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

杉谷,麻伊子

https://doi.org/10.15017/1441108

出版情報:九州大学,2013,博士(医学),課程博士 バージョン: 権利関係:やむを得ない事由により本文ファイル非公開(2)

1 Figure legends

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

4

5 Introduction

6 The evaluation of placental function is very important in the management of cases $\overline{7}$ complicated by fetal growth restriction (FGR) and pregnancy-induced hypertension (PIH). In some cases, these conditions are recognized as causes of placental 8 dysfunction. Although ultrasonography examinations, including Doppler flow studies, 9 10 are widely used for placental evaluation, the clinical utility is still inadequate to detect 11 placental dysfunction before delivery. In some cases of FGR and/or PIH, associated 12placental abnormalities such as infarction, inflammation, and fibrosis are revealed by 13pathological analysis after delivery [1]. However, in some cases, the existence of 14 pathological changes is unclear even after pathological examination.

¹⁵ Ultrasonography has recently been used to evaluate tissue elasticity [2]. One method ¹⁶ of ultrasound-based elastography, acoustic radiation force impulse (ARFI) imaging, ¹⁷ involves the use of a short acoustic push pulse in the target tissue, which causes a ¹⁸ 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 19expressed as Vs (m/s). Since Vs correlates with Young's modulus, a known index of 20elasticity, the value of Vs is thought to reflect tissue elasticity, i.e., faster shear wave 2122speeds and smaller displacements are associated with stiffer tissues, and slower shear 23wave speeds and larger displacements occur in more compliant tissues. 24To 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 25vivo and evaluated the effect of the sampling site on ARFI measurements. In addition, 2627as 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 28with FGR and/or PIH. 2930 Materials and Methods 31

32 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

37	all gave informed consent to participate in this study. The ethical committees of Kyushu
38	University Hospital approved the study protocol. Of the 115 patients, 74 were normal
39	(normal group), defined as no maternal or fetal complications, except for preterm birth.
40	Twenty-four cases were diagnosed with FGR (FGR group), which was defined as an
41	estimated fetal weight less than 1.5 standard deviations below the mean, determined
42	from Japanese standards for gestational age on ultrasonography [3]. Seventeen cases
43	were diagnosed with PIH (PIH group). Seven of the PIH cases were categorized as
44	severe and the remainder as mild [4]. Eight cases complicated by both PIH and FGR
45	were included in the FGR group. The clinical characteristics of the study population are
46	shown in Table 1.

47

48 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 55 determined using the method of analysis described below.

56

57 3 Analysis of the velocity of ARFI-generated lateral shear waves

58 3-1 Biological effects of ARFI on placental tissue ex vivo

59To 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. 60 61 These measurements were performed as soon as possible after the placentas were 62delivered. The placental tissue sample was housed in a rectangular chamber (5 cm \times 2 $cm \times 4 cm$) with the curved ultrasonography probe fixed above the chamber. Each 63 measurement was taken from the ROI at a fixed depth of 2 cm (Figure 2). Following Vs 64 65 measurement, tissue samples were obtained from 2 areas for pathological examination 66 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 67 68 fixed in buffered formalin, dehydrated, and embedded in paraffin wax. Serial 3-µm 69 sections of embedded tissue were stained with hematoxylin and eosin. Microscopic 70examination was performed by a single pathologist (T.T.) to document any evidence of 71tissue damage related to heating. In 10 randomized fields at a magnification of x40, we 72defined positive evidence of tissue damage as the presence of histological changes in more than 3 fields.

74

75	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.

89

90 **3-4** Comparison of placental elasticity among the 3 groups

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

- 93
- 94 **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].

99

100 4 Statistical analyses

The intraclass correlation coefficient (ICC) was used to assess the inter- and 101 102intraobserver reliability of the ARFI measurements; an ICC > 0.8 was considered to 103 reflect good reliability. To compare the placental elasticity from each measurement 104 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 105106 Z-score was determined using a stepwise piecewise linear regression analysis. The 107dependent variable in this model was the Vs value and the candidates for independent 108 variables in the stepwise regression analysis were the piecewise linear variables

109	generated by the Z-score. Z-scores were subdivided into 33 piecewise linear variables
110	with 1 critical point <i>i</i> , Max(0, SD- <i>i</i>), $I = -4.0, -3.75,, 3.75, 4.0$, where the function
111	Max(0, X) represents the maximum of 0 and the Vs value. A value of p < 0.05 was
112	considered statistically significant.

113

114 **Results**

- 115 1 Biological effects of ARFI on placental tissue ex vivo
- 116 We investigated the biological effects of ARFI on 10 full-term delivered placentas.
- 117 Microscopic examination of both tissues that had undergone ARFI and not subjected to
- 118 ARFI showed no thermal or mechanical structural changes.
- 119

120 2 Reliability of Vs measurements

- 121 Ten delivered placentas from the normal group between 33 and 41 weeks gestation
- 122 were randomly selected. Intra- and interobserver reliability values were 0.828 and 0.954,
- 123 respectively, indicating the high reliability of the Vs measurements.
- 124
- 125 3 Comparison of placental elasticity in each region
- 126 In the normal group, the mean ± SD of the Vs values in the cord insertion, intermediate,

127and marginal regions of the placenta were 1.67 ± 0.55 m/s, 1.31 ± 0.35 m/s, and $1.38 \pm$ 1280.38 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 129130 the placenta (p < 0.05).

131

1324 Comparison of placental elasticity among the 3 groups

133The 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 134135FGR group were significantly higher than those in the normal group (1.94 ± 0.74 m/s 136versus 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. $(1.49 \pm 0.52 \text{ m/s})$ 137138versus 1.31 ± 0.35 m/s; p = 0.35; Figure 3). Pathological examination was performed 139on some cases in the FGR group showing increased Vs values. These cases showed 140 histological changes such as widespread infarction and inflammation (Figure 4).

141

1425 Relationship between placental elasticity and birth weight

143The Vs values and Z-score demonstrated a significant negative correlation. Moreover, 144 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).

148

149 **Discussion**

150ARFI technology is a noninvasive method for evaluation of tissue elasticity using an 151ultrasonography device. ARFI generates a shear wave that propagates in the tissue from which tissue elasticity can be quantitatively evaluated and expressed as Vs. One 152153advantage 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. 154Real-time B-mode imaging was used to locate the ROI [2] [6]. ARFI technology may 155156also 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 157158liver fibrosis, liver cirrhosis, and inflammatory pancreatic diseases [8-13]. Since the 159placenta is one of the most important parenchymal organs in obstetrics, we investigated 160 the placental elasticity using ARFI technology as a preliminary study for future clinical 161 use of this method for evaluation of placental function *in vivo*.

162 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.

166The ARFI technique has the potential risk for thermal tissue damage because of the 167long duration and high power of the acoustic push pulse. The duration of the acoustic 168 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 169 170 demonstrated that any transient increase in temperature caused by pulse bursts might 171still be within the safe limits determined by the Food and Drug Administration (FDA) 172[14-16]. The mechanical index of the push pulse generated by ARFI is also less than the 173FDA limit of 1.9, and is consistent with that of color Doppler imaging. In our study, no 174histological 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 175176use 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 181 conditions from surrounding tissue are known to influence ARFI imaging [18]. In the 182 cord insertion region, ARFI might pass through the cord. The resulting unstable 183 boundary conditions might significantly affect Vs values. In clinical settings, 184 measurement of Vs in the intermediate region should be easy, and we selected a value 185 for the placental elasticity parameter in our study.

186 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]. 187 Mateen et al. reported that Vs values may also increase as a result of inflammatory cell 188 189 infiltration and cellular swelling with increased fluid content [13]. Histological analysis of placenta complicated by FGR often shows infarction, inflammation of trophoblastic villi, 190 and vasculitis [1]. Congestion of villous tissues is also seen more often in such cases, 191 192resulting in inefficient oxygen delivery. The Vs values in inflammatory diseases such as 193 acute hepatitis and pancreatitis are increased, but the reasons for the increased 194 stiffness of inflamed organs are still unknown. While pathological examination of the placenta was not performed in all cases, significant histological changes, such as 195196 placental infarction and inflammation were found in some cases with increased Vs 197values. Based on previous reports [7-13] and our pathological findings, we speculate 198 that the increased Vs values in the FGR group might be caused by histological changes

11

199	associated with FGR. Moreover, we found that the data from the FGR group appeared
200	to have a bimodal distribution. From the 6 cases with increased Vs values in the FGR
201	group, 4 cases needed preterm delivery because of growth arrest below -2.5 SD of the
202	Japanese standard for gestational age, and 2 cases had absent end diastolic flow in the
203	umbilical artery. Therefore, we speculate that the more severely complicated cases may
204	have had increased Vs values.
205	In our analysis, we found that Vs values had a negative correlation with the birth weight
206	Z-score, especially for values lower than -0.5 SD. This suggests that -0.5 SD in birth
207	weight may be the critical point that indicates impaired placental function, despite the
208	fact that the clinical definition of "small for gestational age" is birth weight below -1.5 SD
209	from the mean. Moreover, according to the increased Vs values from the placenta,
210	placental dysfunction may be caused by histological changes that may be clarified after
211	birth.
212	In conclusion, this study showed that measuring placenta Vs values using the ARFI
213	technique appears to be safe and does not cause thermal or mechanical damage to the
214	placental tissue ex vivo. Additionally, the delivered placentas from the FGR group were
215	significantly more firm than in cases without FGR. Based on our results, ARFI imaging
216	could potentially be measured in vivo without disrupting placental architecture. In a

217	future study, the usefulness of placental elastography using ARFI imaging for evaluation
218	of placental function should be investigated in vivo.
219	
220	
221	
222	
223	
224	
225	
226	
227	
228	
229	
230	
231	
232	
233	
234	

0	9	5
4	о	υ

236	Re	ference
237	1.	Vedmedovska N, Rezeberga D, Teibe U, Melderis I, Donders GG. Placental
238		pathology in fetal growth restriction. Eur J Obstet Gynecol Reprod Biol.
239		2011;155:36-40.
240	2.	Rifai K, Cornberg J, Mederacke I, Bahr M, Wedemeyer H, Malinski P, et al. Clinical
241		feasibility of liver elastography by acoustic radiation force impulse imaging (ARFI).
242		Dig Liver Dis. 2011;43:491-7.
243	3.	Shinozuka N. Fetal biometry and fetal weight estimation: JSUM standardization.
244		Ultrasound Rev Obstet Gynecol 2002;2:156-61
245	4.	Report of the National High Blood Pressure Education Program Working Group on
246		High Blood Pressure in Pregnancy. Am J Obstet Gynecol. 2000;183:S1-S22.
247	5.	Ogawa Y, Iwamura T, Kuriya N, Nishida H, Takeuchi H, Takada M, et al. Birth size
248		standards by gestational age for Japanese neonates [in Japanese]. Acta
249		Neonatologica Japonica. 1998;34:624-32
250	6.	Kuroda H, Takikawa Y, Onodera M, Kakisaka K, Yoshida Y, Kataoka K, et al. Serial
251		changes of liver stiffness measured by Acoustic Radiation Force Impulse Imaging in
252		acute liver failure: A case report. J Clin Ultrasound. 2012;40:99-104.

253	7.	Bota S, Sporea I, Sirli R, Popescu A, Danila M, Sendroiu M. Factors that influence
254		the correlation of acoustic radiation force impulse (ARFI) elastography with liver
255		fibrosis. Med Ultrason. 2011;13:135-40.
256	8.	Takahashi H, Ono N, Eguchi Y, Eguchi T, Kitajima Y, Kawaguchi Y, et al. Evaluation
257		of acoustic radiation force impulse elastography for fibrosis staging of chronic liver
258		disease: a pilot study. Liver Int. 2010;30:538-45.
259	9.	Tozaki M, Isobe S, Yamaguchi M, Ogawa Y, Homma K, Saito M, et al.
260		Ultrasonographic elastography of the breast using acoustic radiation force impulse
261		technology:preliminary study. Jpn J Radiol. 2011l;29:452-6.
262	10	. Friedrich-Rust M, Romenski O, Meyer G, Dauth N, Holzer K, Grunwald F, et al.
263		Acoustic radiation force impulse-imaging for the evaluation of the thyroid gland: a
264		limited patient feasibility study. Ultrasonics. 2012;52:69-74.
265	11	. Sporea I, Sirli R, Popescu A, Danila M. Acoustic Radiation Force Impulse (ARFI)-a
266		new modality for the evaluation of liver fibrosis. Med Ultrason. 2010;12:26-31
267	12	. Colombo S, Buonocore M, Del Poggio A, Jamoletti C, Elia S, Mattiello M, et al.
268		Head-to-head comparison of transient elastography (TE), real-time tissue
269		elastography (RTE), and acoustic radiation force impulse (ARFI) imaging in the
270		diagnosis of liver fibrosis. J Gastroenterol. 2012;47:461-9.

27113. Mateen MA, Muheet KA, Mohan RJ, Rao PN, Majaz HM, Rao GV, et al. Evaluation 272of ultrasound based acoustic radiation force impulse (ARFI) and eSie touch sonoelastography for diagnosis of inflammatory pancreatic diseases. JOP. 2732012;13:36-44. 27414. Fahey BJ, Nightingale KR, Nelson RC, Palmeri ML, Trahey GE. Acoustic radiation 275276force impulse imaging of the abdomen: demonstration of feasibility and utility. 277Ultrasound Med Biol. 2005;31:1185-98. 15. Herman BA, Harris GR. Models and regulatory considerations for transient 278279temperature rise during diagnostic ultrasound pulses. Ultrasound Med Biol. 2802002;28:1217-24. 16. Palmeri ML, Frinkley KD, Nightingale KR. Experimental studies of the thermal 281effects associated with radiation force imaging of soft tissue. Ultrason Imaging. 2822832004;26:100-14. 28417. Gertner MR, Worthington AE, Wilson BC, Sherar MD, Ultrasound imaging of thermal therapy in in vitro liver. Ultrasound Med Biol. 1998;24:1023-32. 28518. Nightingale K, Soo MS, Nightingale R, Trahey G. Acoustic radiation force impulse 286287imaging: in vivo demonstration of clinical feasibility. Ultrasound Med Biol.

288 **2002;28:227-35**.

16