A new method for measurement of placental elasticity : Acoustic radiation force impulse imaging

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Figure legends

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Introduction

The evaluation of placental function is very important in the management of cases complicated by fetal growth restriction (FGR) and pregnancy-induced hypertension (PIH). In some cases, these conditions are recognized as causes of placental dysfunction. Although ultrasonography examinations, including Doppler flow studies, are widely used for placental evaluation, the clinical utility is still inadequate to detect placental dysfunction before delivery. In some cases of FGR and/or PIH, associated placental abnormalities such as infarction, inflammation, and fibrosis are revealed by pathological analysis after delivery [1]. However, in some cases, the existence of pathological changes is unclear even after pathological examination.

Ultrasonography has recently been used to evaluate tissue elasticity [2]. One method of ultrasound-based elastography, acoustic radiation force impulse (ARFI) imaging, involves the use of a short acoustic push pulse in the target tissue, which causes a tissue displacement of approximately 1 to 20 µm. The displacement generates a lateral shear wave that propagates through the tissue during recoil, the velocity of which is expressed as Vs (m/s). Since Vs correlates with Young's modulus, a known index of elasticity, the value of Vs is thought to reflect tissue elasticity, i.e., faster shear wave speeds and smaller displacements are associated with stiffer tissues, and slower shear wave speeds and larger displacements occur in more compliant tissues.

To the best of our knowledge, no study has reported the use of ARFI technology with placental tissue, so we investigated the biological effects of ARFI on placental tissue *ex vivo* and evaluated the effect of the sampling site on ARFI measurements. In addition, as a preliminary study for clinical use of this method to evaluate placental function in future, we investigated the difference in ARFI values of delivered placentas in cases with FGR and/or PIH.

Materials and Methods

1 Study population

The study population included 115 pregnant women between 26 and 41 weeks gestation. In all cases, the gestational age was calculated from the first day of the last menstrual period and confirmed by ultrasound examination between 9 and 11 weeks gestation. All patients were Japanese and cared for at Kyushu University Hospital, and all gave informed consent to participate in this study. The ethical committees of Kyushu University Hospital approved the study protocol. Of the 115 patients, 74 were normal (normal group), defined as no maternal or fetal complications, except for preterm birth. Twenty-four cases were diagnosed with FGR (FGR group), which was defined as an estimated fetal weight less than 1.5 standard deviations below the mean, determined from Japanese standards for gestational age on ultrasonography [3]. Seventeen cases were diagnosed with PIH (PIH group). Seven of the PIH cases were categorized as severe and the remainder as mild [4]. Eight cases complicated by both PIH and FGR were included in the FGR group. The clinical characteristics of the study population are shown in Table 1.

2 Measurement of the velocity of ARFI-generated lateral shear waves

The delivered placenta was covered with a plastic bag and placed in a test tank filled with water. Buffer material was placed between the placenta and the tank. Experiments were performed using a Virtual Touch Tissue Quantification unit with a 4C1 curved ultrasonography probe (2.0–4.5 MHz) (ACUSON S2000; Mochida Siemens Medical, Tokyo, Japan). Measurement of Vs was performed within a 1–3-cm region of interest (ROI) (Figure 1A). Vs was measured 5 times in each region, and the mean value was determined using the method of analysis described below.

3 Analysis of the velocity of ARFI-generated lateral shear waves

3-1 Biological effects of ARFI on placental tissue ex vivo

To investigate the biological effects of ARFI on placental tissue, 50 consecutive measurements of Vs were obtained from each of the 10 full-term delivered placentas. These measurements were performed as soon as possible after the placentas were delivered. The placental tissue sample was housed in a rectangular chamber (5 cm × 2 cm × 4 cm) with the curved ultrasonography probe fixed above the chamber. Each measurement was taken from the ROI at a fixed depth of 2 cm (Figure 2). Following Vs measurement, tissue samples were obtained from 2 areas for pathological examination and the comparison: one sample from the area of the Vs measurement, and the other from the area of not subjected to ARFI in the same tissue samples. Specimens were fixed in buffered formalin, dehydrated, and embedded in paraffin wax. Serial 3-μm sections of embedded tissue were stained with hematoxylin and eosin. Microscopic examination was performed by a single pathologist (T.T.) to document any evidence of tissue damage related to heating. In 10 randomized fields at a magnification of ×40, we defined positive evidence of tissue damage as the presence of histological changes in more than 3 fields.

3-2 Reliability of the Vs measurements

Repeat measurements of Vs were performed in each of the 10 delivered placentas from the normal group. The Vs values were independently measured 10 times in each placenta to calculate interobserver (M.S., Y.Y., and Y.F.) and intraobserver (M.S.) intraclass correlation coefficients (ICC). All examinations were performed using the same ultrasonography equipment (Siemens ACUSON S2000).

3-3 Comparison of placental elasticity in each region

The elasticity of the placenta as defined by the Vs values was measured and compared in the normal group. Placental tissue was sampled from 3 areas: the cord insertion region, intermediate region, and marginal region of the placenta (Figure 1B). In this study, the marginal region of the placenta was defined as the farthest region from the cord insertion region, and the intermediate region was defined as the region between the cord insertion and marginal regions.

3-4 Comparison of placental elasticity among the 3 groups

To investigate whether the elasticity of placenta differs among groups, the Vs values from the intermediate region were compared.

3-5 Relationship between placental elasticity and birth weight

The relationship between placental elasticity and birth weight of the neonate was investigated through linear regression analysis of the correlations between the Vs values from all cases and from the standard deviation of the birth weight (Z-score). The Z-score was calculated based on Japanese standards for gestational age at birth [5].

4 Statistical analyses

The intraclass correlation coefficient (ICC) was used to assess the inter- and intraobserver reliability of the ARFI measurements; an ICC >0.8 was considered to reflect good reliability. To compare the placental elasticity from each measurement region and in the different complicated pregnancies, a Kruskal-Wallis test and Dunn's post hoc test were used. The correlation between placental elasticity and birth weight Z-score was determined using a stepwise piecewise linear regression analysis. The dependent variable in this model was the Vs value and the candidates for independent variables in the stepwise regression analysis were the piecewise linear variables generated by the Z-score. Z-scores were subdivided into 33 piecewise linear variables with 1 critical point *i,* Max(0, SD-*i*), *I* = -4.0, -3.75, …, 3.75, 4.0, where the function Max(0, X) represents the maximum of 0 and the Vs value. A value of $p < 0.05$ was considered statistically significant.

Results

1 Biological effects of ARFI on placental tissue ex vivo

We investigated the biological effects of ARFI on 10 full-term delivered placentas. Microscopic examination of both tissues that had undergone ARFI and not subjected to ARFI showed no thermal or mechanical structural changes.

2 Reliability of Vs measurements

Ten delivered placentas from the normal group between 33 and 41 weeks gestation were randomly selected. Intra- and interobserver reliability values were 0.828 and 0.954, respectively, indicating the high reliability of the Vs measurements.

3 Comparison of placental elasticity in each region

In the normal group, the mean ± SD of the Vs values in the cord insertion, intermediate, and marginal regions of the placenta were 1.67 ± 0.55 m/s, 1.31 ± 0.35 m/s, and 1.38 ± 0.38 m/s, respectively. The Vs values in the cord insertion region samples were significantly higher than those obtained from the intermediate and marginal regions of the placenta ($p < 0.05$).

4 Comparison of placental elasticity among the 3 groups

The mean ± SD of the Vs values from the intermediate region in the FGR and PIH groups were 1.94 ± 0.74 m/s and 1.49 ± 0.52 m/s, respectively. The Vs values in the FGR group were significantly higher than those in the normal group (1.94 ± 0.74 m/s versus 1.31 ± 0.35 m/s; $p < 0.05$; Figure 3). There were no significant differences between the Vs values in the PIH group and those in the normal group. (1.49 ± 0.52 m/s versus 1.31 ± 0.35 m/s; $p = 0.35$; Figure 3). Pathological examination was performed on some cases in the FGR group showing increased Vs values. These cases showed histological changes such as widespread infarction and inflammation (Figure 4).

5 Relationship between placental elasticity and birth weight

The Vs values and Z-score demonstrated a significant negative correlation. Moreover, 1 critical given SD point was indicated with statistical significance at -0.5 SD, and higher

Vs values were found to be more marked in cases where the Z-score range under -0.5 SD was comparable to the Z-score range over -0.5 SD. This indicated that the Vs values became higher as the Z-score reduced in range, under a Z-score of -0.5 SD (Figure 5).

Discussion

ARFI technology is a noninvasive method for evaluation of tissue elasticity using an ultrasonography device. ARFI generates a shear wave that propagates in the tissue from which tissue elasticity can be quantitatively evaluated and expressed as Vs. One advantage of ARFI technology is that the procedure can be performed in the same session as a conventional fetal ultrasonography screening and with the same device. Real-time B-mode imaging was used to locate the ROI [2] [6]. ARFI technology may also allow noninvasive detection of histological changes in tissue [7]. ARFI has been used in clinical practice to evaluate elasticity in parenchymal organs, for example, in liver fibrosis, liver cirrhosis, and inflammatory pancreatic diseases [8-13]. Since the placenta is one of the most important parenchymal organs in obstetrics, we investigated the placental elasticity using ARFI technology as a preliminary study for future clinical use of this method for evaluation of placental function *in vivo*.

No study has reported the use of ARFI technology on pregnant women. Because the safety of this technique during pregnancy has not been previously studied, a delivered placenta was used for the measurement of Vs values and the determination of any histological changes related to ARFI.

The ARFI technique has the potential risk for thermal tissue damage because of the long duration and high power of the acoustic push pulse. The duration of the acoustic pulse in color Doppler ultrasonography is approximately 1 μs. In contrast, in ARFI technology, the pulse duration is between 200 μs and 300 μs. However, Herman demonstrated that any transient increase in temperature caused by pulse bursts might still be within the safe limits determined by the Food and Drug Administration (FDA) [14-16]. The mechanical index of the push pulse generated by ARFI is also less than the FDA limit of 1.9, and is consistent with that of color Doppler imaging. In our study, no histological evidence of thermal injury, such as coagulation necrosis [17], was detected in tissues subjected to ARFI. Based on these results, ARFI technology appears safe for use in pregnant women.

The present study found that Vs values differed depending on the region of the placenta from which measurements were taken. The Vs values were significantly higher in the cord insertion region than those measured in the intermediate and marginal regions of the placenta. Tissue density, local magnitude of radiation force, and boundary conditions from surrounding tissue are known to influence ARFI imaging [18]. In the cord insertion region, ARFI might pass through the cord. The resulting unstable boundary conditions might significantly affect Vs values. In clinical settings, measurement of Vs in the intermediate region should be easy, and we selected a value for the placental elasticity parameter in our study.

The Vs values in the FGR group were significantly higher than those in the normal group. Bota *et al*. reported that Vs values significantly increase in liver fibrosis [7]. Mateen *et al*. reported that Vs values may also increase as a result of inflammatory cell infiltration and cellular swelling with increased fluid content [13]. Histological analysis of placenta complicated by FGR often shows infarction, inflammation of trophoblastic villi, and vasculitis [1]. Congestion of villous tissues is also seen more often in such cases, resulting in inefficient oxygen delivery. The Vs values in inflammatory diseases such as acute hepatitis and pancreatitis are increased, but the reasons for the increased stiffness of inflamed organs are still unknown. While pathological examination of the placenta was not performed in all cases, significant histological changes, such as placental infarction and inflammation were found in some cases with increased Vs values. Based on previous reports [7-13] and our pathological findings, we speculate that the increased Vs values in the FGR group might be caused by histological changes associated with FGR. Moreover, we found that the data from the FGR group appeared to have a bimodal distribution. From the 6 cases with increased Vs values in the FGR group, 4 cases needed preterm delivery because of growth arrest below -2.5 SD of the Japanese standard for gestational age, and 2 cases had absent end diastolic flow in the umbilical artery. Therefore, we speculate that the more severely complicated cases may have had increased Vs values.

In our analysis, we found that Vs values had a negative correlation with the birth weight Z-score, especially for values lower than -0.5 SD. This suggests that -0.5 SD in birth weight may be the critical point that indicates impaired placental function, despite the fact that the clinical definition of “small for gestational age” is birth weight below -1.5 SD from the mean. Moreover, according to the increased Vs values from the placenta, placental dysfunction may be caused by histological changes that may be clarified after birth.

In conclusion, this study showed that measuring placenta Vs values using the ARFI technique appears to be safe and does not cause thermal or mechanical damage to the placental tissue *ex vivo.* Additionally, the delivered placentas from the FGR group were significantly more firm than in cases without FGR. Based on our results, ARFI imaging could potentially be measured *in vivo* without disrupting placental architecture. In a future study, the usefulness of placental elastography using ARFI imaging for evaluation of placental function should be investigated *in vivo*.

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