ORIGINAL ARTICLE

Placental Elastography in Intrauterine Growth Restriction: A Case–control Study

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ABSTRACT

Background: Intrauterine growth restriction (IUGR) is related to poor fetal outcome. Though, various tools are available for evaluation of IUGR they are notreliable inearly diagnosis of IUGR. Shear wave elastography (SWE) can be used to study the change in mechanical properties of various disease which can be a potential technique for early diagnosis of IUGR. **Objective:** The objective of the study was to compare the differences in SWE values of placentas between IUGR and normal pregnancies. **Methodology:** Normal second- and third-trimester pregnancies and IUGR pregnancies between 24 and 42 weeks period of gestation (POG), meeting the inclusion criteria were matched for age group and POG. SWE of placenta was performed in supine position during quiet respiration. The SWE of placenta was measured by placing the region of interest in relatively homogeneous area. The placental elasticity values obtained in pregnancies complicated by IUGR were compared with that of normal controls. Umbilical artery (UA) and fetal middle cerebral artery (MCA) Doppler findings were correlated with placental elasticity value of IUGR pregnancies. **Results:** Sixty-eight pregnant women (34 cases of IUGR and 34 controls) were evaluated for fetal biometry, amniotic fluid index (AFI), UA, and fetal MCA Doppler, and mean placental SWE. The mean age of the patients was 25.1 years (18–33 years), with no significant difference between case and control groups in regard to age. The mean SWE value of placenta was significantly higher in IUGR cases when compared to matched controls (3.85 kPa vs. 3.38 kPa, $P = 0.007$). There was increase in mean SWE value with POG ($P = 0.005$). No significant correlation of mean SWE was seen with age of mother, parity, or central and peripheral regions of placenta. There were significant correlations between AFI and UA Doppler indices with mean SWE value of placenta in IUGR cases. However, this relation was not seen with MCA Doppler indices. **Conclusion:** SWE of the placenta can be a useful additional US technique to increase the diagnostic confidence of IUGR. However, further studies are needed to evaluate its usefulness in earlier diagnosis and management of IUGR.

Key words: Case control study, elastography, IUGR, placenta

INTRODUCTION

Intrauterine growth restriction (IUGR) is defined as the estimated fetal weight (EFW) below the 10th percentile for gestational age.[1] Incidence of IUGR in developing countries has been estimated to be around 10–15%. Despite devastating consequences of IUGR, treatment options available for IUGR are limited. Ensuring appropriate timing of delivery and balancing the risks of prematurity with the risk of continued exposure to adverse intrauterine environment remains the mainstay of treatment. The inability to diagnosis it early leads to failure of institution of surveillance or appropriate timing of delivery while overdiagnosis exposes fetuses to unnecessary surveillance as well as potential iatrogenic preterm delivery. Hence, early and accurate detection of IUGR is crucial which is not possible however with current detection techniques.[1,2] Clinical examination and ultrasonography (USG) examinations for evaluation of fetal biometry, amniotic fluid index (AFI), and Doppler flow studies are commonly used for assessment of fetal growth and placental function. However, their clinical utility is still inadequate

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for early detection of IUGR. The fetal nutritional supply is through placenta, and its functional capacity is a primary factor determining intrauterine growth. Therefore, the diagnosis of placental insufficiency can provide effective method of early detection of IUGR and reduce neonatal morbidity and mortality.[3,4]

Shear wave elastography (SWE) is a state-of-the-art USG technique, which provides a quantified stiffness map of tissues. In SWE, the acoustic force created by a focused ultrasound beam generates shear waves in tissue.[5] Elastography is a non-invasive technique which can show differences in the mechanical properties of diseased and normal placenta, thus helping us in indirect evaluation of placental function. Studies have shown significant decrease of elastic tissue fibers in blood vessels of placental stem villi in cases of IUGR. Hence, elastography has the potential role of imaging modality to detect IUGR by demonstrating changes in the mechanical properties of the placenta.[2,6] In an *ex vivo* human study by Sugitani *et al*. (n = 115), elastography of delivered placenta done showed significantly higher shear wave velocity in IUGR cases compared to normal pregnancies.[4] In an *in vivo* study done in murine model (n = 18), 217 fetoplacental units studied showed higher placental stiffness in growth-restricted pregnancies compared to normal pregnancy.[5] In an *in vivo* human study (n = 199), placenta in 21 fetal growth-restricted pregnancies was evaluated using SWE which also showed significantly higher shear wave velocity compared to normal pregnancy.[7] However, more studies are needed to establish its usefulness in diagnosis of IUGR. In this study, we try to evaluate potential role of SWE in evaluation of patients with IUGR.

METHODOLOGY

The patients who were referred to the Department of Radiology and Imaging of Tribhuvan University Teaching Hospital for obtaining obstetric USG scan from September 2016 to August 2017 were selected in the study.

Matched case–control study was done with matching done for age group and period of gestation (POG). All cases with suspected IUGR and who met the inclusion criteria and consenting to the study underwent fetal biometry. Pregnant women in whom fetal biometry showed EFW <10th percentile for that POG was included as cases. The first normal pregnancy, i.e., EFW >10th percentile for that POG and meeting the inclusion criteria, matching with the cases and consenting to the study was included as controls.

Inclusion and exclusion criteria

Inclusion criteria

The following criteria were included in the study:

- Anterior and lateral placenta
- Pregnancy from 24 weeks to 42 weeks.

Exclusion criteria

The following criteria were excluded from the study:

- Patients not giving consent
- Posterior placental location
- Multiple gestations
- Placental hematoma
- Abnormal placental adherence or penetration.

Demographics, POG, parity, maternal medical history, and presence of congenital fetal anomaly in anomaly scans were noted. POG was based on last menstrual period or dating obstetric scan. Age was divided into age groups <20, 20–25, 25–30, 30–35, and 35 or above.

All the participants were scanned by a single examiner using C5-1 (1–5 MHz) convex probe on PHILIPS iU22. Fetal biometry, AFI, and Doppler findings were noted. Umbilical Artery (UA) Doppler was performed in free-floating segment of umbilical cord with Doppler angle close to 00. The waveform was evaluated for indices such as resistance index (RI), pulsatility index (PI), and systolic/diastolic (SD) ratios. Middle cerebral artery (MCA) Doppler was also performed in axial view of head with Doppler angle close to 00 and sampled immediately after its origin from internal carotid artery.

Elastography was performed in the supine position during quiet respiration in sagittal imaging plane. Excessive transmission gel was used to eliminate any compression artifact of the probe. The fetal movement was defined as the pushing of a fetal limb against the placental tissue. Measurements were not taken during periods of fetal movement. Elastogram images and gray-scale images were simultaneously displayed. A rectangular electronic box was used for SWE examinations which were kept in relatively homogenous parts of the placenta, avoiding the vascular spaces and calcifications approximately midway between fetal and maternal surface of placenta. Three elastograms were captured from central (2 cm away from where the umbilical cord inserts) and peripheral parts of the placenta. Shear modulus data were automatically displayed for region of interest (ROI). The measured data for each ROI were used for statistical analysis. Values <1 kPa were rejected.

Data were collected in predesigned pro forma, and data were entered into SPSS. The analysis was performed using paired t-test, independent sample t-test, Mann–Whitney U-test, and Pearson correlation.

RESULTS

Demographics

In this study, there were a total of 68 subjects, of which 34 were divided into case groups and remaining 34 into controls based on whether EFW was below 10th percentile (cases) or above it (controls).

The mean age of the control population was 24.91 (range 19–33) and for cases was 25.21 (range 18–32 years). There was no significant difference between these two groups in regard to age distribution ($P = 0.747$) and parity (0.741).

The figure showing example of shearwave placental elastography measurement being taken with abnormal umbilical artery Doppler with absent flow during diastole which is seen in case of IUGR Figure 1.

There was significant positive correlation between placental SWE value and period of gestation ($r = 0.469$, P=0.005) Figure 2.

Change in SWE value of placenta with age in normal pregnancy

	Controls	Cases	*P*
Age in years	24.91±3.71 (19–33)	25.21±3.79 (18–32)	0.747
Parity	1.5±0.749	1.5±0.615	0.741

SWE: Shear wave elastography

Correlation of SWE value of placenta with age

Characteristics studied	Mean SWE value
Age	
Pearson correlation	0.051
Sig. (two-tailed)	0.776
n	34

SWE: Shear wave elastography

The mean SWE value of the placenta for controls was 3.3829 ± 0.83325. There was no significant correlation of mean placental elasticity modulus and age ($P = 0.776$).

Correlation of SWE value of placenta with POG

	Mean	Standard deviation	*n*
Mean SWE value	3.3829	0.83325	34
POG	35.15	3.046	34

SWE: Shear wave elastography, POG: Period of gestation

Change of mean placental SWE with POG

Characteristics studied	Mean SWE value
POG	
Pearson correlation	0.469**
Sig. (two-tailed)	0.005
n	34

SWE: Shear wave elastography, POG: Period of gestation, **<0.005

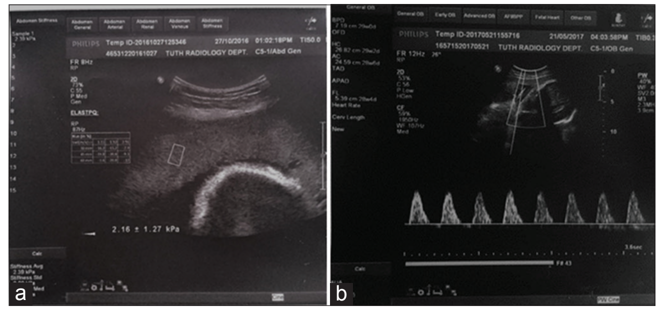


Figure 1: (a) Wave elastography of placenta and (b) umbilical artery Doppler showing absent diastolic flow

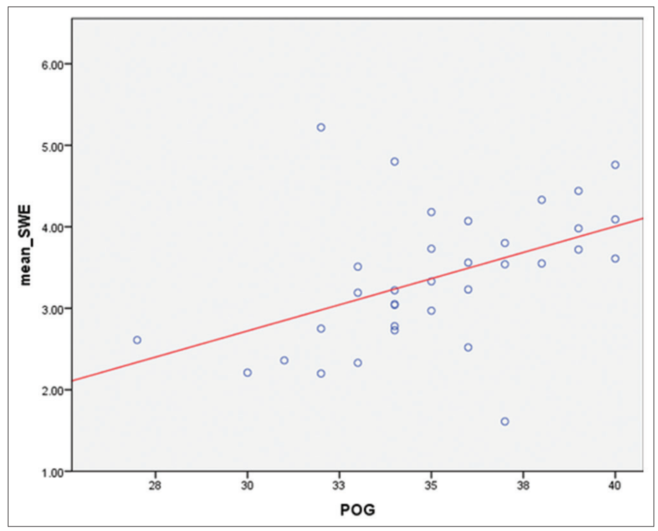
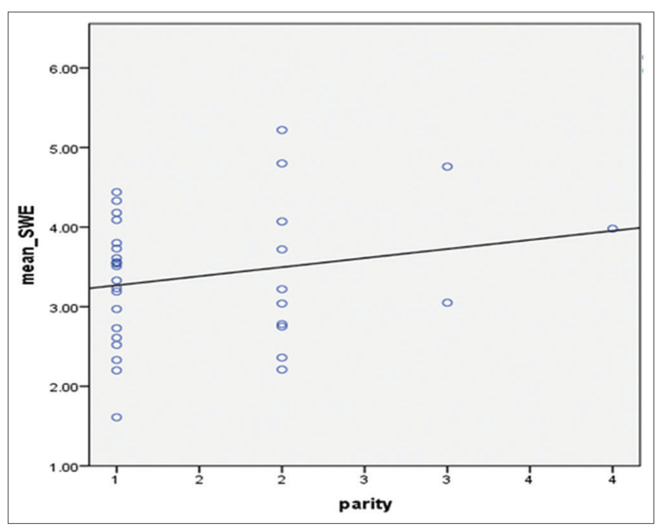
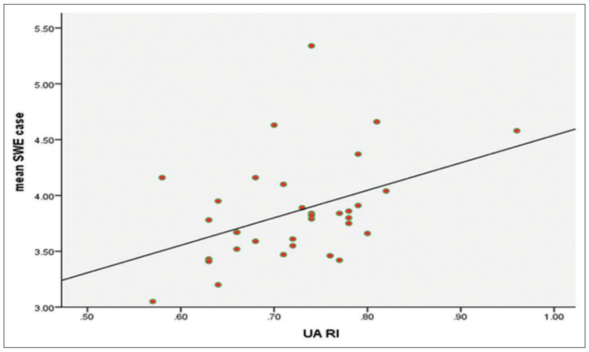


Figure 2: Correlation of mean placental shear wave elastography value with the period of gestation

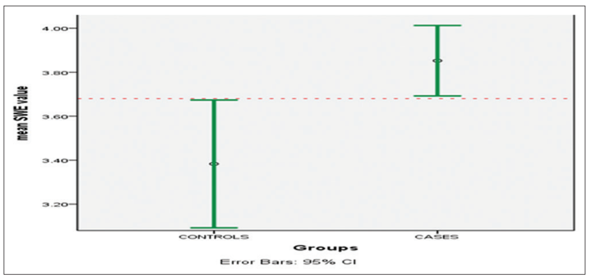


Correlation of parity with mean shear wave elastography value

There was significant positive correlation between placental SWE value and POG ($r = 0.469$, $P = 0.005$).



Correlation of mean shear wave elastography value of placenta with umbilical artery resistance index



Confidence interval of mean shear wave elastography value of placenta of cases and controls

Correlation of parity with SWE value in controls

There was no significant correlation between parity and mean SWE value ($P = 0.245$).

Difference in the frequency of presence of maternal disease in case and control

The incidence of coexistent maternal medical disease was slightly higher in cases compared to controls.

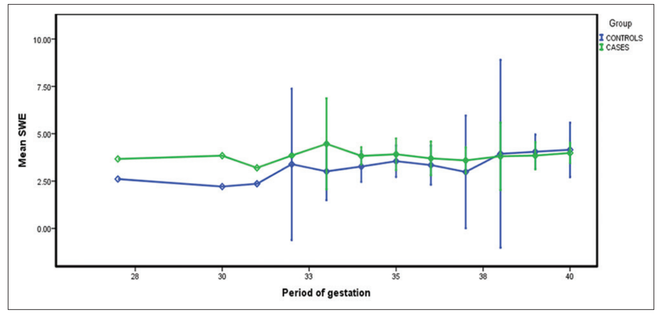
Maternal medical disease frequency		
Maternal disease	**Frequency control**	**Frequency case**
None	31	28
Pregnancy-induced hypertension	2	3
Diabetes mellitus	1	0
Cardiac disease	0	3

Difference in SWE value in central versus peripheral placenta

No significant difference between mean SWE value for the central part of placenta and peripheral part of placenta ($P = 0.833$).

Correlation between AFI and mean SWE value in cases

The AFI value and mean SWE value correlated significantly in cases with lower AFI with higher SWE value ($r = -0.374$, $P = 0.032$) Table 1.



Comparison of mean shear wave elastography with the period of gestation in cases and control

Correlation between mean SWE value and Doppler indices

There was a significant positive correlation of UA Doppler indices SD ratio, RI and PI with mean SWE value Table 2.

There was no significant correlation of MCA Doppler findings RI, PI or MCA, and peak systolic velocity (PSV).

Difference in mean SWE value of placenta in control and cases

There was a significant difference in mean SWE value of placenta in cases and controls (3.85 kPa vs. 3.38 kPa, $P = 0.007$) even when matched for the age group of pregnant women and POG Table 3.

Paired samples statistics				
Pair 1	**Mean**	***n***	**Standard deviation**	**Standard error mean**
Mean SWE value of cases	3.8524	34	0.45908	0.07873
Mean SWE value of controls	3.3829	34	0.83325	0.14290

DISCUSSION

SWE is a state-of-the-art technique which has been studied for evaluation of various organs and their pathologies.[8-14] The usefulness of SWE of placenta has been studied for various conditions such as preeclampsia, diabetes mellitus in

Table 1: Correlation of mean SWE value of placenta with UA SD ratio and PI

Characteristics studied	UA SD ratio	Umbilical artery PI
Mean SWE value		
Pearson correlation	0.350*	0.423*
Sig. (two-tailed)	0.042	0.013
n	34	34

SD: Systolic/diastolic, PI: Pulsatility index, SWE: Shear wave elastography, UA: Umbilical artery, *<0.005

Table 2: Correlation of mean SWE value with MCA Doppler indices

Characteristics studied	MCA resistance index	MCA pulsatility index	MCA PSV
Mean SWE value			
Pearson correlation	−0.024	−0.212	−0.050
Sig. (two-tailed)	0.892	0.229	0.780
n	34	34	34

SWE: Shear wave elastography, PSV: Peak systolic velocity, MCA: Middle cerebral artery

Table 3: Difference in mean SWE of the placenta in cases and controls

Characteristics studied	Paired differences					*T*	Sig. (two-tailed)
	Mean	Standard deviation	Standard error mean	99% Confidence interval of the difference			
				Lower	Upper		
Mean SWE case versus mean SWE control	0.46941	0.95028	0.16297	0.02397	0.91486	2.880	0.007

SWE: Shear wave elastography

pregnancy, and adherent placenta.[15-21] Studies both *in vivo* and *ex vivo* to evaluate the potential role of SWE of placenta in IUGR cases are limited, and their usefulness in managing IUGR cases still remains unclear.[4,7]

In a study by Li *et al*., the average value of elastic modulus was 7.60 ± 1.71 kPa for placental edge and 7.84 ± 1.68 kPa for the central part of placenta in normal pregnant women which was much higher compared to our study of 3.38 ± 0.833 kPa.[3] The study by Joshi *et al*., also found the mean elasticity values in the central and the peripheral part of the placentas of controls to be 5.47 ± 1.74 and 5.23 ± 1.31 kPa, respectively, which is still higher compared to our study.[17] However, most other studies have shown mean placental elasticity values comparable to our study in normal pregnancy.[18,21,22] Study by Joshi *et al*., showed slightly lower mean placental elasticity values of 2.28 kPa at the center of the placenta and 2.48 kPa at the edge.[23] These observations in multiple studies raise a question of appropriate cutoff value for normal placenta. This situation is further complicated by disagreement in studies with regard to change in SWE value of placenta with POG. In a study by Wu *et al*., 50 singleton healthy pregnant women in their second-trimester and 50 healthy singleton pregnant women in their third-trimester showed no significant difference between the second- and third-trimester placental shear wave velocity. Study by Ohmaru *et al*. also failed to show correlation between SWE value and gestational age.[7] However, in our study, there was a significant moderate positive correlation of placental elasticity modulus with POG. This difference can be explained by the fact that though stiffness of placenta does increase with gestational age, however calcification can occur independently of gestational age, which greatly influences the SWE value. This could also explain the variation of SWE value within same POG seen in many studies.[22] In our study, we made efforts to put ROI in areas of best homogeneity of the placenta. This could also explain the lower SWE value in our study compared to other previously described studies. However, despite the variability of SWE value most studies including our study have shown no significant difference in SWE value between central placental and placental edge elastic modulus.[3,17,23] In addition, studies have shown good inter and intraobserver variability in measurement of SWE which contradicts the above observations.[7,24] Hence, demographic variations such as race and difference in measurement techniques could possibly play a role in this variation which needs to be confirmed in further studies.

No study has been done so far to evaluate its ability to predict IUGR earlier compared to available modalities. All the studies so far have only shown higher SWE value of placenta in IUGR cases compared to normal pregnancy. The next challenge for USG SWE is its accuracy as a test for predicting IUGR. Although there was a significant difference in mean SWE value between two groups in our study, SWE may not be useful for individual case as there is only slight difference in SWE value between IUGR case group and control group which can occur by random chance especially considering the huge variability in SWE value of placenta within the same patient and different patients in same POG. In addition, factors such as maternal breathing and fetal movement pose further problems in measurement of SWE values. Shallow breathing and measuring at time when there is no fetal movement may help to mitigate these errors in measurement.[7] Another limitation of SWE is its inability to evaluate posteriorly located placenta which is present in significant proportion of pregnancies.

There was a significant correlation between AFI and mean SWE value in IUGR cases. UA Doppler indices and MCA Doppler are another important tools frequently used in the management of IUGR. In our study, UA Doppler indices such as RI, PI, and SD ratio showed significant positive correlation with mean SWE values in IUGR cases, but no correlation was seen with MCA PSV, RI, or PI. However, Ohmar *et al*. did not find any association with UA RI or brain sparing effect. In this study, the cutoff value used for increased SWE was 1.44 m/s which was higher than mean SWE (1.28 m/s) of fetal growth restriction cases. This might have led to non-significant association of UA RI with mean SWE.[7] Nevertheless, further studies are must to define any possible role of SWE in management and predicting outcome of IUGR cases which is not possible with existing study. Furthermore, diagnosis of IUGR cannot be based solely on Doppler findings, as in many cases of IUGR, Doppler can be initially normal. However, they still have important role in management and deciding optimum timing of delivery.[25-27]

Limitations of the study

The small sample size of the study was one of the major limitations of this study. Hence, the findings of the study may not accurately reflect the general population. Furthermore, SWE cannot be performed in cases with posterior placenta and were excluded from the study which further resulted in low sample size of the study. The Lubchenco's growth curve chart was used during study which may not reflect the actual growth curve chart of the population studied. Another limitation of the study was Hadlock's estimation of fetal biometry and was slightly higher compared to Nepalese population in a study done by Joshi *et al*.[27] These factors may lead to more normal pregnancies being classified as IUGR. All the findings were measured by single observer who was not blinded to the fetal biometry, SWE or Doppler findings which could potentially lead to observer bias.

CONCLUSION

SWE is a relatively new technique with promising future applications. However, multiple challenges exist to its current application. The varied value of normal placental SWE in various studies, small size of existing studies and limited *in vivo* studies makes it difficult to draw a conclusion. Large cohort studies are thus much needed to explore its application in clinical scenarios. SWE of placenta can be a useful additional technique to increase diagnostic confidence of IUGR. However, additional studies are needed to further evaluate its usefulness in earlier diagnosis of IUGR and predicting outcome. With current studies available, its role can be adjunctive to the previous methods of evaluation of IUGR.

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