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Uterine-fundal hypoechoic mass: a possible ultrasound sign for cesarean scar pregnancy

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Summary

Purpose of investigation: Cesarean scar pregnancy (CSP) is a life-threatening condition that requires early pregnancy termination. Its early ultrasound diagnosis is clinically important; however, previous studies focused on the CSP site itself. The present study was conducted to investigate the authors' clinical impression that a uterine-fundal hypoechoic mass is more frequently observed in CSP. Such a finding, if confirmed, may contribute to ultrasound diagnosis of CSP. The authors also determined the relationship between the treatment strategy and outcome, with special emphasis on conditions eventually requiring uterine artery embolization (UAE). *Materials and Methods:* This was a case-control study of CSP, and the authors analyzed all 14 women that were treated in this single tertiary institute over a period of ten years. Control subjects consisted of all pregnant women with prior cesarean section (CS) but no CSP. *Results:* Patients with CSP were significantly more likely to have a hypoechoic mass than controls (42.9 *vs.* 15.4%, respectively; $p = 0.028$). On confining results to a "fundal" hypoechoic mass, only CSP(+) patients showed it (CSP *vs.* control: 28.6 *vs.* 0%, respectively; $p < 0.001$). Six (43%: 6/14) received UAE: four following vaginal evacuation (artificial or spontaneous), and two for bleeding after methotrexate (MTX) treatment. *Conclusion:* Patients with CSP more frequently had a uterine-fundal hypoechoic mass, whose detection may trigger a detailed observation of the CSP site, possibly leading to CSP diagnosis.

Key words: Cesarean scar pregnancy; Cesarean section; Placenta accreta; Intrauterine hematoma; Subchorionic hematoma.

Introduction

In cesarean scar pregnancy (CSP) the conceptus is implanted in a previous cesarean section (CS) scar and chorionic villi deeply invade the myometrium at the site. CSP is a life-threatening condition and should be terminated as soon as possible after its diagnosis. CSP perforates the uterine wall and, thus, uterine rupture with resultant intractable bleeding can occur, or importantly. CSP, if it is not terminated and remains un-ruptured, will lead to placenta accreta (accreta, increta, or percreta) [1-5]. These underlie the importance of its early ultrasound diagnosis, which, however, is not always easy, especially for relatively less experienced practitioners.

The present authors' encounters with three consecutive CSP cases led them to develop the clinical impression that CSP is often accompanied by an ultrasound-detectable hypoechoic mass at the uterine fundus suggestive of hematoma, which they preliminarily described elsewhere [6]; however, they could not determine its validity. They performed a case-control study to determine whether a uterine-fundal hypoechoic mass is more frequently observed in CSP (+) than CSP (-) women, whose confirmation may contribute to its ultrasound diagnosis.

Various treatment protocols for CSP have been proposed, including methotrexate (MTX) administration, evacuation, resection, uterine artery embolization (UAE), or their combination [1, 7, 8]. They also attempted to determine the relationship between the treatment strategy and outcome, with special emphasis on conditions eventually requiring UAE, a relatively invasive treatment.

Material and Methods

This institute is one of the largest tertiary perinatal centers in Japan, performing 1,100 deliveries annually. The study subjects consisted of all 14 CSP women whom the authors treated in this institute over a period of ten years (April 2006 - March 2015). Control subjects (n=78) consisted of all pregnant women with prior CS but no CSP, whom the authors followed from less than 9+0 weeks from January 2014 to December 2014. No patients in either group had hemorrhagic or thrombophilic diathesis based on the history, examination, or laboratory data. All (14+78) women had a singleton pregnancy.

Data were collected from medical records: parity, the conception method, indication, and the number of prior CS, the interval from the latest CS to this pregnancy, obstetrical complications, perinatal outcome (gestational age at delivery/abortion, mode of delivery, and birth weight). As for the CSP group, data on the human chorionic gonadotropin (hCG) level (urine or serum), presence/absence of a fetal heart beat (FHB), gestational sac (GS) size, and CSP treatment were retrieved. Then, experienced obstetricians (authors) examined all the ultrasound records as to the presence or absence of a hypoechoic mass and an echo-free space between the uterine wall and GS in the first trimester, with special

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Table 1. — *Backgrounds and clinical courses of pregnant women with vs. without cesarean scar pregnancy (CSP).*

	CSP (n=14)	Control (n=78)	*p*
Age, years	35.4±4.3	34.8±4.8	0.695
Gravida, number	2.29±0.91	2.21±1.33	0.855
Parity, number	1.71±0.73	1.41±0.61	0.100
Pregnancy by IVF*	0 (0%)	7 (9.0%)	0.590
Interval from last CS, years†	4.6±2.4	4.1±3.0	0.613
Abortion patient‡	13 (92.9%)	6 (7.7%)	<0.001
Delivery, weeks§		37.9±0.7	
Birth weight, gram		2872.4±344.2	

CS: cesarean section, CSP: cesarean scar pregnancy, IVF: in vitro fertilization *IVF included conventional IVF, intracytoplasmic sperm injection, and frozen embryo transfer. †Interval defined the duration between last CS and the first visit in the following pregnancy. ‡Including artificial or spontaneous abortion (shown in Table 3) §One patient (Case 8) in the CSP group continued pregnancy and eventually underwent cesarean hysterectomy due to placenta increta at the 31st week. Data are shown as mean ± standard deviation.

Table 2. — *Intrauterine hypoechoic mass in the first trimester between pregnant women with vs. without cesarean scar pregnancy (CSP)*

Location	CSP (n=14)	Control (n=78)	*p*
Overall	6 (42.9%)	12 (15.4%)	0.028
Fundus	4 (28.6%)	0 (0%)	<0.001

CSP: cesarean scar pregnancy.

attention to a uterine-fundal hypoechoic mass.

CSP diagnosis was made by transvaginal ultrasound, with magnetic resonance imaging (MRI) also employed when ultrasound failed to determine CSP. The diagnostic criteria were: (1) GS located at the anterior uterine wall around a previous cesarean scar and (2) myometrial thinning between GS and the bladder. GS was confirmed by the presence of a "white ring" around it and yolk sac within it. Patients diagnosed with CSP were informed about its potential risks and were advised to terminate their pregnancies. It was the attending physicians' choice regarding the treatment protocol to be used to terminate CSP. Generally speaking, dilatation and evacuation (D&E) were employed in the initial one-third of this study period, and local MTX administration was employed in the latter two-thirds. This was because the authors encountered massive bleeding after D&E requiring UAE (described later), and, thus, they changed their protocol. In the latter protocol, potassium chloride was injected into the embryo in FHB (+) cases. Then, they injected MTX (20-50 mg) into GS under transvaginal ultrasound guidance regardless of the presence or absence of preexisting FHB. When local MTX injection was impossible, MTX was intravenously administered (20 mg/day x5 days), which was repeated until the hCG titer decreased. UAE was performed by experienced interventional radiologists when un-controllable bleeding occurred.

Student's *t*-test (two-tailed) and the χ^2-test were used to compare the parameters between the two groups. When the category was composed of less than five, Fisher's exact test was applied instead of the χ^2 -test. $P < 0.05$ was considered significant. All statistical analyses were performed using JMP version 10. This study was approved by the Jichi Medical University Ethics Committee.

Results

Table 1 shows the maternal characteristics and obstetric outcomes. The maternal age, gravidity, and parity did not differ between CSP (+) *vs.* (-). The CSP (+) group received a lower rate of IVF than the controls, without significance. CSP and control groups showed approximately the same interval between the last CS and current pregnancy.

Table 2 shows the presence/absence of a hypoechoic mass. The CSP group was significantly more likely to have a hypoechoic mass than the controls (42.9 *vs.* 15.4%, respectively; $p = 0.028$). On confining results to a "fundal" hypoechoic mass (Figure 1A), only the CSP group showed it (28.6 *vs.* 0%, respectively; $p < 0.001$).

Table 3 summarizes the clinical course of 14 CSP patients. More than a half (57%: 8/14) had more than two prior CS. Five (36%: 5/14) had FHB. The maximum hCG and GS sizes before treatment were 3,819-157,519 IU/L and 11-43 mm, respectively. Three (21%: 3/14, Cases 2, 4, and 6) were not diagnosed with CSP on the first ultrasound examination.

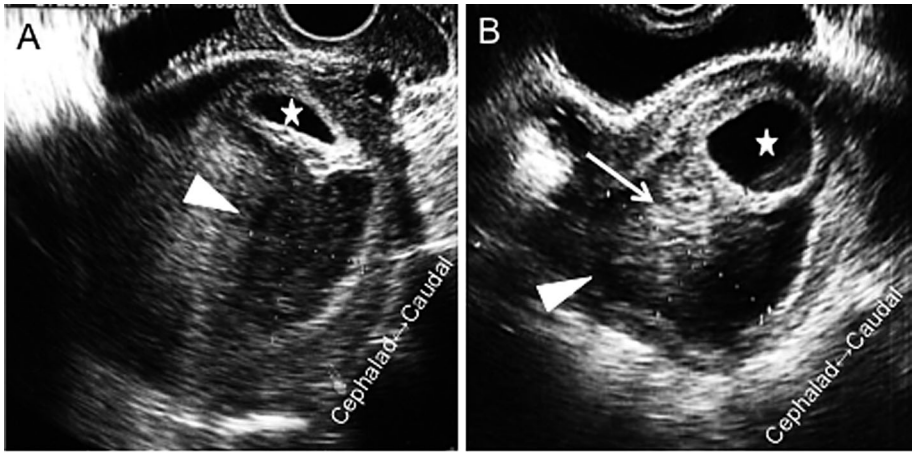

Figure 1. — Hypoechoic mass at the uterine fundus (Case 8). A) At the sixth week. A hypoechoic mass (arrowhead) cephalad to the gestational sac (GS) (star) was observed. The mass has no communication with GS. B) At the eighth week. An iso-echoic area is evident (arrow) within hypoechoic mass (arrowhead). Star indicates GS.

Table 3. — *Clinical characteristics, treatment employed, and outcomes of patients with cesarean scar pregnancy (CSP).*

Case	Age	G	P	Number of CS	Indication at first CS	Interval from last CS (year)	FHB	Max hCG (IU/L)	GS size (mm)	Uterine–fundal hypo-echoic mass	D&E	SE	Local MTX	Systemic MTX	UAE	Time to reach normal hCG level (month)	
1	40	4	2	2	Breech	2	–	NA	NA	+	+	-	-	-	+	2	SE→UAE→MTX
2	38	1	1	1	Abruption	2	–	16724	NA	–	+	–	–	–	+	2	
3	28	2	2	2	NA	4	–	9100	17	+	–	+	–	+	+	2	
4	37	2	3	2	Arrest of labor	3	–	3819	11	–	–	+	–	–	+	2	
5	36	4	2	2	NA	7	–	24214	24	–	–	–	+	+	+	3	MTX→UAE
6	38	2	2	2	HELLP syndrome	2	+	13471	35	–	–	–	+	–	+	1	MTX→UAE
7	28	1	1	1	NRFS	2	–	38480	25	+	–	–	+	–	–	4	
8	38	3	3	3	Breech	7	+	NA	NA	+	–	–	–	–	–	NA	Pregnancy continuation
9	42	2	1	1	Placenta previa	9	–	17544	19	–	–	–	+	+	–	6	
10	38	2	2	2	NA	5	+	8716	12	–	–	–	+	+	–	2	
11	33	2	1	1	Placenta previa	5	+	36186	23	–	–	–	+	–	–	4	
12	35	3	1	1	Breech	3	–	60229	26	–	–	–	–	+	–	5	WE at 5 months
13	31	2	2	2	Arrest of labor	8	+	157519	NA	–	–	–	+	+	–	2	
14	33	2	1	1	Breech	6	–	NA	28	–	–	–	–	+	–	NA	

CS: cesarean section; CSP: cesarean scar pregnancy; D&E: dilatation and evacuation; FHB: fetal heart beat; GS: gestational sac; MTX methotrexate; NA: not available; NRFS: non-reassuring fetal status; SE: spontaneous evacuation; UAE: uterine artery embolization; WE: wedge excision; Cases 1, 7 and 8 were previously reported in reference 6.

As for treatment, two (Cases 1 and 2) had D&E and two (Cases 3 and 4) showed spontaneous evacuation, and, thus, a total of four patients vaginally expelled the conceptus irrespective of artificially or spontaneously. Ten (71%: 10/14) received MTX administration (local: seven, systemic: seven, both: four). Six (43%: 6/14) received UAE: four following vaginal evacuation (artificial or spontaneous) and two for bleeding after MTX treatment. Thus, all patients with vaginal evacuation required UAE, or 67% (4/6) of patients who required UAE were those after vaginal evacuation, indicating a high probability of UAE after vaginal evacuation.

In one case (Case 8), CSP was suggested but not confirmed: GS had been pressed by a fundal hypoechoic mass, and, thus, it was difficult to grasp the topological relationship between GS and the CS site. The echogenicity of the mass changed from hypo- to isoechoic as pregnancy progressed (Figure 1B). Then, vaginal bleeding occurred, after which the size of the mass was decreased. The mass disappeared at the 16th week. Later, placenta previa with abnormally invasive placentation at the CS site became evident. Massive bleeding necessitated cesarean hysterectomy at the 31st week; placenta increta was confirmed histologically [6].

In another case (Case 12), the patient had a prior history of placenta accreta at the previous CS site, in whom MTX was systemically administered at the 17th week: the placenta was absorbed. In this pregnancy, CSP recurred. MTX (four courses) was administered; however, the hCG level did not decline to the normal level and a "niche", ultrasound-detectable defect of the cervical canal, was also observed. Wedge resection was performed five months after systemic MTX.

No patients showed significant complications following the treatments. The hCG level returned to normal (< 5.0 IU/L) within one to six months. One patient had spontaneous abortion, but the authors have no information regarding the subsequent pregnancies in the remaining 13 patients.

Discussion

This study confirmed the authors' clinical impression that CSP tends to accompany a fundal hypoechoic mass. As ultrasound diagnosis of CSP, GS present at the CS scar and myometrial thinning of the site are well-known, which were also used in the present study. However, its ultrasound diagnosis is not always easy, especially for relatively less experienced practitioners. GS located in the lower portion, i.e., low-implanted GS (but not CSP) or GS with abortion progressing, may sometimes be misunderstood as CSP. Advanced gestation, with GS becoming larger and even bulging to the uterine body, may sometimes prevent us from observing the CS scar site [9]. Indeed, the authors misdiagnosed 21% (3/14) of CSP, being similar to previously reported rates of 13.6 and 15.4% [1, 7]. One of the reasons for the difficulties may be that diagnosis was solely based on "subjective" pattern recognition of the CSP site.

To overcome this drawback, an "objective" parameter was introduced: measurement of the GS border - the uterine serosa distance facilitated an accurate diagnosis of CSP with a positive predictive value of 100% and the smallest distance of < three mm [10]. Pulse Doppler [11] or three-dimensional power Doppler with color Doppler imaging [12,

13] increased the accuracy of CSP diagnosis. However, all these were still based on "observation of the CSP site itself".

The present authors changed their viewpoint. Here, they proposed a new approach, which targeted a site other than CSP itself, namely, the detection of a hypoechoic mass at the uterine fundus. A recent study supported their view. As described previously [6], ten CSP patients desired pregnancy continuation; all resulted in placenta percreta and led to cesarean hysterectomy [3]. Although the authors did not mention it clearly, they found an ultrasound-detectable fundal hypoechoic mass in at least four patients in their figures (Cases 1, 2, 3, and 6 of their report) [3], of which findings were described previously (Cases 1, 7, 8 in this report) [6]. Other reports also showed similar images (Liang and He's Figure 1A [14], Cok *et al.*'s Figure 1 [15], and Cheng *et al.*'s Figure 1B [16]). Detection of a fundal mass is quite straightforward even for relatively less experienced practitioners. Even if transvaginal ultrasound is unavailable, transabdominal ultrasound may be able to detect it.

The mechanism of fundal hypoechoic mass formation is unclear. Intrauterine hematoma during pregnancy, especially subchorionic hematoma, is a well-acknowledged phenomenon. The present intrauterine hypoechoic mass within the pregnant uterus, namely, its echogenicity and location, revealed the similarity between the present mass and intrauterine hematoma. In Case 8, pregnancy was not terminated and thus the authors could serially observe the mass: the echogenicity of the mass changed as pregnancy progressed, and, importantly, the mass diminished just after vaginal bleeding. These suggested that this mass may have been hematoma. Although the formation mechanism of intrauterine or subchorionic hematoma is still obscure, detachment of the chorionic membranes from the uterine wall or partial separation of the placenta is considered [17]. Thus, hematoma usually develops adjacent to, or at least not far from, GS or the placenta: it is sometimes located on the uterine vaginal side, possibly due to gravity. In the present study, the mass was present in the uterine fundal area, where the placenta was not present. This leads us to suggest that the mass, if it is a hematoma, may be caused by a mechanism different from an ordinary intrauterine hematoma. As a simple alternative, the "exit" of the hematoma may be blocked by a large GS of CSP, and thus, bleeding or fluid remains accumulated in the uterine fundus. This may be why the present mass existed at the placenta-free uterine fundus. The authors have had no chance to aspirate it or confirm it after hysterectomy. Further study is needed to identify whether this mass is a hematoma, fluid accumulation, or something else.

UAE was performed in six of the 14 (43%) patients. Importantly, all patients with spontaneous evacuation or D&E required UAE due to continuous bleeding, suggesting that vaginal evacuation may lead to a high risk of requiring UAE. Other data support this view. A previous review [7] showed that 76% (16/21) with CSP managed with D&E had bleeding complications following D&E. Another study showed that 40% (3/8) suffered significant bleeding after D&E [11]. This tendency may also hold true for FHB(-) CSP patients: five of 12 FHB (-) CSP patients underwent D&E or were observed over the natural course, and three required UAE, indicating that, even without FHB, massive bleeding can frequently occur following GS evacuation [4]. The choice of treatment (choice of D&E) depended on attending doctors' decision, and D&E had also been performed in the beginning one-third of the study period. Thus, there may have been selection bias regarding any conclusion. However, since physicians may not choose D&E for "severe cases" (cases in which severe bleeding can be expected) and since, in fact, vaginal evacuation cases (both artificial and spontaneous) had a relatively lower hCG level (median: 9,100 IU/L [Cases 1-6] *vs.* 30,200 IU/L [Cases 7-14]) and smaller GS (median: 14 mm [Cases 1-6]) *vs.* 24.5 mm [Cases 7-14]), vaginal evacuation cases may have consisted of "less severe" cases in terms of bleeding. Even so, patients after vaginal evacuation still bled enough to require UAE. Presently, vaginal evacuation (+) *vs.* (-) may have provided, although not strictly, a historical control study. Thus, the present authors believe that vaginal evacuation may lead to a high risk of bleeding requiring UAE.

UAE may also be required after MTX treatment. MTX-based therapy is widely used: some [15, 18] recommend ultrasound-guided MTX injection as the first-line treatment for CSP. In fact, a combination of local injection and systemic MTX administration was found to be effective in all 19 cases of CSP [19]. However, in the present study, two patients had significant bleeding after local MTX injections. Attention should also be paid to bleeding requiring UAE after MTX treatment.

In conclusion, a uterine-fundal hypoechoic mass was significantly more frequently observed in CSP. A detailed observation of the CSP site itself is undoubtedly the most important for CSP diagnosis. Even relatively less experienced practitioners can easily detect a fundal hypoechoic mass, and, thus, its detection may trigger a detailed observation of the CSP site, suggesting that a fundal hypoechoic mass may be a useful adjunct to diagnose this condition. UAE was sometimes required in CSP management, especially for patients with vaginal evacuation. A facility which treats CSP may be better equipped to provide interventional radiology.

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