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Magnetic resonance imaging of the human placental cotyledon: Proposal of a novel cotyledon appearance score

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ABSTRACT

Objective: To determine the magnetic resonance imaging (MRI)-detectable morphology of the placental cotyledon, we proposed the first cotyledon appearance scores on MRI. Cotyledon appearance scores consist of two subscores: orthogonal and parallel cotyledon appearance scores. These represent cotyledon appearance orthogonal or parallel to the placental thickness, respectively.
Study design: This retrospective study was approved by the institutional review board of our hospital. A total of 51 placentas were studied. Two MRI specialists independently evaluated the two cotyledon appearance subscores at various gestational ages. Scores were related to gestational age.
Results: Cotyledons were not evident in the 2nd trimester, but were identified in the 3rd trimester. Cotyledon appearance subscores increased according to gestational age, with subscores showing good inter-observer agreement.
Conclusion: Cotyledon appearance scores determined that placental cotyledons became evident on MRI, suggesting that placental maturity progressed with gestational age. These placental MRI findings may serve as references for placental MRI to detect placental abnormalities.

Introduction

Magnetic resonance imaging (MRI) reveals placental features according to the gestational age: in the 2nd trimester, the placenta is "flat and smooth, homogeneous", whereas in the 3rd trimester, it is "heterogeneous" and, importantly, shows the "formation of cotyledons" [1–3].

The cotyledons are 10–40 macroscopically discernible functional units of the placental parenchyma [4,5] that provide a "landmark" of the placental parenchyma (Fig. 1). Anatomically, the cotyledon becomes evident and discernible with gestational aging. However, MRI findings of the cotyledon are yet to be determined. In many feto-maternal-placental abnormalities, morphological abnormalities of the placenta in relation to gestational age have been reported [6–8]. Since cotyledons represent placental functional/morphological maturity, detailed MRI analyses of the cotyledon may be of value both basically and clinically. In short, understanding and describing the "normal MRI-detectable cotyledon" may provide fundamental data for detecting the "abnormal" placenta, especially in terms of placental maturation disorders.

We undertook the present study to determine whether MRI can identify the cotyledon, and if so, how the cotyledon becomes evident according to gestational age. We developed a new "cotyledon appearance score" to reproducibly demonstrate the cotyledon on MRI.

Materials and methods

Patients

Between May 18th, 2005 and May 30th, 2016, a total of 64 pregnant women underwent MRI. The following cases were excluded: i) placentas with ectopic pregnancies (n = 3); ii) missed abortions (n = 4); iii) ultrasound-detected abnormalities of placental morphology (placental infarction pathologically diagnosed after delivery, n = 2); and iv) histologically proven placenta accreta spectrum (PAS) disorders (n = 5). Because the

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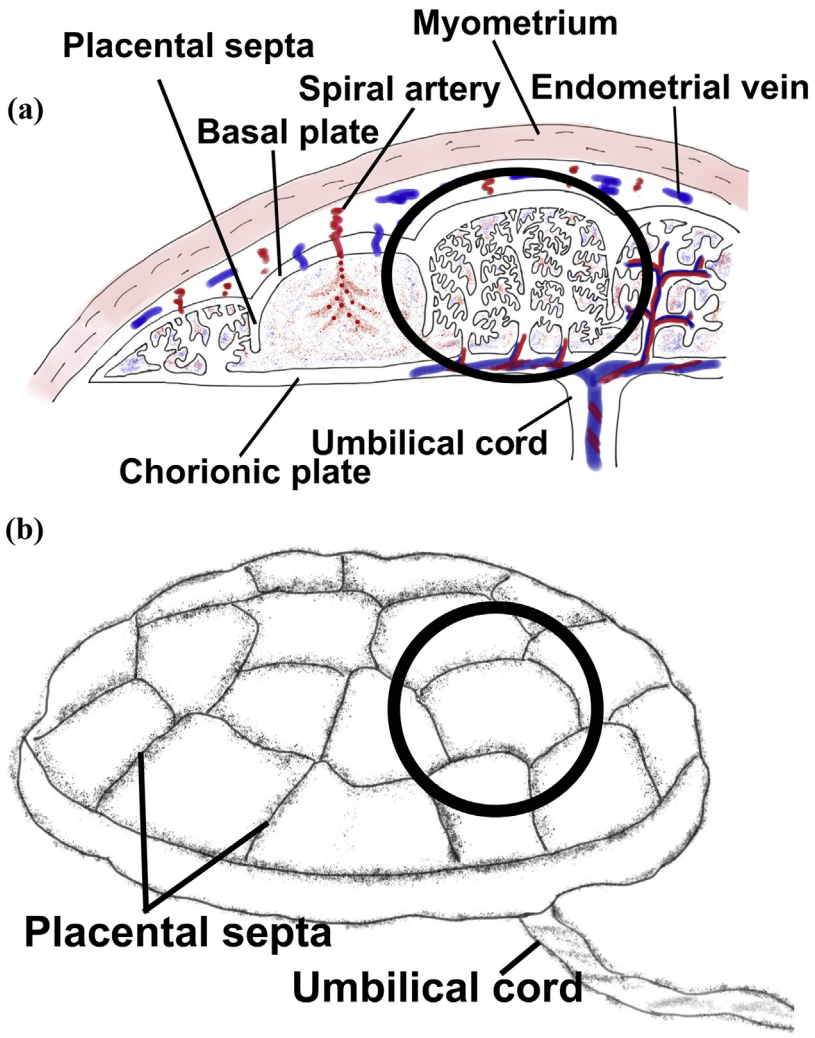

Fig. 1. Placental structures. a) Placenta in the second half of pregnancy. The cotyledon (circle) is a functional and morphological "unit" of the placenta, especially that at term or near-term. b) Schema of the term placenta after delivery, with cotyledon (circle) being evident on the maternal side. Graphics (a and b) are adapted from Refs. [4 and 5].

targets of the present study should represent "normal" placenta, or at least normal at the site of MRI analyses, placentas with histologically proven PAS disorders were excluded from the study.

The remaining 50 women (50 pelvic MRI studies with 51 placentas) were included in the present analysis. One woman with dichorionic diamniotic (DD) twins provided MRI data for a total of two placentas. Placentas studied in the 1st, 2nd, and 3rd trimesters comprised 16 placentas from 15 pregnancies (including 1 case of DD twins), 4 placentas from 4 pregnancies, and 31 placentas from 31 pregnancies, respectively. The indications for MRI are shown in Table 1. This retrospective study was approved by the Institutional Review Board at Jichi Medical University.

Imaging technique for MRI

All MRI studies were performed using a 1.5-T scanner (Avanto and Symphony; Siemens Healthcare, Erlangen, Germany, and Achieva; Philips, Amsterdam, the Netherlands) using a torso phased-array coil. Obtained sequences included T2-weighted imaging with half-Fourier acquisition single-shot turbo spin echo (HASTE) (field of view (FOV) = 280–300 mm; matrix = 256; repetition time (TR) = 800–1000 ms; echo time (TE) = 70–90 ms; flip angle = 120°), true fast imaging with steady-state free procession (true FISP) (FOV = 280–300 mm; matrix = 256; TR = 540–800 ms; TE = 1.65–2.23 ms; flip angle = 70-80°), and/or turbo spin echo (FOV = 280–300 mm; matrix = 256; TR = 2500–5500 ms; TE = 80–

Table 1
Indications for MRI.

Pregnancy period	Number of patients	Ovarian tumor	Uterine leiomyoma	Cervical cancer	PID	Cervical varix	Others	Suspected PAS	
							without placenta previa	with placenta previa	
1st trimester	15	9	2	2			2[a]		
2nd trimester	4	3			1				
3rd trimester	31		2			1		4	24

PID, pelvic inflammatory disease; PAS, placenta accreta spectrum.
[a] Ectopic pregnancy was suspected in all two cases, but was not present.

90 ms; flip angle = 120-140°) in three planes (axial, sagittal, and coronal), with a slice thickness of 3–8 mm. Adequate images to analyze uterus and placenta in detail were obtained in all cases.

Cotyledon appearance scores

We have here introduced a new "cotyledon appearance score". Fig. 2 indicates the method of scoring. MRI-discernible cotyledon was defined as a "round, high-signal group observed in fluid-sensitive sequences, delineated by a subtle peripheral low signal line" [1], which we used here. The score consists of two subscores: i) orthogonal cotyledon appearance score, in a cross-section orthogonal to the placental thickness; and ii) parallel cotyledon appearance score, in a section parallel to the placental thickness. In other words, the cotyledon was observed on MRI in two different sections.

In all 51 placentas on MRI, two board-certified radiologists examined the same cross-sectional MRI, while blinded to the results of analysis by the other radiologist. For orthogonal cotyledon appearance score, scores (1 to 3) were given as follows: score 1 = homogeneous with no discernible cotyledon; score 2 = cotyledon discernible, but not throughout the entire placental thickness (Fig. 2a); and score 3 = cotyledon discernible throughout the entire placental thickness (Fig. 2c). This was fundamentally in accordance with the ultrasound classification of Grannum et al. for placental maturity [9]. For parallel cotyledon appearance score, placentas were also given a score of 1 to 3: score 1 = not visualized at all; score 2 = possibly discernible, but not evident; and score 3 = clearly discernible. In placenta previa, scoring was made far from the internal ostium site (previa site), with scoring made at the normal placental region.

Statistical analysis

The mean of scores from the two board-certified radiologists was used to examine significant differences in scores between trimesters (Kruskal-Wallis test for comparing population medians between three groups, followed by the Steel-Dwass test for multiple comparisons between any two groups: 1^{st} vs. 2^{nd}; 1^{st} vs. 3^{rd}; 2^{nd} vs. 3^{rd} trimester). We evaluated inter-observer agreement between the two readers using weighted kappa statistics, with kappa values interpreted as: poor, <0.4; moderate, ≥0.4 to ≤0.75; and good, >0.75. Values of $P < 0.05$ were considered significant. Statistical analysis was performed using SPSS version 21.0 software (IBM, Armonk, NY) and R version 3.2.2 software (The R Foundation, Vienna, Austria).

Results

Table 2 indicates cotyledon appearance subscores (orthogonal and parallel) according to gestational age classified into three trimesters. The orthogonal cotyledon appearance subscore differed significantly between the 1^{st} vs. 2^{nd} and 1^{st} vs. 3^{rd} trimester. Cotyledons in the parallel view (representing parallel cotyledon appearance score) were not clearly identifiable in the 2^{nd} trimester (mean parallel cotyledon appearance score = 1.5), whereas these appearances were confirmed after $28^{0/7}$ weeks, showing a mean

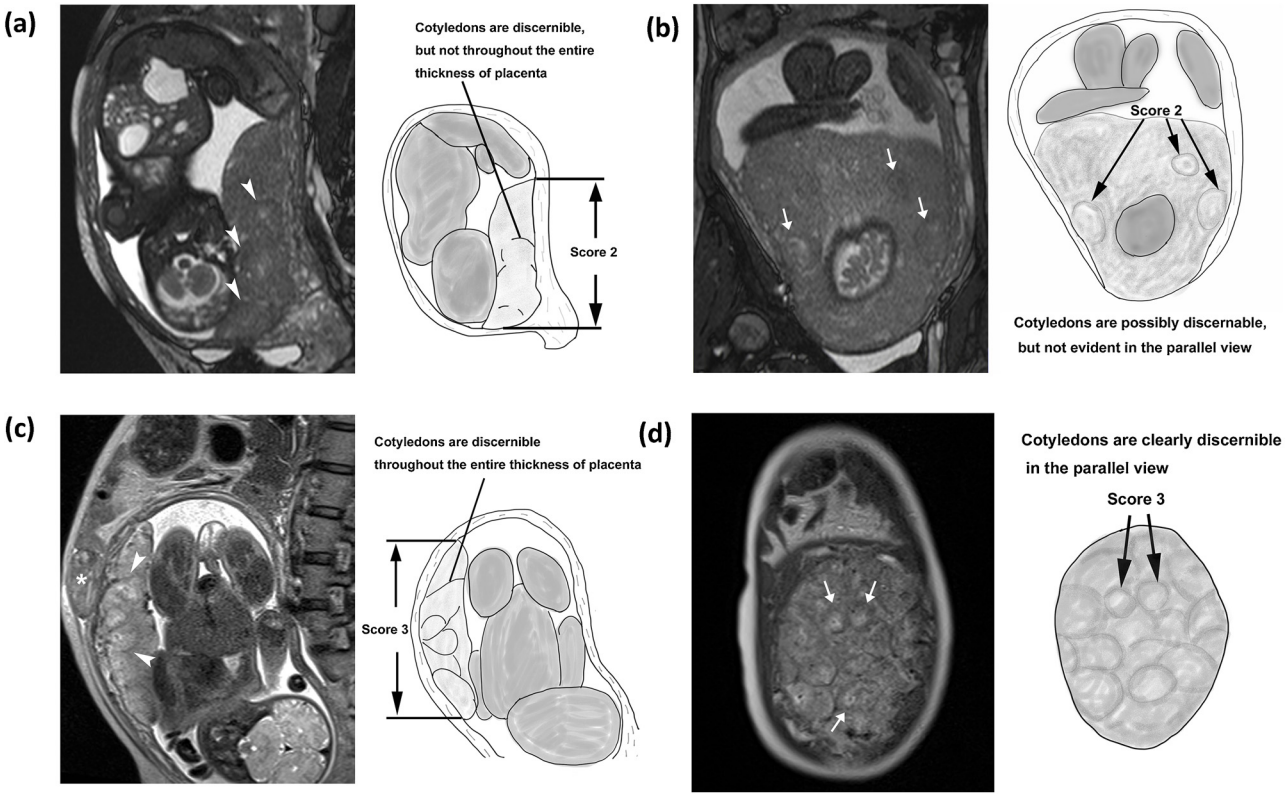

Fig. 2. Magnetic resonance imaging (MRI) of normal placental structure during the 3^{rd} trimester of pregnancy. a, b) A 36-year-old pregnant woman at $35^{1/7}$ weeks of gestation with complete placenta previa. a) Sagittal T2-weighted image shows a heterogeneous placenta: cotyledon can be discernible, but not throughout the entire thickness of the placenta (arrowheads). Orthogonal cotyledon appearance score = 2. b) Coronal T2-weighted image shows cotyledons (arrows) as round, high-signal structure delineated by a peripheral low-signal line. However, cotyledon features are not "evident". Parallel cotyledon appearance score = 2 (not 3). c, d) A 39-year-old pregnant woman at $36^{2/7}$ weeks of gestation with myoma (star). c) Sagittal T2-weighted image shows a heterogeneous placenta. The cotyledon is evident throughout the entire thickness of the placenta (arrowheads). Orthogonal cotyledon appearance score = 3. d) Coronal T2-weighted image shows cotyledons (arrows) as round, high-signal structures delineated by a peripheral low signal line. Compared with Fig. 2b, the cotyledon is "evident". Parallel cotyledon appearance score = 3.

Table 2
Mean grading of orthogonal and parallel cotyledon appearance score in each pregnancy period.

Pregnancy period	Number of placentas	Mean gestational age (range)	Mean cotyledon appearance score (range)	
			Orthogonal	Parallel
1st trimester	16	9w 5d (6w 5d-13w 4d)	1.1 (1-2)	1.13 (1-2)
2nd trimester	4	21w 3d (16w 6d-27w 2d)	2.13 (1-3)	1.5 (1-2)
3rd trimester	31	33w 3d (28w 0d-36w 2d)	2.66 (1-3)	2.58 (1-3)
p value			<0.01[a]	<0.01[a]
1st vs. 2nd trimester			<0.05[b]	<0.05[b]
1st vs. 3rd trimester			<0.01[b]	<0.01[b]
2nd vs. 3rd trimester			**0.291**[b]	<0.01[b]

[a] Kruskal-Wallis test.
[b] Steel-Dwass test.

Table 3
Inter-observer agreement.

Pregnancy period	Number of placentas	Cotyledon appearance score (weighted kappa)	
		Orthogonal	Parallel
1st trimester	16	0.953	0.906
2nd trimester	4	0.938	0.750
3rd trimester	31	0.847	0.887
Total	51	0.887	0.882

parallel cotyledon appearance score >2. With gestation advancing from 1st to 2nd to 3rd trimester, parallel cotyledon appearance score increased, with significant differences in both scores between 1st and 2nd, 1st and 3rd, and 2nd and 3rd trimesters.

Table 3 indicates inter-observer agreement. The weighted kappa was "good" for cotyledon appearance scores (range, 0.750–0.953) in each pregnancy period.

Comment

We have introduced a new cotyledon appearance score to demonstrate MRI-detectable cotyledons, using the two subscores for orthogonal and parallel appearance. As gestation advances, both orthogonal and parallel scores increased, suggesting that placental maturity progressed with gestational age. For example, parallel appearance score confirmed cotyledons after $28^{0/7}$ weeks in most cases. In this sense, cotyledons were definitively confirmed at the beginning of the 3rd trimester of pregnancy, which may agree with our decade-long experience regarding macroscopic placental examination after every placental delivery.

Cotyledon appearance scores may provide basic data to distinguish placental abnormalities. Since cotyledon formation is considered to be closely associated with placental maturity (functional/morphological unit), these scores may provide data specifically for the study of abnormalities of placental maturation. In some placental conditions, if "placental immaturity" or "placental dysmaturity" is present, cotyledon appearance score or simply the fact of an "MRI-detectable cotyledon being evident after 28 weeks" may provide a tool to detect such disorders of placental maturity. For example, dysmaturation may be present in placental mesenchymal dysplasia [8]. Although this condition itself is usually revealed by ultrasound or MRI, morphological findings for the prodromal stage remain unknown. Placentas from intrauterine fetal death near term [9,10] or preeclamptic women [11] also reportedly show dysmaturity or immaturity. MRI findings for these placental disorders are not well understood. The present cotyledon appearance scores, especially in terms of changes over the course of gestation, may help identify various such disorders of placental maturity.

Some limitations to this study must be considered. First, some selection bias may have been present. Placental morphology may change in some maternal-fetal conditions/disorders, including intrauterine infection (frequently observed in placentas with preterm labor) or various maternal abnormalities (diabetes mellitus or anemia) [1,12]. The present study excluded PAS disorders, but whether placentas with findings clinically suggestive of PAS can still be considered to represent normal placenta is unclear. The placentas studied in this investigation included cases of placenta previa. We scored these placentas in the peripheral area from the internal ostium, not at the site of or adjacent to the internal ostium (previa itself). This is because placental morphology at the site of "previa" may not be the same as sites of non-previa placenta in terms of cotyledon appearance. In short, whether the present findings actually reflect completely "normal" placenta is unclear. MRI is usually performed in pregnant women when some form of "abnormality" is suspected, and may thus represent a weakness inherent to this type of study. Second, although we determined "cotyledon appearance scores" according to gestational age, whether these scores are practically useful to identify or predict any placental abnormalities has yet to be determined.

In conclusion, we have introduced MRI-detectable cotyledon appearance scores and revealed that these scores increased with gestational age. The next issues to address are determination of the conditions for which this score can be practically utilized and how the present findings contribute to basic and clinical research in placentology.

Conflict of interest

None.

Acknowledgments

None.

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