Risk Factors Associated With Failure of Initial Treatment for Cesarean Scar Pregnancy

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Title page

Risk factors associated with failure of initial treatment for cesarean scar pregnancy

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Abstract

This study aimed to provide reference for CSP treatment. It's a cohort study. Ultrasound-guided evacuation, hysteroscopy-guided evacuation and uterine artery embolization were used during the initial treatment. The treatment methods failed in 77 of the CSP patients (study group). 1560 of the CSP patients were treated successfully (control group). Multivariate logistic regression analysis found that in model 1, distance between gestational sac and serosal layer (OR: 0.04, 95%CI: 0.00–0.82, p= 0.037) and fetal heartbeat (OR: 8.91, 95%CI: 3.81–20.81, p= 0.000) are risk factors for CSP initial treatment failure. Model 2 showed that gestational age (OR: 0.96, 95%CI: 0.92–1.00, p= 0.043) and fetal heartbeat (OR: 2.15, 95%CI: 1.02–4.52, p= 0.000) are the risk factors. Model 3 indicated that mean sac diameter (OR: 1.56, 95%CI: 1.21–2.01, p= 0.001), fetal heartbeat (OR: 4.75, 95%CI: 2.23–10.14, p= 0.000) and pretreated with UAE (OR: 5.05, 95%CI: 2.36–10.83, p= 0.000) are risk factors. In model 4, fetal heartbeat (OR: 2.87, 95%CI: 1.28–6.42, p= 0.010) and pretreated with UAE (OR: 4.24, 95%CI: 1.98–9.07, p= 0.000) are the risk factors. In conclusion, for CSP patients with different treatment, if the relevant risk factors exist, it should be more cautious.

Keywords: Cesarean scar pregnancy; Risk factors; Evacuation; Uterine artery embolization

Introduction

Cesarean scar pregnancy (CSP) refers to the pregnancy occurring at the original cesarean section scar in the lower part of the uterus[1]. Due to Chinese unique high cesarean section rate and the implementation of the second-child policy, the incidence of CSP among women of childbearing age in China has increased significantly[2]. Due to the high risk of CSP for massive vaginal bleeding and uterine rupture, once the diagnosis is confirmed, it is often recommended to terminate it[3]. The CSP treatment methods used now are mainly surgical treatment which includes uterine evacuation under ultrasound or hysteroscopy surveillance, uterine artery embolization (UAE) combined with evacuation (under ultrasound or hysteroscopy surveillance), MTX combined with UAE and evacuation, and excision of scar pregnancy lesions. So far, there is no uniform standard for the treatment of CSP[4].

Each of the approach has its own advantages and disadvantages. In fact, a patient with CSP may have poor treatment result with any treatment method. The poor treatment results include that the serum β-HCG drops unsatisfactorily or even rises after the surgery, the ultrasound examination found persistently exit mass in the follow-up or vaginal bleeding (>500ml) after discharge occurs. The patients need to be admitted to the hospital for treatment again. In recent years, some reports revealed that CSP patients failed to be treated with different methods[5].

This study collected the data of 1637 CSP patients admitted to a hospital in the past four years. It analyzed the risk factors of CSP initial treatment failure, and aimed to provide reference for treatment of CSP.

Results

1. Treatment methods and outcomes in study group and control group

The treatment methods used in the study group and the control group are shown in Table 1.

Table 1 Treatment methods of study group and control group

	Study group (n=77)	Control group (n=1560)
ultrasound-guided evacuation	19	706
ultrasound-guided evacuation +UAE	26	202
Hysteroscopy-guided evacuation	15	485
Hysteroscopy-guided evacuation +UAE	17	167

In the study group, 19 patients underwent ultrasound-guided evacuation. 26 patients underwent ultrasound-guided evacuation pretreated with UAE. 15 patients underwent Hysteroscopy-guided evacuation, and 17 patients underwent hysteroscopy-guided evacuation UAE pretreated with UAE.

After the initial treatment, 31 patients were re-admitted to the hospital due to postoperative vaginal bleeding >500mL or sudden increase in vaginal bleeding, 2 patients also had lower abdominal pain, and 5 patients combined with elevated serum β-HCG. Two patients re-admitted due to lower abdominal pain alone. 17 patients were re-admitted to the hospital for elevated serum β-HCG (>5.3IU/L). 20 patients were re-admitted because of the increased mass. After re-treatment, the vaginal bleeding of the patients and the serum β-HCG decreased to normal level (<5.3IU/L) in the study group gradually. Ultrasound images indicated that the mass was reduced. No further treatment was required.

For the 1560 patients in the control group, 706 patients underwent ultrasound-guided evacuation. 202 patients underwent ultrasound-guided evacuation pretreated with UAE. 458 patients underwent hysteroscopy-guided evacuation, and 167 patients underwent hysteroscopy-guided evacuation UAE pretreated with UAE.

2. Clinical characteristics of patients, and comparisons between study group and control group in different models.

Table 2 showed the characteristics of CSP patients in different models. Various clinical parameters in CSP patients were compared between study group and control group. Model 1 shows that, in study group, age is statistically younger (p=0.036), gestational age is longer (p=0.045), mean sac diameter is significantly larger (p=0.001) , initial serum β-hCG level is higher (p=0.011), distance between gestational sac and serosal

layer is smaller (p=0.035), intraoperative bleeding (p=0.004) is more than those in the control group . Also, the fetal heartbeat presence rate in the study group is significantly higher than that in the control group (p=0.000).

In model 2, fetal heartbeat is the only significant different indicator between study group and control group (p=0.019).

In model 3, it showed that, in study group, age is significantly younger (p=0.048), gestational age is longer (p=0.004), mean sac diameter is significantly larger (p=0.000), initial serum β-hCG level is higher (p=0.000), distance between gestational sac and serosal layer is smaller(p=0.001), intraoperative bleeding (0.000) is more than those in the control group. Also, in the study group, the proportion of patients with CSP II type is higher (p=0.033). The fetal heartbeat rate in the study group is significantly higher than that in the control group (p=0.000).

Model 4 shows that, compared with control group, gestational age is shorter (p=0.045), mean sac diameter is significantly larger (p=0.001), initial serum β-hCG is higher(p=0.011) and distance between gestational sac and serosal layer is smaller (p=0.035) in study group. The fetal heartbeat presence rate in the study group is significantly higher than that in the control group(p=0.00). The UAE pretreatment rate in the study group is higher than that in the control group(p=0.004).

Table 2 Clinical characteristic among women with CSP

	Model 1		Model 2		Model 3		Model 4	
	Study group (N=43)	Control group (N=369)	Study group (N=34)	Control group (N=1191)	Study group (N=43)	Control group (N=369)	Study group (N=43)	Control group (N=369)
Age, y	32(28-36) *	33(30-37)	32.5(30-37.25)	34(31-38)	32(29.5-37) *	34(31-38)	33(29.25-36)	34(30-37)
Gravity	4(3-5)	4(3-5)	4(3-5)	4(3-5)	4(3-5)	4(4-5)	4(4-6)	4(3-5)
Parity	1(1-2)	1(1-2)	1(1-2)	1(1-2)	1(1-1)	1(1-2)	1(1-2)	1(1-2)
Previous uterine curettages	1(1-2)	1(1-2)	1(1-1)	1(1-2)	1(1-1)	1(1-2)	1(1-2)	1(1-2)
Time since the last cesarean section, y	6(2-9)	6(3-9)	7(4.75-9.25)	6(4-9)	6(3-9)	6(3-9)	6(3-9.75)	6(3-9)
Gestational age, d	52(42-68) *	47(41-57)	45.5(39-50.5)	47(41-54)	51(44-67.5) *	46(41-53)	44(40-51.25) *	48(42-57)
Mean sac diameter, cm	3.4(2.5-4.9) *	2.6(1.8-3.8)	2.6(1.6-3.9)	2.4(1.6-3.5)	3.5(2.5-5.1) *	2.2(1.5-3.1)	2.45(1.6-3.7)	2.9(1.9-4.2)
Initial serum β-hCG, IU/L	43024(18936-62532) *	29295 (12354-56053)	26758.5(13977.5-70235)	24484(9523-53575)	43122(16130-66610.5) *	19885(7572-41984)	36982(14863-69678)	36096(14989.5-68273)
Distance between gestational sac and serosal layer, cm	0.16(0.09-0.23) *	0.20(0.13-0.30)	0.2(0.13-0.31)	0.24(0.16-0.40)	0.2(0.13-0.3) *	0.27(0.19-0.43)	0.15(0.1-0.2)	0.18(0.12-0.28)
Subtype					*			
I	6(13.95%)	42(11.38%)	8(23.53%)	374(31.40%)	9(20.00%)	322(35.46%)	5(15.63%)	94(14.42%)
II	37(86.05%)	327(88.62%)	26(76.47%)	817(68.60)	36(80.00%)	586(64.53%)	27(84.38%)	558(85.58%)
Fetal heartbeat	19(55.84%) *	41(23.65%)	12(35.29%)*	228(19.14%)	19(42.22%) *	127(13.99%)	12(37.50%) *	154(23.62%)
UAE pretreatment					26(57.78%) *	202(22.22%)	17(53.13%) *	167(25.61%)
Treatment approach								
ultrasound-guided evacuation	26(60.47%)	202(54.74%)	19(55.88%)	706(59.28%)				
hysteroscopy-guided evacuation	17(39.53%)	167(45.26%)	15(44.12%)	485(40.72%)				
Intraoperative bleeding, mL	25(10-100) *	20(10-30)	10(8.75-30)	10(5-20))	100(30-280) *	20(10-50)	10(10-30)	10(10-20)

* Compared with the control group, the characteristic in study group is significantly different. ($p<0.05$)

3. Multiple logistic regression analysis of the association between CSP initial treatment failure and other factors.

Multiple logistic regression analysis was employed to examine whether age, gravity, parity, previous uterine curettages, time since the last cesarean section, gestational age, mean sac diameter, initial serum β-hCG, distance between gestational sac and serosal layer, CSP subtype, fetal heartbeat, UAE pretreatment, treatment approach and intraoperative bleeding (Table3).

Model1, in which patients all pre-treated with UAE, demonstrated that distance between gestational sac and serosal layer (OR: 0.04, 95%CI: 0.00–0.82, p= 0.037) and fetal heartbeat (OR: 8.91, 95%CI: 3.81–20.81, p= 0.000) significantly associated with the presence of the initial treatment failure. Figure1A showed the ROC curves using distance between gestational sac and serosal layer to predict initial treatment failure. The area under the distance between gestational sac and serosal layer curve was 0.402 (p=0.036, CI:0.31-0.50) and the optimal cutoff was 0.11 cm with sensitivity of 0.628 and specificity of 0.190.

In model 2, all the patients were not pre-treated with UAE. It was found that gestational age (OR: 0.96, 95%CI: 0.92–1.00, p= 0.043) and fetal heartbeat (OR: 2.15, 95%CI: 1.02–4.52, p= 0.000) are significantly associated with the presence of initial treatment failure. Figure1B showed the ROC curves using gestational age to predict initial treatment failure. The area under the curve was 0.438 (p=0.220, CI:0.34-0.54) and the optimal cutoff was 39.5 days with sensitivity of 0.706 and specificity of 0.160.

Model 3, which patients all treated with ultrasound-guided evacuation, showed that mean sac diameter (OR: 1.56, 95%CI: 1.21–2.01, p= 0.001), fetal heartbeat (OR: 4.75, 95%CI: 2.23–10.14, p= 0.000) and pretreated with UAE (OR: 5.05, 95%CI: 2.36–10.83, p= 0.000) are associated with the presence of initial treatment failure. Figure1C showed the ROC curves using mean sac diameter to predict initial treatment failure. The area under the curve was 0.748 (p=0.000, CI:0.68-0.82) and the optimal cutoff was 2.85cm with sensitivity of 0.69 and specificity of 0.68.

In model 4, all patients were treated with hysteroscopy-guided evacuation. The results showed that fetal heartbeat (OR: 2.87, 95%CI: 1.28–6.42, p= 0.010) and pretreated with UAE (OR: 4.24, 95%CI: 1.98–9.07, p= 0.000) are associated with the presence of initial treatment failure.

Figure 1

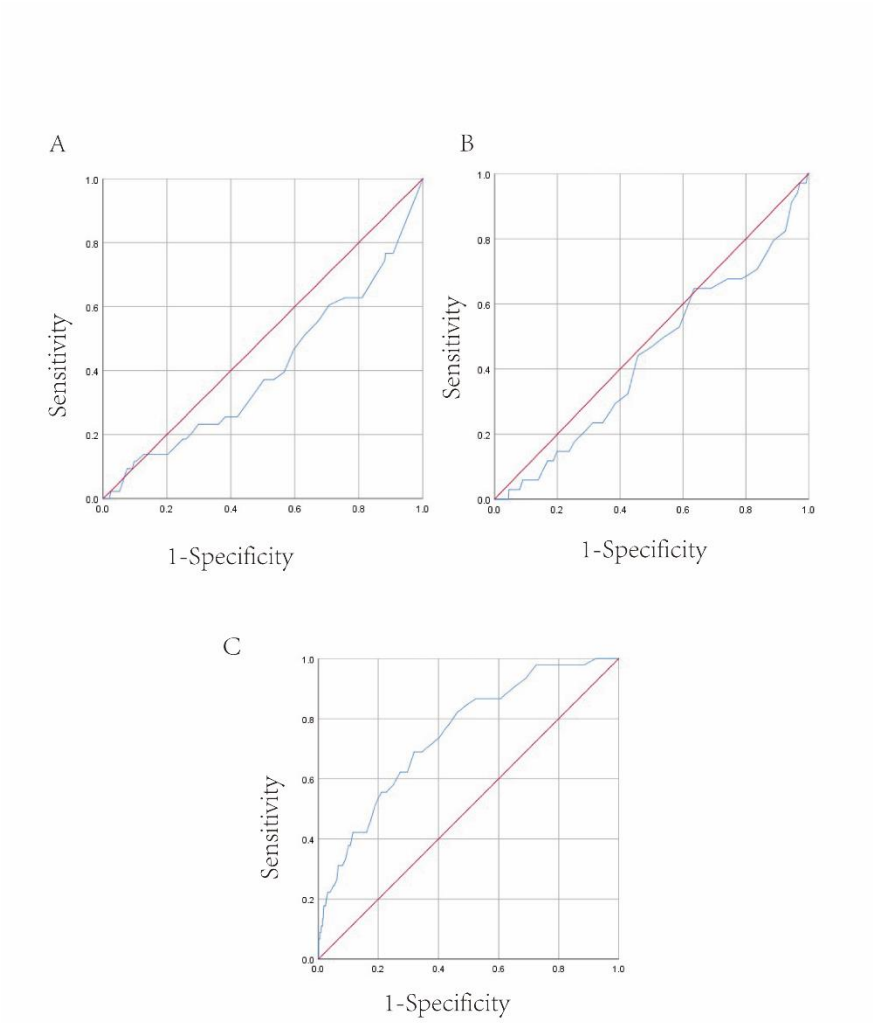

Table 3 Multivariate logistic regression analysis for risk factors of CSP initial treatment failure

	Model 1			Model 2			Model 3			Model 4		
	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value	OR	95%CI	P value
Age, y	0.93	0.84-1.03	0.149	0.95	0.87-1.04	0.235	0.94	0.86-1.04	0.215	0.94	0.86-1.02	0.149
Gravity	1.20	0.90-1.59	0.220	0.94	0.71-1.23	0.640	0.89	0.68-1.17	0.404	1.14	0.86-1.51	0.378
Parity	0.44	0.07-2.75	0.346	1.64	0.52-5.19	0.404	0.50	0.09-2.84	0.434	1.54	0.47-5.03	0.477
Previous uterine currettages	0.74	0.12-4.74	0.747	0.46	0.12-1.69	0.241	0.76	0.13-4.24	0.750	0.43	0.11-1.64	0.218
Time since the last cesarean section, y	0.90	0.79-1.04	0.150	1.04	0.93-1.17	0.471	0.97	0.86-1.11	0.675	1.02	0.90-1.15	0.795
Gestational age, d	1.02	0.99-1.04	0.296	0.96	0.92-1.00	0.043	1.00	0.98-1.03	0.896	0.98	0.94-1.02	0.251
Mean sac diameter, cm	1.19	0.90-1.57	0.235	1.08	0.81-1.44	0.615	1.56	1.21-2.01	0.001	0.71	0.48-1.06	0.093
Initial serum β-hCG, IU/L	1.00	1.00-1.00	0.477	1.00	1.00-1.00	0.301	1.00	1.00-1.00	0.291	1.00	1.00-1.00	0.732
Distance between gestational sac and serosal layer, cm	0.04	0.00-0.82	0.037	0.13	0.01-1.21	0.073	0.13	0.02-1.00	0.051	0.11	0.01-2.10	0.142
Subtype	0.29	0.09-0.95	0.061	0.75	0.29-1.97	0.559	0.54	0.20-1.42	0.209	0.48	0.15-1.52	0.212
Fetal heartbeat	8.91	3.81-20.81	0.000	2.15	1.02-4.52	0.045	4.75	2.23-10.14	0.000	2.87	1.28-6.42	0.010
UAE pretreatment							5.05	2.36-10.83	0.000	4.24	1.98-9.07	0.000
Treatment approach	0.49	0.22-1.08	0.075	0.81	0.38-1.70	0.569						
Intraoperative bleeding, mL	1.00	1.00-1.01	0.130	1.00	1.00-1.01	0.658	1.00	1.00-1.01	0.147	1.00	1.00-1.01	0.677

Discussion

In this study, a multivariate regression analysis found that, for patients pre-treated with UAE, smaller distance between gestational sac and serosal layer, with fetal heart beat are two risk factors for CSP initial treatment failure. In patients not pretreated with UAE, smaller gestational age and with fetal heart beat are risk factors for CSP initial treatment failure. For patients treated by ultrasound-guided evacuation, it showed that larger mean sac diameter, with fetal heartbeat and pretreated with UAE are risk factors for CSP initial failure. For patients treated by hysteroscopy-guided evacuation, with fetal heartbeat and pretreated with UAE are risk factors.

In recent years, the risk factors of CSP treatment failure have become a hot topic. It is reported that when the thickness of the uterine scar is ≥3mm, the use of hysteroscopic surgery can achieve a better treatment effect[6]. Our research shows that if the patient chooses UAE pretreatment before the surgery, distance between gestational sac and serosal layer <0.11cm is more likely to fail in treatment. This result is in line with previous studies. Also, this study revealed that the presence of fetal heartbeat is a risk factor for CSP treatment failure in all situations. Fetal heartbeat may mean a greater gestational age, higher serum β-HCG level, and rich blood flow around the gestational sac.

A retrospective analysis showed that mass diameter ≥ 4cm is an independent risk factor for CSP initial treatment (uterine evacuation and MTX treatment) failure [7]. In a meta-analysis of 3101 patients with CSP, it was found that big diameter of gestation sac, long gestational age, high β-HCG and rich blood flow around the lesion are risk factors for massive bleeding[8]. This study revealed that, for patients treated with ultrasound-guided evacuation, mean sac diameter >2.85cm, the treatment is more likely to fail. A study reported that as the gestational age increases, the difficulty of treatment increases[9]. For patients not pre-treated with UAE, the small gestational age is a risk factor for treatment failure. This result is inconsistent with previous studies, but the OR value of 0.96 indicates that the reduction of the gestational age does not have a great influence on the failure of the treatment.

To reduce the risk of massive intraoperative bleeding, UAE pretreatment is used

for some CSP patients before surgery. UAE is a minimally invasive procedure, initially used for conservative treatment of abnormal postpartum hemorrhage and uterine fibroids [10, 11]. It plays an important role in the prevention and control of severe life-threatening bleeding and protecting the fertility of patients[12]. For patients with a higher risk of bleeding, UAE is performed before the operation[13]. It is reported that UAE combined with other surgical methods can effectively reduce the amount of intraoperative blood loss and reduce the possibility of treatment failure[14]. In this study, it was completely contrary to previous studies. This may for that in the selection of treatment methods for CSP patients, clinicians performed UAE pretreatment based on diagnosis and treatment experience. The patients pretreated with UAE usually have a higher possibility of massive intraoperative bleeding. Thus, further research is needed.

There are various treatment methods for CSP. Each of them has its own advantages and disadvantages. Among them, ultrasound-guided evacuation and hysteroscopy-guided evacuation are widely used in the treatment of CSP. Our research found that these two treatment methods have no significant difference in the initial treatment failure. However, some studies reported that hysteroscopic surgery is more likely to completely remove pregnancy tissue due to its direct vision. Compared with ultrasound-guided evacuation, the vaginal bleeding time and postoperative bleeding time, time for serum β-HCG dropping to normal after operation is shorter, the safety and effectiveness are better. This is different from the results of our study. The reason may be for that this study the grouping of treatment methods is not completely random for the consideration of the patient's medical history, clinical imaging examination results and informed choice. And it may also be related to the experience of surgeons and radiologists.

The limitation of the present study is not completely random. Because CSP has a great risk of massive intraoperative bleeding and uterine rupture, it is clinically very cautious in its treatment. There are few randomized controlled trials on the treatment of CSP. In this case, it is not appropriate to analyze the risk factors of treatment failure for all patients. This study cannot be used to compare which treatment has a higher success rate, because the method has been evaluated when the patient chooses the

surgical method. For this reason, the authors analyzed the risk factors for CSP initial treatment failure under different models. According to our current knowledge, this is the first time someone has made such an attempt. Another thing worth noting is that with the passage of time, the surgeon's operating experience and diagnostic experience continue to accumulate, and the diagnosis and operation on a patient are also improved. This study didn't list the time as a possible risk factor.

In conclusions, for CSP patients with different treatment, if the relevant risk factors exist, it should be more cautious and a safer methods should be considered when necessary.

Methods

1.Subjects

From January 2016 to December 2019, there were 1637 cases of CSP patients who were hospitalized in the Women's Hospital, Zhejiang University School of Medicine involving in this study. It was approved by the ethics committee of the Women's Hospital, Zhejiang University School of Medicine (ID:2019052)., and all patients signed informed consent. All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The inclusion criteria of the study subjects: (1) Patients were ≥20 years old; (2) Vital signs were stable at admission; (3) CSP diagnostic criteria was met; (4) Complete medical record information and imaging data can be obtained. (5) Postoperative pathological diagnosis showed early placental tissue.

The criteria for diagnosis of CSP is that the ultrasound examination shows an empty uterus and cervical canal, a gestational sac in the lower segment of the anterior corpus with a diminished myometrium between the bladder and the sac, and prominent blood flow around the gestational mass. [15]

The exclusion criteria were: 1) patients with severe internal and external diseases; 2) patients with abnormal coagulation and pelvic inflammatory disease; 3) not the initial treatment; 4) clinical data incomplete.

If the patient met the inclusion criteria at the time of admission, she would be included

in the study. A total of 1637 patients met the inclusion criteria. Treatment methods were failed in 77 patients. They needed to be hospitalized again and were included as the study group.

Criteria for failure of initial treatment: After the initial treatment, CSP patients needed other measures or reoperation in the following situations: (1) Massive bleeding (From intraoperative to 2 hours after operation, bleeding > 500 ml; vaginal bleeding suddenly increases, which is more than twice the usual menstrual volume postoperation). (2) The patients had persisting postoperative serum β-HCG (Serum β-hCG was measured for 4 consecutive times and it was in a plateau state (±10%), or the weekly decrease rate is less than 15%); (3) Ultrasound examination revealed a persistently exiting mass at the cesarean section scar.

A total of 1560 patients who were successfully treated were included as the control group.

Criteria for the success of initial treatment: the pregnancy tissue is completely removed, β-hCG returns to normal levels (<5.3IU/L), and no further treatment is required.

2.Criteria for CSP classification by ultrasound [16]:

Type I (endogenic): CSP with progression to the cervico-isthmic space or uterine cavity.

Type II (exogenic): CSP with deep invasion of caesarean scar defect with progression toward the bladder and abdominal cavity.

3. treatment methods

The primary surgical methods include ultrasound-guided evacuation, hysteroscopy-guided evacuation. Some patients were pretreated with UAE before surgery. The choice of surgical method is according to the ‘2016 Expert consensus on the diagnosis and treatment of uterine scar pregnancy (China)’ and informed choice.

3.1 Ultrasound-guided evacuation: under the guidance of ultrasound, the gestational tissue was removed through suction curettage.

3.2 Hysteroscopy-guided evacuation: the uterus was dilated with 5% glucose solution (Glucose, GS). the pregnancy tissue in the scar diverticulum was removed with ring electrodes. The hysteroscope was placed again to observe that whether there was no obvious residue in the diverticula of the isthmus.

3.3 UAE: A modified Seldinger technique is used to puncture the needle. Insert the 5-Fcobra catheter after inserting the catheter sheath. After confirming the route of the bilateral uterine arteries, the bilateral uterine arteries were embolized with gelatin sponge embolization particles (Hangzhou Alikang Company, 560-710um).

According to the use of different methods, four models were built. In model 1, all patients used UAE. In model 2, no patient used UAE. In model 3, all patients used ultrasound-guided evacuation. In model 4, all patients underwent hysteroscopy-guided evacuation.

4. Follow-up

The serum β-HCG was checked once a week until it fell to the normal range. Ultrasound examination was checked 24 hours, 2 weeks, 4 weeks, and 1 month after the operation until the mass disappeared.

5. Statistical analysis

Statistical analysis is performed by SPSS 23.0 software. If the data confirms to be the normal distribution and the variance is uniform, the result is expressed as the mean ± standard deviation, and the t test is used. Otherwise, a non-parametric test is used, and the results are expressed as median (25th-75th percentile) value. The comparison between the count data uses the chi-square test (χ^2 Test), and then the results are expressed in the number of cases and percentages. Multiple logistic regression analysis was performed to examine the influence of the following variables on failure of CSP treatment: age, gravity, parity, previous uterine curettages, time since the last cesarean section, gestational age, mean sac diameter, initial serum β-hCG, distance between gestational sac and serosal layer, CSP subtype, fetal heartbeat, UAE pretreatment, treatment approach and intraoperative bleeding. The odds ratios with 95% CIs, were calculated. $P<0.05$ was considered statistically significant. All the tests were two-tailed.

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Availability of data: The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Figure legend

Figure1 ROC curves of different indicators in CSP. A. ROC curves of distance between gestational sac and serosal layer in model 1. B. ROC curves of gestational age in model 2. C. ROC curves of mean sac diameter in model 3.

Figures

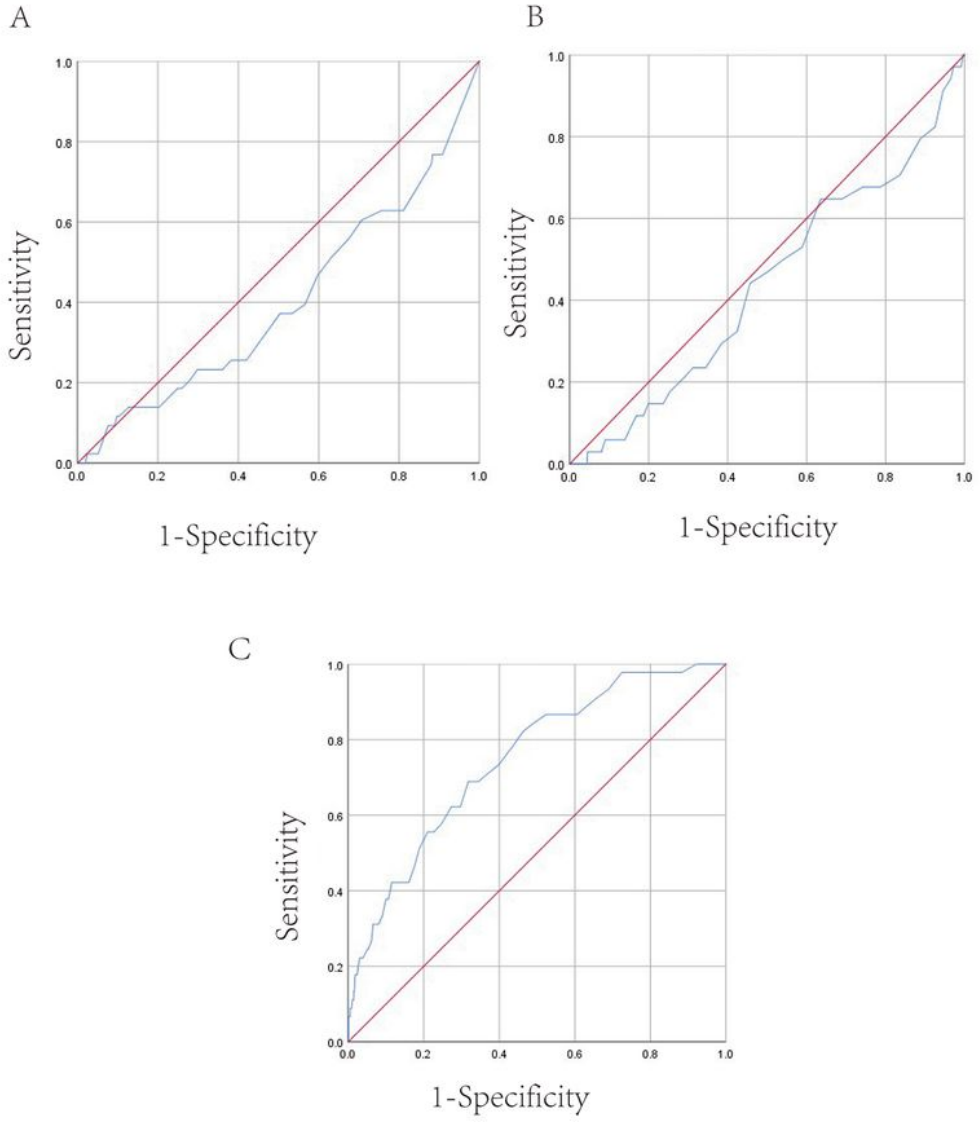

Figure 1

ROC curves of different indicators in CSP. A. ROC curves of distance between gestational sac and serosal layer in model 1. B. ROC curves of gestational age in model 2. C. ROC curves of mean sac diameter in model 3.