

Evaluation of the placenta with relative apparent diffusion coefficient and T2 signal intensity analysis

Ali Kemal Sivrioğlu, Ümit Aksoy Özcan, Ali Türk, Sıla Ulus, Mehmet Erdem Yıldız, Güner Sönmez, Hakan Mutlu

PURPOSE

We aimed to test the null hypothesis that relative apparent diffusion coefficient (rADC) and relative signal intensity values (rSI_{HASTE}) do not change in the evaluation of placental maturation with advancing gestational age.

MATERIALS AND METHODS

Fifty-six fetuses with diffusion-weighted magnetic resonance imaging (DW-MRI) data were enrolled in this retrospective study. Fetuses were analyzed in three different gestational age groups: group 1, 18–23 weeks; group 2, 24–28 weeks; and group 3, 29–38 weeks. The rADC (mean ADC/ADC_{globe}) and rSI_{HASTE} values (mean SI_{HASTE}/SI_{globe}) were obtained. Two radiologists experienced in fetal MRI who were blinded to the patient information reviewed MRI images independently. Kruskal-Wallis Test was used to compare the rADC and rSI_{HASTE} with gestational age groups. The agreement between the two blinded readers was tested using Krippendorff's alpha ratio.

RESULTS

Both placental rADC values and placental rSI_{HASTE} values were not significantly different between the gestational age groups ($P = 0.688$ and $P = 0.280$, respectively). rADC and rSI_{HASTE} measurements were reproducible with a good agreement between the two readers (Krippendorff's alpha ratio was 0.613 and 0.778, respectively).

CONCLUSION

The rADC and rSI_{HASTE} values do not change with advancing gestational age.

The course of pregnancy depends on the placenta, which is directly related to perinatal mortality and morbidity. The fetal growth rate and well being rely on the healthy development of the utero-placental unit. Ultrasonography (US) is the primary modality for the evaluation of placental maturation, and color Doppler US enables indirect assessment of the utero-placental circulation during pregnancy (1).

In recent years, antenatal magnetic resonance imaging (MRI) has been increasingly used for the evaluation of fetuses. Many studies have been published regarding fetal MRI of the placenta (2, 3). However, studies that address diffusion-weighted imaging (DWI) as an adjunct to routine fetal MRI are limited (3, 4). In addition to assessment of fetuses, MRI may provide useful information concerning the placenta (5). DWI is based on random Brownian motion of water molecules in the tissue, and it is performed using an echo-planar imaging technique. Apparent diffusion coefficient (ADC) maps provide quantitative information regarding water diffusion (6). Placental ADC values are affected by tissue perfusion rather than by diffusion restriction or gestational age (4). Biologic factors such as patient age and body temperature, and technical factors such as the b value, sequence parameters, location, and region of interest may affect and change placental ADC values. The normalized ADC, also known as the relative ADC (rADC), is proposed to minimize the relativity of the ADC measurements, which are calculated by dividing the lesion ADCs by the ADC values of the reference organ (7).

Advancing gestational age causes a density change in the placental tissue (8). Placental tissue density change may be demonstrated by the signal intensity of the placenta on half-Fourier single-shot turbo spin-echo (HASTE) sequence images. In the present study, our aim was to test the null hypothesis that placental rADC and relative SI_{HASTE} (rSI_{HASTE}) values do not change with advancing gestational age.

Materials and methods

Between June 2008 and September 2012, consecutive fetal MRI examinations including DWI of the placenta and fetus were retrieved from our database, revealing 94 singleton fetuses. Written informed consent was obtained before all fetal MRI procedures, and no sedation was administered to mothers during MR examination. The Institutional Ethics Committee had approved this retrospective study. Exclusion criteria were as follows: examinations with gross fetal movements, intrauterine growth retardation, complex fetal anomalies, fetal cardiovascular anomalies, abnormal Doppler US findings and placental anomalies (i.e., placenta accreta, placenta percreata, and giant myomas), and maternal conditions such as diabetes, preeclampsia, eclampsia, intrauterine

From the Department of Radiology (A.K.S. ✉ draksivrioglu@gmail.com), Aksaz Military Hospital, Muğla, Turkey; the Department of Radiology (Ü.A.Ö., A.T., S.U., M.E.Y.), Acıbadem University School of Medicine, Istanbul, Turkey; the Department of Radiology (G.S., H.M.), GATA Haydarpaşa Teaching Hospital, Istanbul, Turkey.

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infection, and hematologic disorders. The resulting 56 fetuses were included in the present study. Gestational age ranged from 18 to 38 weeks (mean, 26.3 weeks) and were estimated according to the last menstrual period. The antenatal diagnoses of the fetuses were mild ventriculomegaly (unilateral in eight, and bilateral in four fetuses), mega cisterna magna (n=3), unilateral renal agenesis (n=1), dacryocystocele (n=2), neck lymphangioma (n=1), and normal findings (n=37). Fetuses were analyzed in three different gestational age groups: group 1, 18–23 weeks (15 fetuses [26.8%]); group 2, 24–28 weeks (24 fetuses [42.9%]); and group 3, 29–38 weeks (17 fetuses [30.4%]).

MRI

All examinations were performed using a 1.5 Tesla (T) system (Magnetom Symphony, Siemens Healthcare, Erlangen, Germany) with a body array coil during free maternal breathing. The mothers were supine during the examination. If the mother could not tolerate lying on her back, the examination was performed in the left lateral decubitus position. After acquiring localizer images, if necessary, the coil was repositioned to receive the maximal signal from the area of interest. All patients were examined with our routine fetal MRI protocol, including HASTE, and/or true fast imaging with steady-state precession (True FISP), and two-dimensional (2D) fast low-angle shot (FLASH) T1-weighted sequences. The images were obtained in fetal orthogonal planes using the following parameters: one signal acquired; slice thickness, 3–4 mm; no intersection gap; rectangular field of view matrix, 240×256; field of view, 26–35 cm (optimized for gestational week of each fetus); acquisition, 1. The other imaging parameters were as follows for HASTE: TE, 78 ms; TR, 1000 ms; flip angle, 150; echo train length, 179; bandwidth, 230 Hz/pixel. The parameters for True FISP were as follows: TE, 2.3 ms; TR, 4.6 ms; flip angle, 80; bandwidth, 501 Hz/pixel; 2D FLASH T1 TE, 166 ms; TR, 4.76 ms; flip angle, 70; bandwidth, 110 Hz/pixel. After T2-weighted HASTE imaging, and 2D T1-weighted gradient echo images, DWI was performed in the ax-

ial plane with single-shot echo-planar sequence (TR, 3400 ms; TE, 94 ms; FOV, 23 cm; matrix, 128×128; slice thickness, 4 mm; interslice gap, 10%; bandwidth, 1346 Hz/pixel; spatial resolution, 1.8×1.8×4.0 mm³). The acquisition time of the DWI sequence was 1 min 32 s. Gradients were applied in three orthogonal directions using different b values (0, 500, and 1000 s/mm²). ADC maps were automatically calculated by the vendor's preset algorithm using the given b values immediately after the sequences were completed. All fetal MR examinations were performed under real-time radiologist supervision. If the fetus moved in the first set of DW images, a repeat scan was obtained subsequently. If there was no movement artifact, the image quality was considered adequate. The patients who still had motion artifacts in the second set of images were excluded from the study. The total acquisition time was no more

than 20 s for each sequence and 20 min for each fetus.

Image analysis

Two radiologists experienced in fetal MRI who were blinded to patient information reviewed images independently. HASTE sequences and ADC maps were used to measure SI_{HASTE} and ADC values at three different sites in the placenta (Figs. 1, 2). Care was taken when positioning appropriate regions of interest (ROIs) to avoid cystic, calcific, hemorrhagic, and necrotic parts of the placenta. The ROIs were at least 24 mm² and contained 12 pixels as a minimum. The fetal ocular globe was used as the reference tissue in the same series (Figs. 3, 4). SI_{HASTE} and ADC values were obtained from the vitreous humour of the ocular globe. The mean value of three different ROI measurements on the same slice of placenta was calculated for ADC and SI_{HASTE} separately.

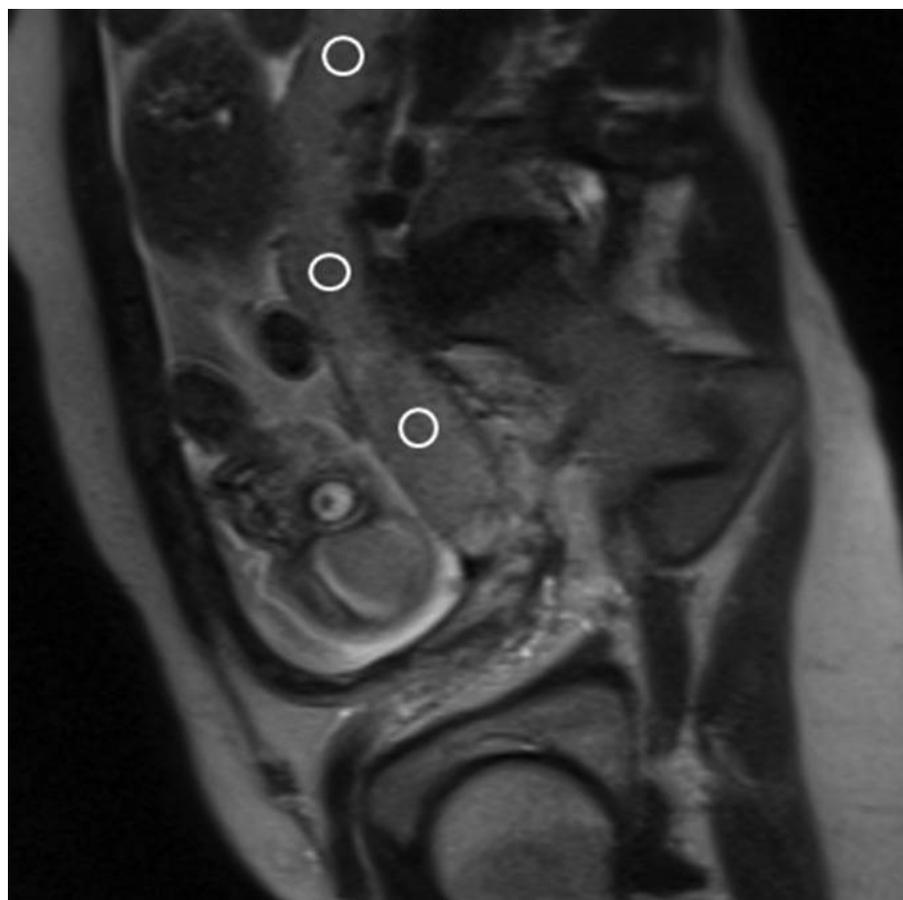


Figure 1. T2-weighted HASTE image obtained from a fetus at 24 weeks of gestation. On the sagittal maternal plane, the placenta shows insertion into the posterior uterine wall. The three regions of interest (circles) are positioned on three different sites of the placenta for T2 signal measurement.

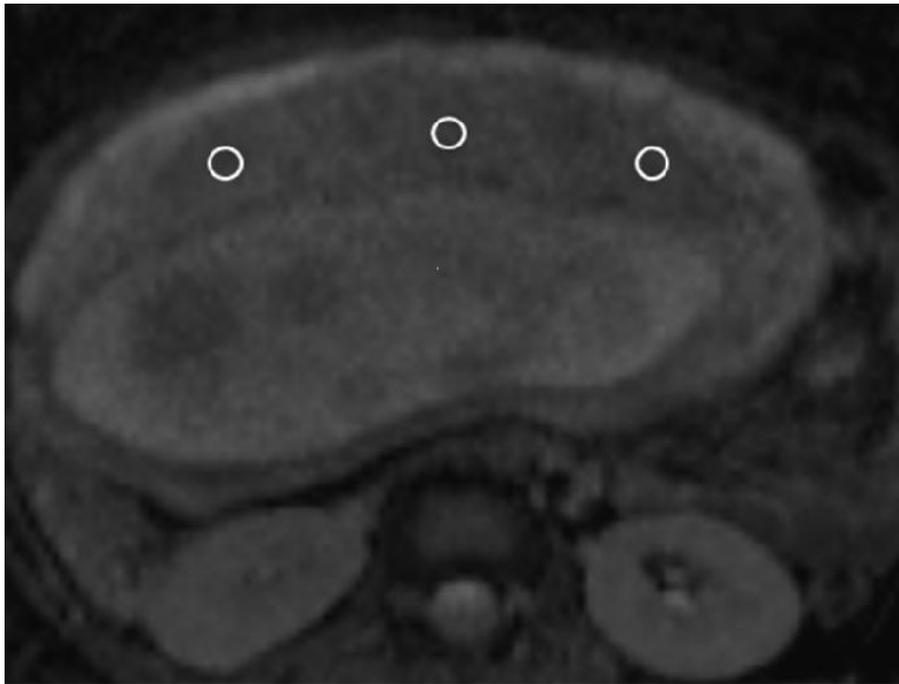


Figure 2. ADC maps obtained from a fetus at 24 weeks of gestation. On the axial ADC map, the three regions of interest (*circles*) are positioned on different sites of the placenta for ADC value measurement.

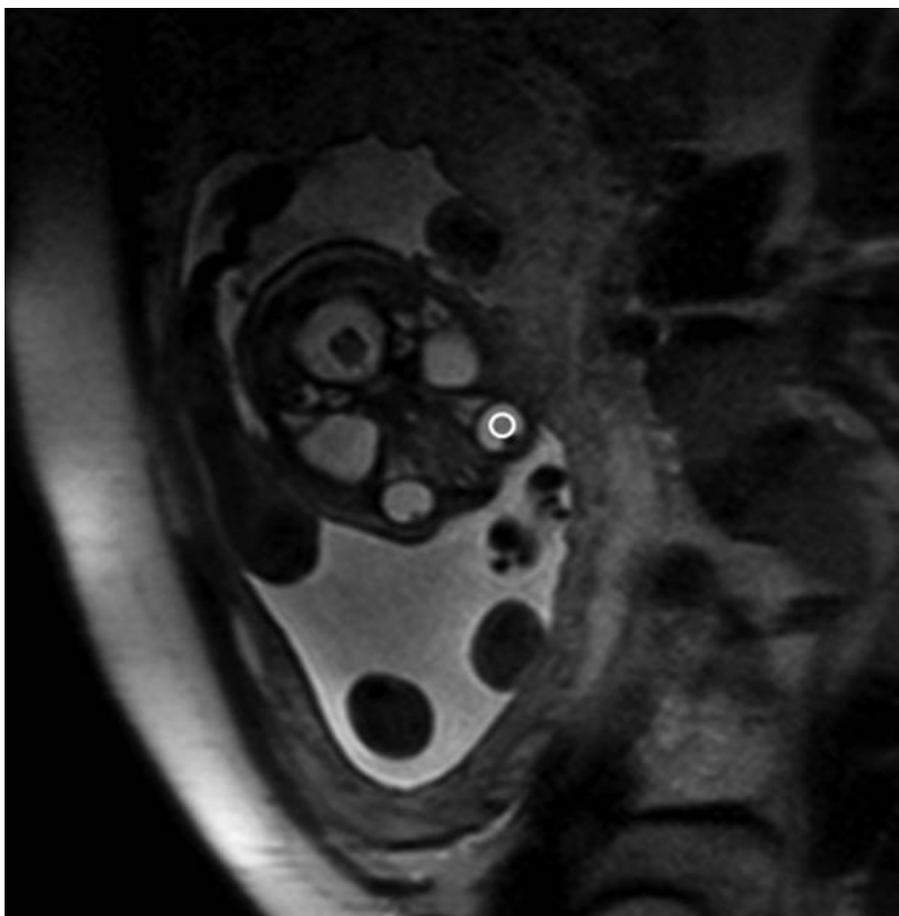


Figure 3. In the fetus at 26 weeks of gestation, the fetal ocular globe is used as the reference tissue on sagittal T2-weighted HASTE imaging. The region of interest (*circle*) is positioned in the fetal ocular globe.

The $rADC$ and rSI_{HASTE} values were calculated to eliminate the signal differences due to equipment, technical parameters, and tissue properties. The $rADC$ and rSI_{HASTE} values were obtained by dividing the mean values by the ADC_{globe} and SI_{globe} measurements, respectively:

$$rADC = \text{placental mean } ADC / ADC_{globe}$$

$$rSI_{HASTE} = \text{placental mean } SI_{HASTE} / SI_{globe}$$

Statistical analysis

Kruskal-Wallis test was used to compare the rSI_{HASTE} ratio and $rADC$ values between three gestational age groups. The agreement between the two blinded readers was tested using Krippendorff's alpha ratio. Krippendorff's alpha values were classified as follows: 0.01–0.20, poor agreement; 0.21–0.40, slight agreement; 0.41–0.60, fair agreement; 0.61–0.80, good agreement; 0.81–0.92, very good agreement; 0.93–1, excellent agreement. Statistical significance was interpreted when P values were less than 0.05. All statistical analyses were performed using a commercially available software (Statistical Package for Social Sciences, version 15.0, SPSS Inc., Chicago, Illinois, USA) with the exception of Krippendorff's alpha ratio for which the Recal 0.1 Alpha program was used (<http://dfreelon.org/recal/recal3.php>).

Results

The median placental $rADC$ value was 0.71 (min, max; 0.35, 1.31). The placental $rADC$ value was not significantly different between gestational age groups ($P = 0.688$).

The median rSI_{HASTE} on axial HASTE images was 0.56 (min, max; 0.32, 1.02). The placental rSI_{HASTE} ratio was not significantly different between gestational age groups ($P = 0.280$).

Median $rADC$, median rSI_{HASTE} , and number of investigated fetuses according to gestational age groups were shown in the Table. In addition, box plot of $rADC$ and rSI_{HASTE} measurements were shown in the Figs. 5 and 6, respectively.

According to Krippendorff's alpha ratio, the agreement between the two radiologists was good with 0.778 for rSI_{HASTE} measurements and 0.613 for $rADC$ measurements.

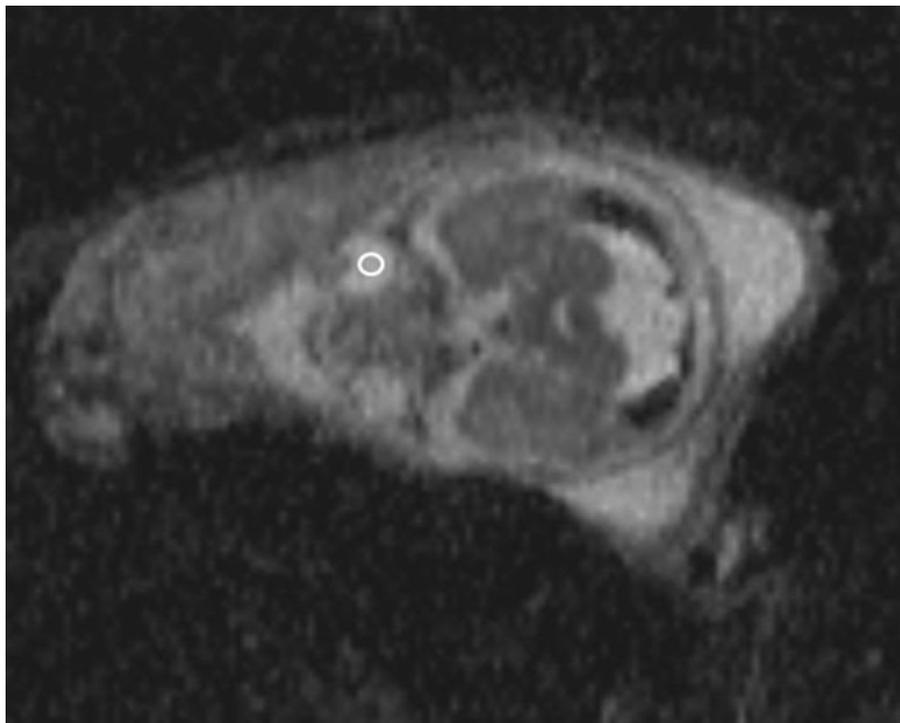


Figure 4. In the fetus at 28 weeks of gestation, the region of interest (*circle*) is positioned in the fetal ocular globe on the axial ADC map.

Table. rADC, rSI_{HASTE}, and number of investigated fetuses according to gestational age groups

Gestational age groups	rADC median (min, max)	rSI _{HASTE} median (min, max)	n (%)
1 (18–23 week)	0.68 (0.35, 1.31)	0.50 (0.36, 0.85)	15 (26.8)
2 (24–28 week)	0.70 (0.38, 1.05)	0.56 (0.38, 0.74)	24 (42.9)
3 (29–38 week)	0.74 (0.52, 1.10)	0.61 (0.32, 1.02)	17 (30.4)

rADC, relative apparent diffusion coefficient; rSI_{HASTE}, relative signal intensity values on half-Fourier single-shot turbo spin-echo.

Discussion

DWI is used increasingly commonly during the antenatal period, providing an opportunity for quantitative analysis of ADC values of fetal and placental tissues. Various uses of ADC measurements for characterization of renal and lung lesions and as a potential noninvasive biomarker of fetal lung maturity have been reported (2, 9, 10). However, the reproducibility of the ADC measurements remains controversial (7). Our data show that evaluation of the placenta by means of rADC and rSI_{HASTE} measurements is reproducible with good inter-reader agreement. To our knowledge, this is the first MRI study of the placenta to evaluate rADC and rSI_{HASTE} parameters.

The connective tissue density of the placental villi decreases in the second trimester, and the function of extra-embryonic circulation increases. Although the connective tissue density varies according to the type of placental villi, it may increase partially with advancing gestational age and increasing fibrous component of the connective tissue (11). Placental calcifications also increase with advancing gestational age. Calcifications may cause inaccurate measurements by decreasing ADC values (6). In the present study, T2 hypointense or heterogeneous areas, which might represent calcifications, are avoided during ADC and signal intensity measurements. Calcification was considered an indi-

cator of placental maturation; however, recent studies did not support this assumption (12, 13). In favor of those studies, the stable rADC values during gestation implicates that water diffusion in the normal placental tissue is not affected by the amount of connective tissue or calcification.

Abnormal placental angiogenesis is associated with development of intrauterine growth retardation (IUGR), which is responsible for neonatal morbidity and mortality in 8% of all pregnancies (14). Evaluation of placental maturation is important for early diagnosis of placental insufficiency and IUGR. Abnormal flow velocity waveforms of uterine and umbilical arteries on Doppler US are indirect indicators of increased placental resistance in IUGR. However, Doppler US evaluation of placental circulation does not reflect the dynamics of placental perfusion (15). In a study comparing 75 normal and 27 IUGR fetuses in a 1.5 T MR system, Bonel et al. (3) reported a statistically significant decrease in the ADC values of IUGR fetuses. Loss of cellular integrity, decreased perfusion, and reduced oxygen exchange in the extracellular space were assumed to be causes of decreased ADC values. Moreover, Bonel et al. (3) reported that the ADC value did not show a statistically significant relationship with gestational age in fetuses without placental insufficiency, a result that was similar to ours.

In a study with 157 fetuses in a 1.5 T MR system by Manganaro et al. (4), ADC values and gestational age were correlated at a b value of 0–700 s/mm² but not at a b value of 50–700 s/mm². That study was based on the placental ADC values being mainly affected by capillary perfusion and microcirculation rather than by diffusion of extracellular water. Water in normal tissues is located in three compartments: the extracellular, intracellular, and intravascular compartments (16). Upon development of extravascular tissue fibrosis, water diffusion might be restricted due to extracellular space changes. One important finding of our study is that placental rADC is not affected significantly by extravascular tissue fibrosis of placental aging. Our data demonstrated that changes in advanced placental maturation such as

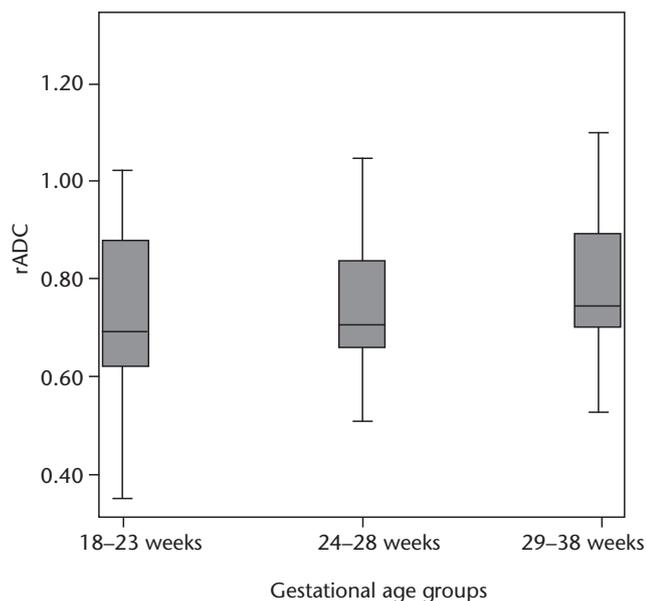


Figure 5. Box plot of relative apparent diffusion coefficient (rADC) measurements. The length of the vertical line represents range of data, and the extension of the boxes show weighted data and median values. Extreme data are not shown. There was no statistically significant difference between rADC values of gestational age groups.

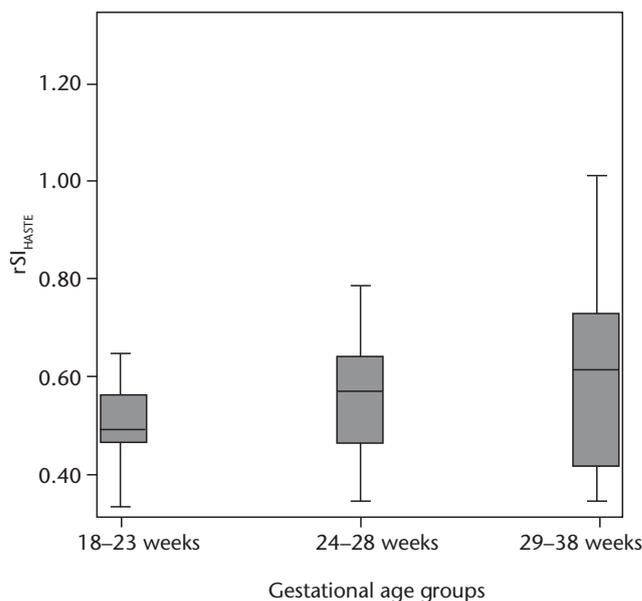


Figure 6. Box plot of relative signal intensity values on half-Fourier single-shot turbo spin-echo (rSI_{HASTE}) measurements. The length of the vertical line represents range of data, and the extension of the boxes show weighted data and median values. Extreme data are not shown. There was no statistically significant difference between the rSI_{HASTE} ratios of gestational age groups.

development of cavernous spaces, internal hemorrhage, calcification, and sclerosis do not affect water diffusivity in the extracellular space. However, care must be taken to avoid such morphological changes when placing the ROI for the ADC measurements.

ADC values are affected by many factors, such as the type of the selected sequence, b values, localization and area of the ROI, patient age, and temperature. Thus, rADC was proposed to reduce this variability in ADC and optimization of the DWI findings (7). In a previous study, the renal cortex was suggested to be the appropriate localization of the reference ADC measurement site in the abdomen (7). In our study, the fetal ocular globe was used as the reference area for ADC measurements because both kidneys were not completely included in the field of view in every study, particularly when the study was designed for fetal brain MRI. Conversely, the fetal ocular globe is easy to define and free from excessive fluid motion. It is also clearly delineated from adjacent organs and exhibits a good signal-to-noise ratio.

Blaicher et al. (8) described a reduction in the placental to amniotic flu-

id signal intensity ratio with increasing gestation in normal pregnancies that was thought to be a reflection of morphological changes during placental aging. However, the use of amniotic fluid for signal intensity measurements is controversial because fetal movements and pulsations of surrounding tissues create artifacts in the amniotic fluid, decreasing SI values. Therefore, we used the fetal ocular globe as a reference area to calculate the ratio of the fetal rSI_{HASTE} in the present study. Contrary to the study by Blaicher et al. (8), we did not find a statistically significantly different between gestational age groups and rSI_{HASTE} of the placenta.

Both Manganaro et al. (4) and Blaicher et al. (8) did not evaluate reproducibility in their studies. However, Bonel et al. (3) reported that two readers strongly agreed with the ADC assessments. In the present study, there was good agreement between the radiologists in measurements of rADC and rSI_{HASTE} . Reproducibility of the measurements improves the efficiency of placental evaluation and may be used for further studies to establish a standardized parameter.

The present study possessed some limitations. First, the results are based on a given b value. Comparison of different b values, particularly low b values, may provide more information regarding the perfusion characteristics of the placenta. Second, in the current study, IUGR patients were not included to establish the normal ranges of rADC and rSI_{HASTE} . The results of the present study may serve as a parameter for a target population with IUGR findings such as pathological placenta in uteroplacental insufficiency in future studies.

In conclusion, measurement of the rADC and rSI_{HASTE} are highly reproducible when measurement sites are selected carefully. The null hypothesis that rADC and signal intensity values do not change in the evaluation of placental maturation with advancing gestational age is accepted.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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