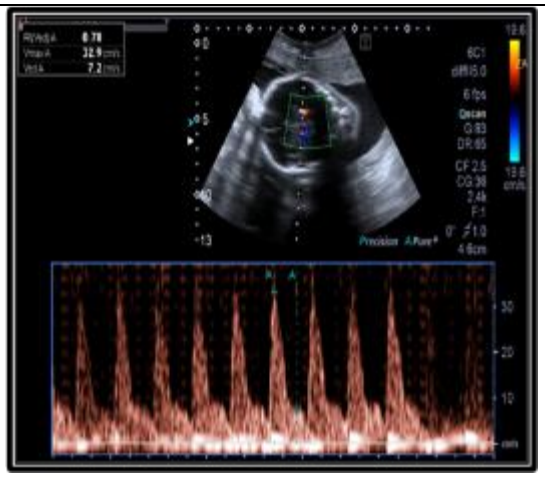
	
(A) Shear wave elastography (SWE) reading of the central placenta with two split shear wave elastography images at the same level. Color spectrum show areas of changed color scale to yellow and red. Round and free regions of interests (ROI) are placed in the denser area. SWE values were measured as 66.4---37.1--38.6---49.1--15.7 Kpa from T1, T2, T3 , T4 and T5, respectively with the mean elasticity value at the center of the placenta =41.38 Kpa	(B) SWE reading of the peripheral placenta with two split images at the same level. ROI are placed in the denser area. SWE values were measured as 39.8---20.4---17.7---8.8---21.1 Kpa from T6, T7, T8 , T9 and T10 respectively with the mean elasticity value at the periphery of the placenta =21.56 Kpa
	
(C) Color and pulsed Doppler of the Umbilical Artery (UA) shows low diastolic wave form with calculated Resistive Index (RI)=0.7.	(D) Color and pulsed Doppler of the Middle Cerebral Artery (MCA) shows normal high systolic and low diastolic wave form with calculated Resistive Index (RI)=0.7 with cerebro-placental ratio=1:1.

Figure (2): Twenty-four female patient G2P1 with moderate pre-eclampsia. Expected fetal age by LMP (at the day of exam): 30 weeks and calculated fetal age by ultrasound was 28 weeks**.** Shear wave Elastography: readings were recorded from 10 different sites of central and peripheral placenta.

DISCUSSION

SWE allows a more thorough examination of the placenta, the primary catalyst in the pre-eclampsia cascade. This is in contrast to ultrasound and Doppler, which play important roles in detecting pre-effects eclampsia's on fetal blood supply, fetal growth, and maternal organ affection **(7).**

Since SWE relies on the generation of shear waves and the subsequent measurement of the velocities at which those waves propagate in various tissue consistencies, it can be used to assess the degree to which pathological conditions, such as the increased placental stiffness seen in pre-eclampsia, contribute to tissue structure **(11).**

Assessment of the perinatal outcome was made in our study with comparison between the two studied groups regarding birth weight, fetal age at delivery (birth age) and presence of Intra Uterine Fetal Death (IUFD) as the following: Out of 38 pre-eclamptic included cases, 7 (7.9%) cases were small for age, while 31 (81.6%) cases were normal far age with the net result showing a highly statistically significant decrease in the birth weight (mean=2529.5 g; range from 2000 to 3200 g) among preeclampsia patients than the control group with the birth weight (mean=3171 g; range from 2800 to 3600 g). Out of 38 pre-eclamptic included cases, 29 (76.6%) cases were born at term while 9 (23.7%) cases were born preterm before 37 week with the net result showing a highly statistically significant decrease in the birth age (mean=36 weeks + 5d; range from 35 to 38 weeks) among pre-eclampsia patients than the control group with the birth age (mean=38 weeks + 4d; range from 38 to 40 weeks). IUFD: no cases were recorded among the studied groups.

These findings are similar to **Khan *et al.*** **(12)** who discovered, across the board, that birth weights were lower in preeclamptic cases (mean 2372 g; range 1691-2531 g) compared to normal instances (mean 2974 g; range 2529-3325 g).

While **Mayrink *et al.*** **(13)** found that Patients with pre-eclampsia had a significantly lower gestational age at delivery than the control group, with preterm births occurring at a lower gestational age (3.97-fold higher).

Fetal Doppler indices can be used as a monitor for worsening of the condition or termination of pregnancy in most severe cases, since they highlight the underlying hemodynamic impairment in the maternal-fetal circulation happening in pre-eclampsia. In our study; Resistive Index of both Umbilical artery (RI UA) and Middle Cerebral Artery (RI MCA) was measured and the findings were compared between the two groups as the following: Abnormal Doppler findings were found in pre-eclamptic pregnancies as there was a highly statistical significant increase of RI UA (mean RI UA= 0.67 +/-0.11) in pre-eclamptic patient compared to (mean RI UA= 0.55 +/- 0.06) in the control group. While there was a significant decrease of RI MCA (mean RI MCA= 0.72 +/- 0.04) among pre-eclampsia patients compared to (mean RI MCA= 0.81 +/- 0.05) in the control group.

Similar findings were reached by **Konwar *et al.*** **(14)** they found that severe PIH cases had significantly higher Mean UmA-RI than moderate PIH cases ($P<0.05$). The MCA-Resistive Index (RI) value was substantially different between patients with mild and severe PIH, with the RI being lower in severe PIH than in mild PIH or normal PIH ($P<0.01$).

Our results showed that there was a highly statistically significant increased central and peripheral placental shear wave elastography values among preeclampsia patients than the control group with the central placenta being more stiffer than the periphery, this was in match with **Cimsit *et al.*** **(11)** SWE ranges and mean values in group B (preeclamptic pregnancies) were substantially larger than those in group A (normal pregnancies) with the same standard deviations, as stated in his comparison study between the same investigated groups. Group B had placental elasticity values of 6.67 kPa at the placental midpoint and 6.64 kPa at the placental margins, while group A had placental elasticity values of 2.28 kPa at the placental midpoint and 2.48 kPa at the placental margins.

In contrast, **Spiliopoulos *et al.*** **(2)** found a different regional distribution of stiffness within the same placenta, finding that, in pre-eclampsia patients, the placental periphery was significantly stiffer than the placental core (31.9 ± 4.1 kPa vs. 21.9± 3.04 kPa), while there was no such difference between the placental core and periphery in the control group.

In our study Both central and peripheral elastography mean elastography values and ranges increased with increasing severity of the disease being higher in severe cases then moderate cases then mild cases, Similar finding was mentioned by **Zhuang *et al.*** **(15)** who observed an excellent positive association ($r=0.712$) between placental Young's modulus values and illness severity; however, no link was mentioned between central or peripheral elastography values and disease severity.

Further observation was made about the correlation between measured central and peripheral elastography values with Maternal Factors as age, BMI and gravidity, Doppler Indices (both UA and MCA) and Perinatal Outcome as birth age and birth weight. The results were as the following maternal factors: Neither of central or peripheral placental elasticity values had a statistical significant correlation with mentioned maternal factors. Similar findings were mentioned by **Spiliopoulos *et al.*** **(2),** as none of the aforementioned maternal characteristics were shown to significantly correlate with placental stiffness, with the exception of BMI, which was found to link negatively with placental stiffness; however, this association was not attained by our investigation.

Doppler Indices: Central placental SWE showed a statistical significant positive correlation with changes

in fetal Doppler Indices of both RI of UA and MCA (increased RI of UA, decreased RI of MCA), on the other hand, there was no statistical significant correlation between peripheral placental elastography and changes in Doppler Indices. Different finding was reached by **Zhuang *et al.* [15]** who found that There was no statistically significant relationship (P>0.05) between fetal or maternal Young's modulus values and S/D, RI, or PI values of the umbilical artery.

To determine a cut point of placental stiffness that indicates the presence of PE, we constructed a receiver operating characteristic (ROC) curve. The area under the curve (AUC) of the ROC curve was 0.97 for central placenta and 0.88 for peripheral placenta and the optimized cutoff value of placental stiffness value for the presence of PE was 18.47Kpa and 14.39 Kpa for central and peripheral placenta respectively. Using the optimized cutoff value for placental stiffness, the positive predictive value PVP, negative predictive value PVN, Sensitivity and Specificity for the presence of pre-eclampsia were 92.1%, 94.7%, 92.3% and 94.7 % for central placenta and 81.6%, 89.5%, 88.6% and 82.9% for peripheral placenta with accuracy of 97.4% and 86.5% for central and peripheral placenta respectively. According to **Kılıç *et al.* [7],** in this investigation, he found that only median elasticity values obtained from the central placental region were most predictive of pre-eclampsia. 7.35 kPa was chosen as the cutoff value (area under the curve=0.895; 95% CI=0.791-0.998); its sensitivity=90%, specificity=82%, PPV=92%, and NPV=88%, and its diagnostic accuracy=88%.

Our study had limitations that include our overall number of patients decreased since we didn't include pregnant women whose placentas were placed in the back (for concern of insufficient shear wave penetration and consequently flawed calculations). Although it is hypothesized that the placenta's hardness will grow with gestational age, our study was unable to definitively demonstrate this hypothesis because it focused on comparing elasticity values between normal and pre-eclamptic pregnancies at varying stages of pregnancy.

CONCLUSION

Difference in placental stiffness between healthy and pre-eclamptic pregnancies can be assessed using SWE, and it can be used for mentoring early perinatal outcome together with routine obstetric and Doppler ultrasound study.

Supporting and sponsoring financially: Nil.
Competing interests: Nil.

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