First-trimester ultrasound diagnosis and risk factor analysis of cesarean scar pregnancy after in vitro fertilization-embryo transfer

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Background: Cesarean scar pregnancy (CSP) is one of the rarest ectopic pregnancies which may be associated with life-threatening complications. Owing to the rarity of CSP, little is known about it. This study aimed to evaluate the value of the first-trimester transvaginal sonography (TVS) diagnosis and the risk factors of CSP after in vitro fertilization-embryo transfer (IVF-ET).

Methods: This was a retrospective study of women undergoing IVF-ET between January 2013 and December 2018. Women who were diagnosed with a CSP using TVS and confirmed by surgery and histological examination were included. The clinical data and ultrasound findings were collected and analyzed. Univariate and multivariate logistic regression analyses were performed for evaluation of possible influence factors. Diagnostic parameters including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of TVS were calculated for the diagnosis of CSP.

Results: Overall, 75,438 consecutive women who underwent IVF-ET had received TVS during this period. Of these, 4,817 women (6.4%) had a history of cesarean section and 83 cases were found to have a CSP. Due to the absence of histological data, 19 cases treated conservatively were excluded. Finally, 64 cases were included, among whom 63 cases were correctly diagnosed [including 17 cases of heterotopic CSP (HCSP)] and 1 case was missed using TVS. Another 1 case of inevitable miscarriage was misdiagnosed as a CSP. The maternal age at the initial scan [34.0 (range, 26.0–44.0) years], the infertility duration [4.0 (range, 1–12) years], and the initial diagnostic time after ET [27 (range, 20–50) days] were recorded. A gestational sac (GS) was observed in all 63 cases during ultrasound examinations, including 28 with fetal pole, 25 with a yolk sac only, and 10 with an empty sac. The sensitivity and specificity of first-trimester TVS in diagnosing CSP were 98.44% and 99.98%, respectively; the PPV and NPV were 98.44% and 99.98%, respectively. Multivariate logistic regression analysis showed thinner endometrial thickness (ET) on transfer day [adjusted odds ratio (aOR): 0.83; 95% confidence interval (CI): 0.76–0.93, P<0.001] and multiple ET (aOR 53.60, 95% CI: 5.31–1,736.00, P=0.008) were independent risk factors for CSP and HCSP, respectively.

Conclusions: First-trimester TVS performed by an experienced sonographer has a high sensitivity for making the correct diagnosis of CSP after IVF-ET, which is helpful for clinical intervention and avoiding

severe complications. For patients with a history of cesarean section, thinner ET on the transfer day and bigger body mass index (BMI) seem to be risk factors for CSP; single blastocyst transfer should be recommended to decrease the possibility of HCSP. The clinical significance of this study still needs to be considered.

Introduction

Caesarean scar pregnancy (CSP) refers to a pregnancy implanted in the transverse lower segment caesarean section (CS) scar (1,2). A heterotopic CSP (HCSP) implies the coexistence of an intrauterine pregnancy (IUP) and a CSP. CSP is one of the rarest ectopic pregnancies and the prevalence has been estimated to range from 1/2,216 (local population, Taiwan, China) to 1/1,800 (local population, UK) (3,4). The incidence of CSP has increased with increasing cesarean section rates, the availability of *in vitro* fertilization-embryo transfer (IVF-ET) techniques, and the improved diagnostic accuracy of transvaginal sonography (TVS) (5). CSP can be diagnosed when the following features are detected: gestational sac (GS) located low in the uterus close to the internal os and anterior implantation with trophoblast invading into the myometrium (2).

Various hypotheses have been proposed regarding the mechanism of CSP, but the exact etiology remains unclear. One probable mechanism is that an implanting blastocyst abnormally invades the affected myometrium from the endometrial canal through a microscopic dehiscent tract caused by CS (6,7). A recent study (8) found that anterior myometrial thickness at the scar and the diameter of the GS were independent risk factors for intraoperative hemorrhage during treatment and a new clinical classification system was proposed based on these factors with recommended surgical strategy.

This type of pregnancy may be associated with life-threatening complications such as uterine rupture, placenta accrete, and hemorrhage. The diagnosis of CSP has mainly been accomplished by TVS together with the measurement of serum β-human chorionic gonadotropin (β-hCG) (9). Magnetic resonance imaging (MRI) might be used as an adjunct in cases of diagnostic uncertainty (10). There has been no standard protocol or optimal method for the management of CSP until now. The therapeutic strategies include, but are not limited to, medical treatment with systemic and/or local methotrexate (MTX), uterine curettage, hysteroscopy, laparoscopy, uterine artery embolization (UAE), and expectant management (7).

Early diagnosis enables rapid treatment and helps to reduce maternal morbidity and mortality. Generally, 2-dimensional (2D) TVS alone or in combination with 3-dimensional (3D) TVS and color Doppler has been regarded to be the gold standard for the diagnosis of CSP (11). In this study, we misdiagnosed a low IUP as a CSP. Great care must be taken in order not to overdiagnose CSP. Applying gentle pressure with the transvaginal probe helped to distinguish between CSP and miscarried IUP; if the 'sliding organs' sign was positive, then it was more likely to be a miscarriage rather than an implanted CSP. Additionally, the presence of trophoblastic circulation signal around the sac using color Doppler meant that the pregnancy sac was being implanted at the site rather than passed through the lower uterine cavity (12). When a GS appeared in the isthmus region of the uterus, it was also crucial to differentiate CSP from cervical pregnancy (CP). In this study, in a case of CP, the sac was visualized in the endocervical canal below the level of the internal os, so the history of CS was very important for the differential diagnosis.

In these 63 surgically treated cases, the follow-up TVS scans confirmed that the conceptions in the CS site were all cleared completely. In the 19 patients who were excluded due to conservative treatment, 4 healthy infants of CSPs were delivered. CSP can be classified into 2 types based on imaging findings and pregnancy progression (13,14). Endogenic CSP occurs when implantation occurs on the scar and grows towards the uterine cavity. Exogenic CSP is where the GS deeply embeds in the scar and grows towards the bladder. Our review of the ultrasound images of the 4 CSPs that survived revealed that they were more inclined to be endogenic CSPs. This indicated that there was a hope

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for continuous pregnancy after conservative treatment of endogenic CSP. Therefore, early classification using TVS is crucial for the choice of management.

However, owing to the rarity of this condition, only small studies and a few case reports were available in the literature (3,4,7). Herein, we present our experience, in order to evaluate the value of the first-trimester TVS diagnosis and the risk factors of CSP after IVF-ET. To the best of our knowledge, the present study had the largest sample size of CSP after IVF-ET in a single assisted reproductive center to date. We present this article in accordance with the STARD reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1239/rc).

Methods

Patient selection

A retrospective study of consecutive women who were found to have a CSP after IVF-ET between January 2013 and December 2018 was conducted in the Reproductive and Genetic Hospital of CITIC-Xiangya. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the Reproductive and Genetic Hospital of CITIC-Xiangya (No. LL-SC-2019-015). The requirement for informed consent was waived due to the retrospective nature of the study.

All enrolled patients underwent IVF-ET and received first trimester ultrasound diagnosis to confirm clinical pregnancies in Reproductive and Genetic Hospital of CITIC-Xiangya. Only women who were diagnosed with a CSP using TVS and confirmed by surgery and histological examination were included in the final analysis. Histological examination was the gold standard for the CSP diagnosis (12,15); patients managed non-surgically were excluded from the final analysis, as histological confirmation of the diagnosis was impossible to perform. The ultrasound findings and clinical data of included patients were collected and analyzed. Among the patients with a history of CS who underwent IVF-ET and received TVS examination in our hospital during the study period, we chose those with eutopic pregnancies (n=4,557) as the control group to investigate the risk factors for CSP and HCSP.

IVF procedure

In the fresh cycles, conventional control ovarian hyperstimulation (COH) was performed using long or short protocols with gonadotrophin-releasing hormone agonists (GnRHa, Ferring Pharmaceuticals, Saint-Prex, Switzerland) and recombinant FSH (rFSH; Gonal F, Merck-Serono, Geneva, Switzerland). Human chorionic gonadotrophin (hCG) was administered when 3 or more follicles measuring at least 18 mm in diameter were observed on the ultrasound. Oocyte retrieval was performed by TVS 34–36 hours after hCG injection. Fertilization was achieved using either standard IVF or intracytoplasmic sperm injection, depending on the cause of infertility.

Endometrial preparation protocols for frozen-thawed embryo transfer (FET) cycles included natural cycle (NC) with or without (modified natural cycle, MNC) hCG trigger, and artificial cycle (AC) with or without GnRHa suppression. NCs were performed only in women who had spontaneous ovulation. Hormone replacement treatment was performed in women with amenorrhea or irregular menstrual cycles (16).

Either 1 or 2 fresh or frozen embryos with good quality were transferred to each patient at the day-3 or -5 stage under ultrasound guidance. The embryo morphology was scored according to the criteria by Hardarson *et al.* (17). A routine blood test for serum β-hCG was performed on day 14 post IVF-ET (blastocysts on day 12).

Ultrasound diagnosis

Patients undergo at least 1 ultrasound examination during the first trimester to confirm the number and location of clinical pregnancies. The routine first examination is usually arranged at day 28 (blastocysts on day 26) after ET (18). If low serum β-hCG levels (<200 mIU/mL) are measured, or if patients have symptoms such as vaginal bleeding or abdominal pain, they will receive an earlier TVS scan on about day 20–22 day after transfer to exclude ectopic pregnancy (EP). If EP is not found on the first ultrasound, follow-up TVS scans with β-hCG is scheduled every 7–10 days or so. GE VOLUSON E8/730 (GE Tech Co., Ltd., Schenectady, NY, USA) equipped with a 5–9 MHz vaginal color Doppler probe was used.

The diagnosis of CSP was based on a history of at least 1 caesarean delivery, a positive serum β-hCG level, and the following ultrasonographic criteria (3,19-21): (I) an empty uterine cavity and cervical canal; (II) a GS with or without an embryo presenting cardiac activity located anteriorly at the level corresponding to the prior lower uterine segment of the CS scar; (III) an inhomogeneous mass embedded at

the lower uterine segment and implanted in the location of the previous CS scar; (IV) a thin or absent myometrial layer between the bladder and GS on a sagittal view of the uterus; (V) evidence of functional trophoblastic or placental circulation, which was defined by the presence of increased surrounding blood flow in the location of previous CS scar on color Doppler ultrasound examination; (VI) a negative 'sliding organs' sign, which meant the position of the GS could not be moved by gentle pressure applied by the transvaginal probe. Meanwhile, a patient with HCSP met the above criteria and had an IUP. Once the diagnosis of CSP was made, detailed ultrasound findings and clinical data would be recorded in an electronic database.

All sonographers were well trained for at least 5 years and followed the same examination procedures and diagnostic criteria. If a CSP was suspected during an examination, another doctor was consulted, and if there were still doubts, a senior doctor (more than 10 years of experience) was consulted for further confirmation. Thus, the diagnosis of CSP was the consensus of at least 2 doctors. As a routine part of the early pregnancy examination, a 3D volume examination was also applied. We selected the entire uterus in the sagittal plane and performed volume rendering or if necessary; the acquisition was repeated in the transverse plane, which is more recommended for a uterus with a larger transverse diameter (22).

Outcome measures

Treatment modalities consisted of expectant management, medical treatment, and surgery (23); combinations of various treatment methods were also performed. Informed consent was provided by all patients before treatment. All patients were tracked until the end of the pregnancy by a specific team at our center. The main outcome measures were the risk factors of CSP/HCSP and the accuracy of TVS in diagnosing CSP. Secondary outcomes were the preservation of fertility and the live birth of IUP for patients with a HCSP. Live birth was defined as the complete expulsion or extraction of fertilized products from a woman after 22 completed gestational weeks, and after such separation, the newborn breathed or showed any other signs of life, regardless of whether the umbilical cord had been cut or the placenta was attached (24).

Statistical analysis

The distribution of patient demographics and clinical characteristics was analyzed using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation (SD) or median [range/interquartile range (IQR)] according to variables' distribution. Categorical variables were described as the frequency and percentage. Either t-test or Mann-Whitney U test was used for comparison according to the distribution of continuous variables; chi-squared or Fisher's exact test was used to compare differences between categorical variables. Univariate and multivariate logistic regression analyses were further performed for evaluation of possible influencing factors based on clinical experience or literature report for CSP/HCSP, and variables with P<0.2 in univariate logistic regression analysis were included in multivariate logistic regression analysis; odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Diagnostic parameters including sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of TVS were calculated for the diagnosis of CSP. A receiver operating characteristic (ROC) curve was used to discriminate the predictive values of endometrial thickness (ET) for the risk of CSP and to acquire the cut-off value of ET. All statistical analyses were performed using R 4.3.1 (R Core Team, Vienna, Austria), and 2-tailed value of P<0.05 was considered statistically significant.

Results

Overall, 75,438 consecutive women who underwent IVF-ET had received TVS during this period. Among them, 4,817 women (6.4%) had a history of CS and 83 cases were retrospectively found with a CSP. The prevalence of CSP was approximately 1:909 (83/75,438). Due to the absence of histological data, 19 cases treated conservatively (either medically or expectantly) were excluded from the analysis. In total, 64 cases (including 17 cases of HCSP) who were treated surgically with the subsequent pathological confirmation were included and analyzed (*Figure 1*).

Patient characteristics

The characteristics of these 63 patients diagnosed with a CSP by TVS are presented in *Table 1*. All patients had only 1 previous CS. More than half of patients (33, 52.4%) had no symptoms at the time of the first diagnosis, painless vaginal bleeding was the second most common (15, 23.8%), 9 cases (14.3%) had low abdominal pain alone, and the other 6 cases (9.5%) presented with abdominal pain and
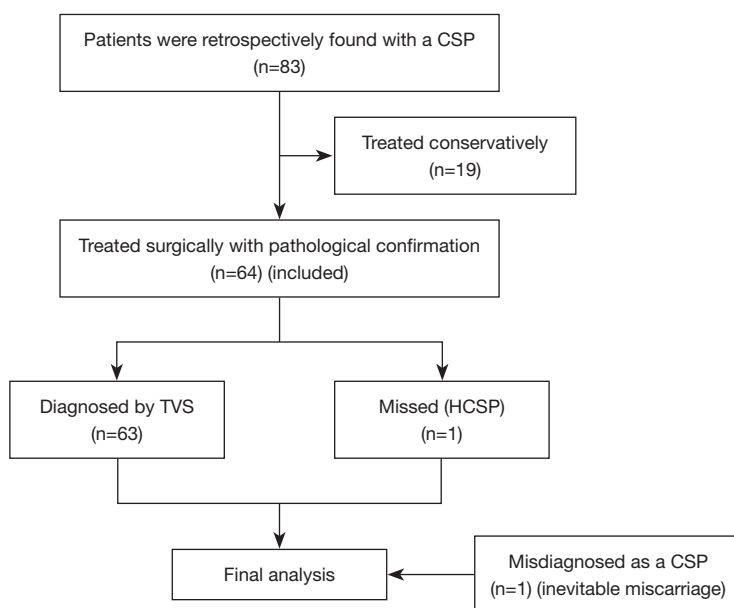
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┌─────────────────────────────────────┐
│ Patients were retrospectively found │
│        with a CSP (n=83)            │
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                 │
                 │        ┌──────────────────┐
                 ├───────▶│ Treated          │
                 │        │ conservatively   │
                 │        │ (n=19)           │
                 │        └──────────────────┘
                 ▼
┌─────────────────────────────────────┐
│ Treated surgically with pathological│
│   confirmation (n=64) (included)    │
└─────────────────────────────────────┘
          │                    │
          ▼                    ▼
┌──────────────────┐  ┌──────────────────┐
│ Diagnosed by TVS │  │ Missed (HCSP)    │
│ (n=63)           │  │ (n=1)            │
└──────────────────┘  └──────────────────┘
          │                    │
          └────────┬───────────┘
                   ▼
          ┌──────────────┐    ┌────────────────────────┐
          │ Final        │◀───│ Misdiagnosed as a CSP  │
          │ analysis     │    │ (n=1) (inevitable      │
          └──────────────┘    │ miscarriage)           │
                              └────────────────────────┘
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Figure 1 Flowchart of the study group. CSP, cesarean scar pregnancy; TVS, transvaginal sonography; HCSP, heterotopic cesarean scar pregnancy.

Table 1 Characteristics of the 63 cases of CSP

Characteristics	Value
Maternal age (years)	34.0 (26.0–44.0)
BMI (kg/m^2)	22.1 (18.2–30.2)
Duration of infertility (years)	4.0 (1.0–12.0)
Gravida (times)	3.0 (1.0–7.0)
Para (times)	1.0 (1.0–2.0)
Transferred embryos (n)	2.0 (1.0–2.0)
Day 14 β-hCG levels of CSP (except HCSP) (blastocysts on day 12) (mIU/mL)	279.0 (28.0–1073.0)
Day 14 β-hCG levels of HCSP (blastocysts on day 12) (mIU/mL)	1,030.0 (298.0–1,909.0)
Initial diagnosis time (the days after ET)	27 (20–50)
Clinical symptoms	
No symptoms	33 (52.4)
Abdominal pain	9 (14.3)
Vaginal bleeding	15 (23.8)
Abdominal pain and vaginal bleeding	6 (9.5)

Data were expressed as median (range) and n (%). CSP, caesarean scar pregnancy; HCSP, heterotopic caesarean scar pregnancy; BMI, body mass index; hCG, human chorionic gonadotropin; ET, embryo transfer.

mild vaginal bleeding concurrently.

Ultrasound diagnosis

Of the 64 cases of CSP, 63 were diagnosed by TVS and 1 HCSP was missed. Additionally, another 1 case of inevitable miscarriage of IUP was misdiagnosed as a CSP. The single initial scan detected almost 81.3% (52/64) of all CSPs and subsequent scans detected 91.7% (11/12) of the remaining CSPs. The total sensitivity and specificity of first-trimester TVS in diagnosing CSP were 98.44% (63/64) and 99.98% (4,733/4,734), respectively; the PPV and NPV were 98.44% (63/64) and 99.98% (4,733/4,734), respectively (*Table 2*).

GS were observed in all 63 cases of CSPs during ultrasound examinations, among whom, 1 case had 2 visible GS in the CS at the same time (*Figure 2*). Thus, there was a total of 64 CS GSs. Among them, a fetal pole was detected in 28 cases, including 26 with embryonic cardiac activity and 2 without. There was a yolk sac only in 25 cases with 26 sacs, and an empty sac was seen in 10 cases. The mean gestational sac diameter (GSD) at diagnosis was 13.1±6.5 mm. In the IUPs of the 17 cases of HCSPs, 7 cases had an embryo with cardiac activity, 9 had a yolk sac only, and 1 had an empty sac at initial diagnosis. Other ultrasound findings including

pelvic fluid and uterine cavity fluid are shown in *Table 3*.

Comparisons of characteristics and risk factors for CSP/HCSP

Compared with eutopic pregnancies, patients with a CSP had a markedly longer duration of infertility [5.0 (3.0–7.0) *vs.* 3.0 (2.0–5.0) years, P=0.016] and a thinner ET on transfer day [11.5 (10.3–12.3) *vs.* 12.1 (11.0–13.5) mm, P<0.001]. Univariate logistic regression analysis showed that the duration of infertility [odds ratio (OR) 1.09, 95% CI: 1.00–1.17, P=0.045], body mass index (BMI) (OR 1.12, 95% CI: 1.00–1.24, P=0.045) and ET on transfer day (OR 0.82, 95% CI: 0.75–0.91, P<0.001) were significantly correlated with CSP; multivariate logistic regression analysis showed the thinner ET on transfer day [adjusted odds ratio (aOR) 0.83, 95% CI: 0.76–0.93, P<0.001] and the bigger BMI

(aOR 1.12, 95% CI: 1.00–1.25, P=0.044) were independent risk factors for CSP during IVF-ET procedure (*Table 4*). The ROC curve (*Figure 3*) showed that ET of 12 mm is the cut-off value for predicting CSP.

Compared with eutopic pregnancies, patients with a

Table 2 The diagnostic value of TVS

TVS	Histological examination		Total
	+	−	
+	63	1	64
−	1	4,733	4,734
Total	64	4,734	4,798

Sensitivity: 63/64=98.44%; specificity: 4,733/4,734=99.98%; positive predictive value: 63/64=98.44%; negative predictive value: 4,733/4,734=99.98%. "+" indicates to a positive result; "−" indicates to a negative result. TVS, transvaginal sonography.

Table 3 Ultrasound findings at initial diagnosis

Ultrasound findings	n (%)
Gestational structure of CSP (n=63)	
Fetal pole (cardiac activity +)	26 (41.3)
Fetal pole (cardiac activity −)	2 (3.2)
Yolk sac only	25 (39.7)
Empty gestational sac	10 (15.9)
Gestational structure of IUP (n=17)	
Fetal pole (cardiac activity +)	7 (41.2)
Yolk sac only	9 (52.9)
Empty gestational sac	1 (5.9)
Other findings	
Pelvic fluid	25 (39.7)
Anechoic fluid	23 (36.5)
Ground glass appearance	2 (3.2)
Uterine cavity fluid	35 (55.6)

"+" indicates to a positive result; "−"indicates to a negative result. CSP, caesarean scar pregnancy; IUP, intrauterine pregnancy.
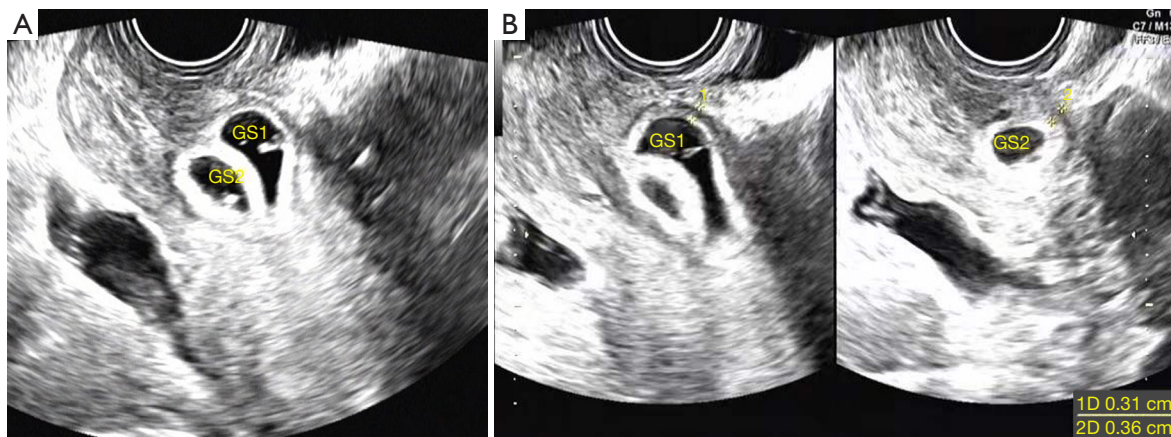

Figure 2 The transvaginal gray-scale ultrasound image at 28 days after embryo transfer. (A) GS1 and GS2 are shown at the caesarean section scar. (B) The thinnest myometrial layer thickness of the 2 gestational sacs at the location of the previous caesarean section scar is shown separately. GS, gestational sac.

Table 4 Comparison of characteristics and analysis of the risk factors for CSP

Characteristic	Eutopic pregnancy[†] (n=4,557)	CSP[†] (n=52)	P value	Univariate logistic regression		Multivariate logistic regression	
				OR (95% CI)	P value	aOR (95% CI)	P value
Maternal age (years)	34.0 (31.0–37.0)	34.5 (32.0–37.2)	0.105	1.06 (0.99–1.13)	0.088	1.03 (0.96–1.10)	0.420
Duration of infertility (years)	3.0 (2.0–5.0)	5.0 (3.0–7.0)	0.016*	1.09 (1.00–1.17)	0.045*	1.06 (0.97–1.15)	0.200
BMI (kg/m^2)	22.2 (20.6–23.8)	22.7 (20.8–24.7)	0.148	1.12 (1.00–1.24)	0.045*	1.12 (1.00–1.25)	0.044*
Transfer cycle (n)	1.0 (1.0–1.0)	1.0 (1.0–1.3)	0.911	0.94 (0.57–1.34)	0.770		
AFC (n)	17.0 (11.0–25.0)	16.0 (12.0–23.0)	0.398	0.98 (0.95–1.01)	0.210		
FSH (mIU/mL)	5.9 (5.0 –7.0)	5.8 (5.0–6.4)	0.466	0.94 (0.79–1.09)	0.480		
AMH (ng/mL)	3.6 (2.0–5.9)	3.5 (2.8–5.5)	0.616	0.97 (0.87–1.06)	0.490		
Cause of infertility			0.137				
Male factor	181 (4.0)	1 (1.9)		–			
Female factor	2,887 (63.4)	40 (76.9)		2.51 (0.54, 44.60)	0.360		
Combined factors	1,489 (32.7)	11 (21.2)		1.34 (0.26–24.50)	0.780		
Endometrial thickness (mm)	12.1 (11.0–13.5)	11.3 (10.2–12.2)	<0.001*	0.82 (0.75–0.91)	<0.001*	0.83 (0.76–0.93)	<0.001*
Type of embryo transfer			0.218				
Frozen embryo	2,450 (53.8)	23 (44.2)		–		–	
Fresh embryo	2,107 (46.2)	29 (55.8)		1.47 (0.85–2.57)	0.170	1.44 (0.77–2.69)	0.250
Number of embryos transferred			0.522				
1	1,999 (43.9)	20 (38.5)		0.80 (0.45–1.39)	0.440		
≥2	2,558 (56.1)	32 (61.5)					
Stage of embryo transferred			0.291				
Cleavage-stage embryo	1,903 (41.8)	26 (50.0)		–			
Blastocyst	2,654 (58.2)	26 (50.0)		0.72 (0.41–1.24)	0.230		

"n" refers to the number of cases, the number of cases of eutopic pregnancy is 4,557, and the number of cases of CSP is 52. [†], data are presented as 50th (25th–75th) or number (percentage). *, statistical difference. CSP, caesarean scar pregnancy; OR, odds ratio; CI, confidence interval; aOR, adjusted odds ratio; BMI, body mass index; AFC, antral follicle count; FSH, follicle-stimulating hormone; AMH, anti-Müllerian hormone.

HCSP had a higher proportion of fresh embryo transfer (77.4% *vs.* 46.2%, P=0.001), multiple ET (100.0% *vs.* 56.1%, P<0.001), and cleavage-stage embryos (83.9% *vs.* 41.8%, P<0.001). Univariate logistic regression analysis displayed that the fresh embryo transfer (OR 3.99, 95% CI: 1.81–10.00, P=0.001) and blastocyst transfer (OR 0.14 95% CI: 0.05–0.33, P<0.001) were significantly correlated with HCSP; multivariate logistic regression analysis indicated blastocyst transfer (aOR 0.19, 95% CI: 0.05–0.59, P=0.008) was an independent protective factor for HCSP (*Table 5*).

The pregnancy and obstetric outcomes regarding types

of FET protocols are displayed in Table S1. The AC was associated with a higher early miscarriage rate (23.9% *vs.* 17.4%, P=0.018) compared with NC, yet a lower live birth rate compared with either MNC (69.8% *vs.* 82.9%, P=0.032) or NC (69.8% *vs.* 78.0%, P=0.004).

Interventions and outcomes

The surgical methods and outcomes of the 63 patients are displayed in *Figure 4*. Among the 63 cases, 61 underwent hysteroscopy (including 17 with HCSP and 1 with twin
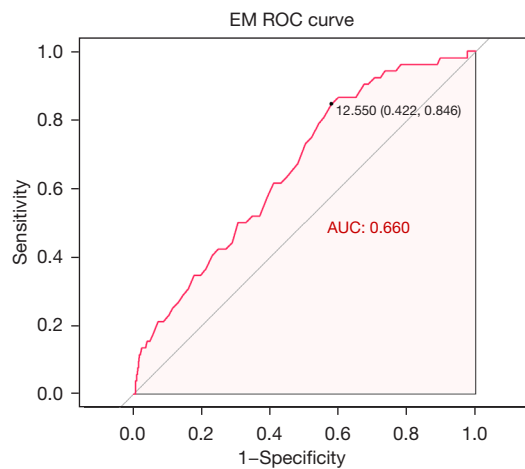
Figure 3 ROC curve showed the predictive values of EM for the risk of CSP. EM, endometrial thickness; AUC, area under the curve; ROC, receiver operating characteristic; CSP, cesarean scar pregnancy.

CSPs), 1 underwent laparoscopy to remove CSP after confirmed by MRI, and 1 was treated by laparotomy. The uterus was preserved in all patients and the IUPs of 2 patients were successfully born (*Figure 5*).

The missed case

A case of HCSP was missed on ultrasound examination. The patient was 31 years old and had undergone 1 previous CS. She had 2 frozen-thawed embryos transferred at the same time and the β-hCG on day 14 was 240 mIU/mL. After transfer, she only underwent 1 ultrasound examination in our hospital on day 28, which revealed twin IUPs, and there was no discomfort at that time. Due to uterine rupture in the 12th gestational week, she was subsequently confirmed to have HCSP during an emergency laparotomy.

Discussion

This study showed that TVS has high diagnostic value for CSP. The early and accurate diagnosis was important for timely clinical intervention, maintaining patients' fertility and avoiding severe complications. Thinner ET on transfer day and higher BMI were independent risk factors for CSP. Patients with an HCSP had a higher proportion of multiple ET and blastocyst transfer was an independent protective factor for HCSP.

In this large population of 75,438 women undergoing IVF-ET in our center, the vast majority of CSP (81.3%) were detected by the initial TVS scan, and the remaining 91.7% of CSPs were detected by subsequent scans, which indicates that the initial scan has high diagnostic value for CSP, and subsequent scans are essential to further improve diagnostic accuracy and reduce missed diagnosis.

The incidence of CSP after IVF-ET was about 1:909 in this research, which seemed slightly higher than the prevalence in the population of spontaneous conception (3,4), although it was consistent with the previous literature (3,18). Having a pregnancy normally located in the uterine cavity is an extraordinary concern during IVF procedures, and sonographers are more vigilant with those with a history of CS, thus, the heightened awareness of this condition could be a contributor. Additionally, the rising incidence of CSP might also be due to the relatively high CS rate and the liberalization of the 2-child policy in China, and that the increasing routine availability of TVS has improved the diagnostic accuracy in early pregnancy (5).

The diagnostic reliability of transabdominal sonography (TAS) was shown to be only 70% (25), thus high-resolution TVS is a first-line method for diagnosing CSP. All included patients in the present study were diagnosed by TVS during the first trimester. In addition, the real-time 3D TVS was able to demonstrate the GS in the anterior wall of the uterus with high certainty; it could enhance our diagnostic confidence. A case of uncertain CSP suspected by TVS in this research was verified by MRI, then an emergency laparoscopy was performed, which suggested that MRI could be used as an adjunct to ultrasound scanning when the ultrasound findings are inconclusive (26).

The vast majority of the CSPs in the present study were asymptomatic at diagnosis. Others presented with low abdominal pain and/or slight vaginal bleeding. Therefore, in patients with a previous CS, even if there are no symptoms, it should not be taken lightly and CSP still needs to be excluded (27). Additionally, EP could not be ruled out if only an intrauterine embryo was seen, especially when 2 embryos were transferred. In this study, thinner ET (11.5 *vs.* 12.1 mm) was found to be an independent risk factor for CSP, which indicated that clinicians should closely monitor the thickness of the endometrium before ET, and for patients with a relatively thin ET, they should be alert to the possibility of CSP. However, due to the limitations of this study design, the clinical significance still needs to be considered. Higher BMI was showed to be an independent risk factor in this study, suggesting that heavier patients should try to reduce their BMI to a normal

Table 5 Comparison of characteristics and analysis of the risk factors for HCSP

Characteristic	Eutopic pregnancy[†] (n=4,557)	HCSP[†] (n=31)	P value	Univariate logistic regression		Multivariate logistic regression	
				OR (95% CI)	P value	aOR (95% CI)	P value
Maternal age (years)	34.0 (31.0–37.0)	34.0 (31.0–36.0)	0.575	0.97 (0.89–1.06)	0.540		
Duration of infertility (years)	3.0 (2.0–5.0)	3.0 (2.0–6.0)	0.775	1.02 (0.90–1.14)	0.720		
BMI (kg/m^2)	22.2 (20.6–23.8)	22.1 (20.7–23.5)	0.464	0.93 (0.79–1.08)	0.340		
Transfer cycle (n)	1.0 (1.0–1.0)	1.0 (1.0–1.0)	0.319	0.78 (0.35–1.33)	0.460		
AFC (n)	17.0 (11.0–25.0)	15.0 (11.8–24.5)	0.486	0.99 (0.95–1.02)	0.620		
FSH (mIU/mL)	5.9 (5.0–7.0)	5.4 (4.9–6.1)	0.090	0.80 (0.60–1.02)	0.100	0.80 (0.60–1.02)	0.093
AMH (ng/mL)	3.6 (2.0–5.9)	4.8 (2.5–6.0)	0.312	1.03 (0.91–1.13)	0.640		
Cause of infertility			0.499				
Male factor	181 (4.0%)	1 (3.2%)		–			
Female factor	2,887 (63.4%)	17 (54.8%)		1.07 (0.22–19.30)	0.950		
Combined factors	1,489 (32.7%)	13 (41.9%)		1.58 (0.31–28.80)	0.660		
Endometrial thickness (mm)	12.1 (11.0–13.5)	12.2 (10.8–13.1)	0.582	0.98 (0.84–1.16)	0.790		
Type of embryo transfer			0.001*				
Frozen embryo	2,450 (53.8%)	7 (22.6%)		–		–	
Fresh embryo	2,107 (46.2%)	24 (77.4%)		3.99 (1.81–10.00)	0.001*	1.61 (0.56–5.66)	0.410
Number of embryos transferred			<0.001*				
1	1,999 (43.9%)	0 (0.0%)		0.00 (0.00–25,279,171.00)	0.980		
≥2	2,558 (56.1%)	31 (100.0%)		–			
Stage of embryo transferred			<0.001*				
Cleavage-stage embryo	1,903 (41.8%)	26 (83.9%)		–		–	
Blastocyst	2,654 (58.2%)	5 (16.1%)		0.14 (0.05–0.33)	<0.001*	0.19 (0.05–0.59)	0.008*

"n" refers to the number of cases, the number of cases of eutopic pregnancy is 4,557, and the number of cases of HCSP is 31. [†], data are presented as 50th (25th–75th) or number (percentage). *, statistical difference. HCSP, heterotopic caesarean scar pregnancy; OR, odds ratio; CI, confidence Interval; aOR, adjusted odds ratio; BMI, body mass index; AFC, antral follicle count; FSH, follicle-stimulating hormone; AMH, anti-Müllerian hormone.

range before entering the IVF procedure. NC treatment was associated with a higher chance of live birth and a lower possibility of early miscarriage, which was consistent with previous studies (28,29). During the IVF procedure, 2 or more embryos are sometimes transferred, which may lead to a higher risk of HCSP. We speculate that single embryo transfer may contribute to the reduction of HCSP occurrence, but whether it also reduces CSP occurrence needs further study (30).

We missed an HCSP and treated it as an intrauterine twin pregnancy in this study. After transfer, the patient only had 1 TVS scan in our hospital and then went back to her hometown without further follow-up examination. When we retrospectively analyzed the examination images, we found that the GS was near to the CS, but due to the lack of subsequent examinations, we have not further clarified its location. Although a single TVS can diagnose the vast majority of CSP, there are still a small number of missed and misdiagnosed cases, and follow-up examinations can greatly reduce such situations. Therefore, it is necessary to
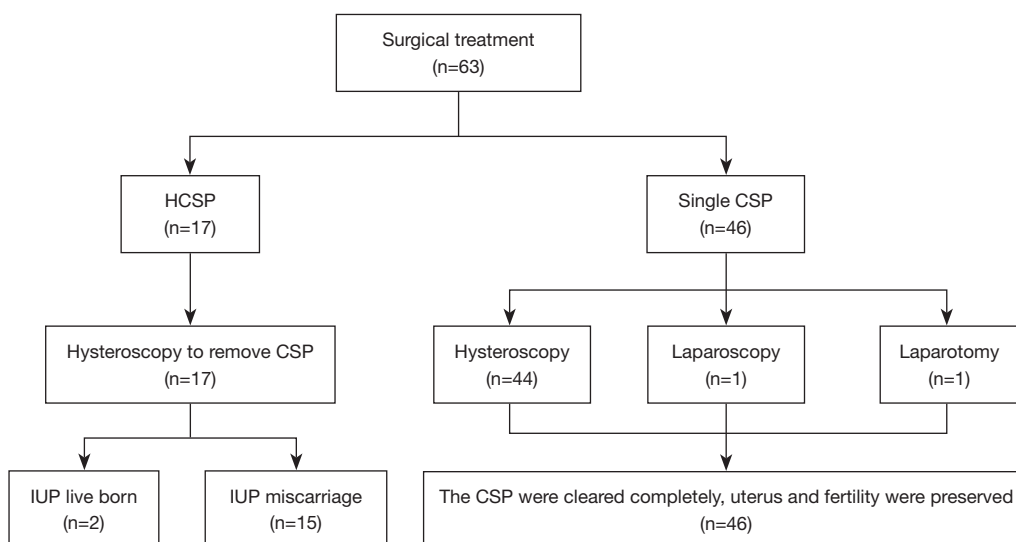
Figure 4 Surgical methods and outcomes in 63 patients with CSP. HCSP, heterotopic cesarean scar pregnancy; CSP, cesarean scar pregnancy; IUP, intrauterine pregnancy.
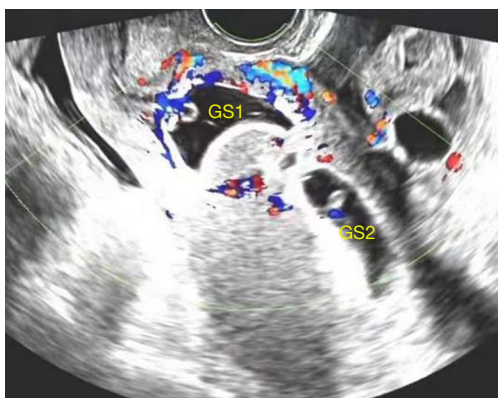

Figure 5 Transvaginal color Doppler ultrasound showing a live cesarean scar pregnancy (GS1) surrounded with abundant blood flow and a coexisting live intrauterine pregnancy (GS2) at 28 days after embryo transfer. GS, gestational sac.

conduct routine follow-up examinations for patients after transfer.

Our study had several strengths. All patients' early pregnancy ultrasound examinations were performed in our center as a routine protocol, and all sonographers were well-trained and followed the same examination procedures and diagnostic standards. Some limitations in this study included the retrospective design and unsatisfactory sample size due to the rarity of this condition. The proportion of multiple ET in HCSP patients was significantly higher than in eutopic patients at the univariate test, but logistic regression analyses did not show obvious significance, which may be due to the small sample size. A prospective study with a larger sample is needed in future. Additionally, we are an assisted reproductive center without an obstetrics department, some patients were referred to other hospitals for treatment, and could only be followed up by telephone or fax, which might have led to partial deviation of the results. The medical records about whether the patient's previous CS was medically induced or elective surgery were not complete, which was another limitation of this study. It is worth noting that because this retrospective study was conducted in a single center and the sample size was limited, the generalization of the results of this study needs to be further verified.

Conclusions

CSP is one of the rarest types of EP for which early and accurate diagnosis is crucial. First trimester TVS performed by an experienced sonographer has a high sensitivity for making the correct diagnosis of CSP after IVF-ET, which was helpful for early clinical intervention and avoiding severe complications. Doctors should be alert to the possibility of this condition for patients with a thinner ET and a higher BMI. Single blastocyst transfer is recommended to reduce the likelihood of HCSP. The clinical significance of this study still needs to be considered.

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Acknowledgments

Footnote

Reporting Checklist: The authors have completed the STARD reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-1239/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1239/coif). All authors report the funding from the Research Grant of CITIC-Xiangya (Nos. YNXM-202220 and YNXM-202310) and Hunan Provincial Grant for Innovative Province Construction (No. 2019SK4012). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of the Reproductive and Genetic Hospital of CITIC-Xiangya (No. LL-SC-2019-015). The Ethics Committee waived the need for informed consent due to the retrospective study design.

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