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Analysis of risk factors for intraoperative hemorrhage of cesarean scar pregnancy

Yan Ma, MD[a], Minfang Shao, MD[b], Xiaonan Shao, MD[c,*]

Abstract

The current commonly used treatments for cesarean scar pregnancy (CSP) include multiple treatments such as medication, uterine artery embolization, curettage and surgery, and their combinations. However, every treatment option has risks of excessive hemorrhage from uterus. In this study, we retrospectively analyzed the risk factors for intraoperative hemorrhage of different treatments for CSP patients, with the hope to provide the guidance for CSP treatment.

Fifty-eight cases of CSP patients who were treated with curettage after medication, curettage after uterine artery embolization, or surgery were retrospectively analyzed and compared for the clinical efficacy, length of hospital stay, and hemorrhage rate. Further, they were divided into the bleeding group (≥200 mL, 15 cases) and the control group (<200 mL, 43 cases). The hemorrhage-related risk factors were subjected to univariate analysis, including age, pregnant times, delivery times, abortion times or curettage times, the time from last cesarean section, menolipsis time, serum human chorionic gonadotropin level, ultrasound typing, maximum diameter of gestational sac or mass under ultrasound, peritrophoblastic blood flow around the mass, and the distance of gestational sac or mass from the uterine serosa layer. The significant indexes in univariate analysis were further analyzed using both receiver operating characteristic (ROC) analysis and multivariate logistic regression analysis.

The success rate, length of hospital stay, and hemorrhage rate were not significantly different among the 3 treatment groups ($P > .05$). Univariate analysis found that patients in the bleeding group had significantly longer menolipsis time and greater maximum diameter than patients in the control group ($P < .05$). ROC analysis showed that the optimal cutoff for menolipsis time and maximum diameter were 51 days and 27 mm, respectively, and the areas under their corresponding ROC were 0.680 and 0.787, respectively. Multivariate analysis showed that only the maximum diameter in the retrospective equation was of significance ($P < .05$, odds ratio: 1.067, 95% confidence interval: 1.014~1.123].

All treatments have high success rates and no significant effects on intraoperative bleeding. Both menolipsis time and maximum diameter can be used to predict the risk of intraoperative bleeding, and the latter have a greater predictive value.

Abbreviations: CSP = cesarean scar pregnancy, MTX = methotrexate, TVS = transvaginal sonography, UAE = uterine artery embolization.

Keywords: cesarean scar pregnancy, hemorrhage, risk factors, uterine artery embolization, uterine curettage

1. Introduction

The cesarean scar pregnancy (CSP) is an ectopic pregnancy of a fertilized egg implanting on the previous cesarean scar. Since CSP case was first reported in 1978,[1] its incidence incessantly increases with the cesarean section rate rising. CSP incidence is estimated at 1: 1800 to 1: 2216 pregnancies. In addition, CSP incidence is as high as 0.15% in women with cesarean history, accounting for 6.1% of ectopic pregnancy.[2,3] The latest data indicate that CSP incidence is in the range of 1:2500 to 1:8000.[4]

At present, there is no universal management guideline for CSP treatment worldwide.[5] The main aim of the clinical management for CSP is to achieve early diagnosis and provide single or combined medical and surgical treatments so as to avoid uterine rupture and hemorrhage, thus preserving the uterus and fertility, and improve their health and quality of life. Because most patients with CSP have no specific symptoms, they are prone to be misdiagnosed, resulting in life-threatening hemorrhage, uterine rupture, disseminated intravascular coagulation, shock, and even death.[6]

Recent studies have shown that the patients' pregnancy age, gestational age, serum human chorionic gonadotropin (β-hCG), gestational sac or CSP mass size, myometrial layer thickness, and peritrophoblastic perfusion were independent risk factors for excessive intraoperative hemorrhage.[7,8] Besides suction evacuation combined with preventive uterine artery embolization (UAE) treatments mentioned above, the current commonly used treatments for CSP include multiple treatments such as medication, UAE, curettage and surgery, and their combinations. However, every treatment option has risks of excessive hemorrhage from uterus. In this study, we retrospectively analyzed the risk factors for intraoperative hemorrhage of

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[a] Gynecological Department, the Third Affiliated Hospital of Soochow University, Changzhou, [b] Gynecological Department, the Second Affiliated Hospital of Soochow University, Suzhou, [c] Department of Nuclear Medicine, the Third Affiliated Hospital of Soochow University, Changzhou, China.

[*] Correspondence: Xiaonan Shao, Department of Nuclear Medicine, the Third Affiliated Hospital of Soochow University, Changzhou 213003, China (e-mail: scorey@sina.com).

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different treatments for CSP patients, with the hope to provide the guidance for CSP treatment.

2. Methods

2.1. General information

The study was approved by the Ethics Committee of the Soochow University. All patients and their family members signed the informed consent form. Patients' medical records were anonymous. This study retrospectively analyzed 58 CSP patients who admitted to our hospital from March 2012 to May 2016. These patients had average age of 33 ± 6 years, ranging from 21 to 45, median pregnancy times of 3, ranging from 1 to 8, and median abortion or curettage times of 1, ranging from 0 to 5. Among them, 45 patients had delivered once and 13 patients had delivered twice. All patients had the history of cesarean section at their lower uterine segments. Among them, 47 patients underwent cesarean section once and 11 twice. The median time to last cesarean section was 5 years, ranging from 1 to 19, and the median menolipsis time was 47 days, ranging from 30 to 180.

2.2. Diagnosis and typing

The most common symptom of CSP is painless vaginal bleeding, with occasional abdominal pain in some patients. Thus, its diagnosis mainly depends on transvaginal sonography (TVS) and serum β-hCG level. With advances in ultrasound, the sensitivity of early diagnosis of CSP by TVS is up to 84.6%.[9] Criteria of TVS diagnosis[10] include an empty uterine cavity and cervical canal, an gestational sac located at the anterior wall of the isthmic portion, separated from endometrial cavity or fallopian tube in previous cesarean scar, a gestational sac embedded within the myometrium and the fibrous tissue of cesarean section scar at the lower uterine segment with an absence of defect in the myometrium between the bladder and the sac, and a high-velocity, low-impedance vascular flow surrounds the gestational sac. A Philips-made IU22 (Philips, Bothell, WA) color ultrasound diagnostic apparatus with transvaginal probe and its probe frequency of 3.5~6.5 MHz was used for CSP diagnosis. Patients were asked to empty the bladder and take the lithotomy position so as to fully expose their perineum. The 6.5-MHz probe was used to scan the vagina vertically, horizontally, and semi-circularly and measure the maximum diameter of gestational sac or mass, the distance to the uterine serosa layer, peak systolic velocity, and resistance index around the mass.

The serum β-hCG was determined by using the Beckman Coulter UniCel DxI 800 Immunoassay Analyzer (Beckman Coulter, Brea, CA) with the reference of 0.00~5.00 mIU/mL, and used for auxiliary diagnose and monitoring treatment outcomes.

According to Vial et al,[11] CSP falls into 2 types, Type I CSP (also called the endogenous CSP) and Type II (also called the exogenous CSP). Type I CSP is defined as an implantation on the prior scar with progression toward the cervico-isthmic space or the uterine cavity, while Type II CSP is defined as a deep implantation into the cesarean scar defect growing toward the bladder and abdominal cavity and more prone to scar rupture.

2.3. Treatment and assessment of intraoperative blood loss

Ten patients were grouped in the medication group. They first received the systemic or topical administration of methotrexate (MTX) (Among them, 6 patients also received oral administration of mifepristone) and then received the ultrasound-guided curettage. Forty-five patients were grouped in the UAE group. They were treated with bilateral uterine artery infusion of 50 to 100 mg MTX (25–50 mg on each side) and then polyvinyl alcohol particles or gelatin sponge particles embolization of transcatheter artery, and received the ultrasound-guided curettage within 1 to 5 days. Three patients were in the surgery group. Among them, 1 received laparotomy for CSP mass resection, 1 received laparoscope-guided CSP mass resection along with neoplasty and curettage, and the other one received the subtotal abdominal hysterectomy along with bilateral oviduct resection.

The intraoperative bleeding amount in this study was estimated directly by the surgical operator or by measuring weight change of gauze before and after blood immersion.[12] Patients with bleeding ≥200 mL were grouped in the bleeding group (15 cases), and patients with blood loss < 200 mL were in the control group (43 cases).[8]

2.4. Cure standards

The clinical cure standard is serum β-hCG dropping to the normal level. The criteria for hospital discharge is no or only small amount of vaginal bleeding. After discharge, patients were asked for weekly outpatient visits for their serum β-hCG and ultrasound until cure.

2.5. Statistical analysis

The SPSS 13.0 (SPSS Inc., Chicago, IL) statistical software was used for statistical analysis. Metrical data with normal distribution were denoted with $\overline{x} \pm s$, metrical data with skewed distribution were expressed as median value P50 (P25, P75), and the count data were presented as the number or percentage. The Mann–Whitney U test was used to compare 2 sets of data with non-normal distribution, the Kruskal–Wallis H test was used to compare multiple sets of data, and the χ^2 test was used to compare the rates. The ROC curve and the area under it were utilized to compare the diagnostic effects of different indicators, and the logistic regression analysis was applied to perform the multivariate analysis and calculate the regression coefficient and the odds ratio (OR). Differences with $P < .05$ were considered as statistically significant.

3. Results

3.1. Outcomes of the 3 treatment regimes

Among the 10 patients in the medication group, 9 patients were cured. Among the 9 patients, 8 underwent ultrasound-guided curettage and 1 did not undergo curettage. The patient, who was not cured, suffered from excessive vaginal bleeding along with hemorrhagic shock during curettage and was subjected to laparotomy. Later, she received hysterectomy along with bilateral salpingo oophorectomy due to postoperative breast cancer.

Among the 45 patients in the embolization group, 41 patients were cured, of whom, the serum β-hCG level of 1 patient dropped to the normal level without uteral curettage after UAE. Among the 4 uncured patients, 1 patient first received systemic and local MTX therapy due to unsatisfied β-hCG level after UAE, then another embolization due to excessive vaginal bleeding, and finally curettage after 24 hours; 2 patients received supplementary MTX therapy after UAE due to insufficient decline in serum

Table 1

Univariate analysis of risk factors associated with intraoperative hemorrhage in CSP patients.

Group	Bleeding group (n = 15)	Control group (n = 43)	Z/χ^2 value	*P*
Age, y	33 (29, 38)	33 (29, 37)	−0.133	.894
No. of pregnancy	3 (2, 4)	3 (2, 4)	−0.291	.771
No. of abortion or curettage	1 (1, 2)	1 (0, 2)	−0.138	.890
Time from last cesarean, y	5 (4, 7)	6 (3, 10)	−0.036	.971
Menolipsis time, d	56 (39, 81)	45 (41, 50)	−2.001	.045*
Max diameter, mm	37 (28, 58)	21 (15, 30)	−3.008	.003*
Peak systolic velocity around the mass, cm/s	25.76 (17.68, 32.88)	20.70 (15.95, 25.16)	−1.281	.200
Resistance index around the mass	0.50 (0.39, 0.56)	0.52 (0.43, 0.59)	−0.968	.333
Distance from uterine serosa layer (mm)	3.3 (2.5, 8.5)	4.0 (2.7, 5.5)	−0.045	.964
β-hCG at admission, mIU/mL	9780.00 (744.82, 44,184.75)	18,480.00 (10,114.75, 43,983.25)	−1.495	.135
β-hCG at discharge, mIU/mL	432.45 (17.04, 4888.00)	1960.00 (532.09, 3893.00)	−1.402	.161
β-hCG change rate (%)	95.2 (84.6, 99.4)	94.4 (86.1, 96.6)	−1.208	.227
No. of delivery 1	11 (73.3%)	34 (79.1%)	0.010	.921
No. of delivery 2	4 (26.7%)	9 (20.9%)		
No. of cesarean section 1	12 (80.0%)	35 (81.4%)	0.000	1.000
No. of cesarean section 2	3 (20.0%)	8 (18.6%)		
Ultrasound type I	4 (26.7%)	14 (32.6%)	0.344	.558
Ultrasound type II	2 (13.3%)	18 (41.9%)		

The metrical data with skewed distribution are denoted by the median value P50 (P25, P75) and the count data are denoted by number (percentage). Twenty cases in the ultrasound type differentiation were difficult to identify, thus they were not involved in the statistical analysis.

β-hCG = serum human chorionic gonadotropin.

* $P < .05$.

β-hCG level; and 1 patient suffered from intraoperative vaginal bleeding with hemorrhagic shock and underwent abdominal CSP mass resection.

All 3 patients in the surgical group were cured. Among them, 1 patient received abdominal CSP mass resection, 1 patient received laparoscopic CSP mass resection along with neoplasty along with curettage, and the other one received abdominal hysterectomy along with bilateral salpingectomy.

3.2. Comparison of the 3 treatment regimes

Patients in the 3 groups showed no significantly differences in age, pregnancy times, delivery times, menolipsis time, abortion or curettage times, time to the last cesarean section, serum β-hCG level, maximum diameter of gestational sac or mass, abundance of blood flow around the mass (peak systolic velocity and resistance index), and the distance to the uterine serosa layer ($P > .05$) (data not shown).

In addition, among patients in the medication group, UAE group, and the surgery group, there were no differences in successful rate [90.0% (9/10) vs 91.1% (41/45) vs 100.0% (3/3), $\chi^2 = 0.568$, $P = .753$], hospital stay [11 (7, 14) days vs 10 (8, 12) days vs 10 (8, 10) days, $\chi^2 = 0.109$, $P = .947$], and hemorrhage rate [30.0% (3/10) vs 22.2% (10/45) vs 66.7%(2/3), $\chi^2 = 2.597$, $P = .273$].

3.3. Analysis of risk factors for intraoperative hemorrhage

Table 1 lists the results of univariate analysis of risk factors for intraoperative hemorrhage in CSP patients. It is clearly shown that menolipsis time (days) and the maximum diameter (mm) were significantly higher for patients in the bleeding group than in the control group (all $P < .05$).

Figures 1 and 2 showed the ROC curves using both menolipsis time and maximum diameter to predict intraoperative hemorrhage. The area under the menolipsis time curve was 0.680 [$P = .046$, 95% confidence interval (95% CI): 0.478~0.883] and the optimal cutoff was 51 days with sensitivity of 0.714 and specificity of 0.780. The area under the maximum diameter was 0.787 ($P = .003$, 95% CI: 0.632~0.942) and the optimal cutoff was 27 mm with sensitivity of 0.833 and specificity of 0.738.

Multivariate logistic regression analysis using the hemorrhage amount as the variable and the significant factors in the univariate analysis (the menolipsis time and the maximum diameter) as the dependent variables found that only the maximum diameter was of significance ($P < .05$, Table 2).

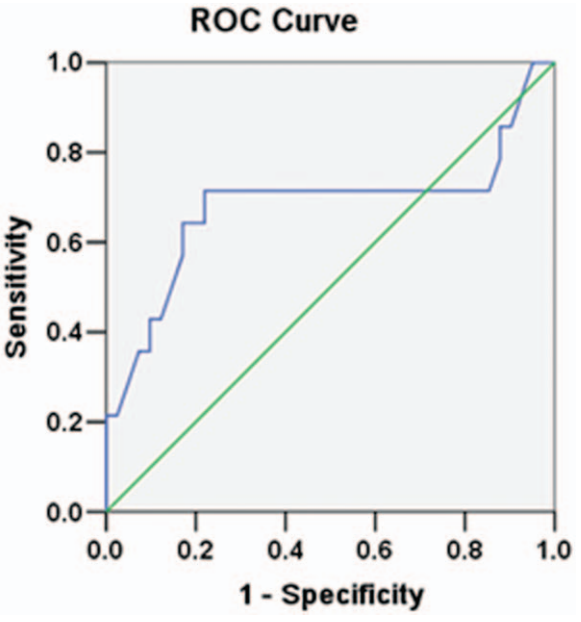

Figure 1. ROC curve of menolipsis time (days) to predict intraoperative hemorrhage.

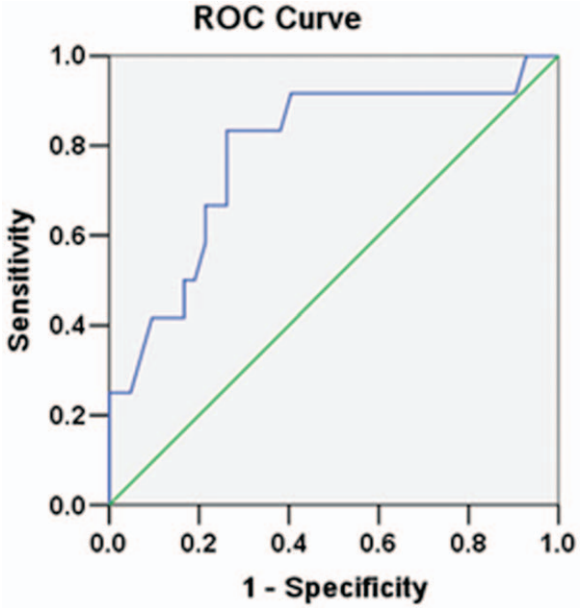

Figure 2. ROC curve of maximum diameter (mm) of gestational scar or mass to predict intraoperative hemorrhage.

4. Discussion

The therapeutic targets of CSP treatment are terminating pregnancy, removing CSP mass, and protecting the safety of patients. Pregnancy scar rupture bleeding is likely to occur in the first trimester and should be detected and treated as early as possible to reduce complications, avoid expectant treatment and blind curettage.[9,13]

Currently, MTX is commonly used in drug therapy. Although it has efficiency close to 80% and advantages of retaining fertility, it also has certain disadvantages such as slow reduction of serum β-hCG level, need of long-term follow-up, as well as possible bleeding, uterine rupture, placenta implantation, and other complications.[2,9,14] If patients experience intracurettage bleeding after drug treatment, one can use intrauterine balloon tamponade by Foley catheter or place iodoform gauze pack in the vagina to prevent local hemorrhage.[15] If necessary UAE, even surgery can be applied.

UAE for CSP treatment was first reported by Ghezzi et al in 2002.[16] Currently, it is widely used as a conservative first aid intervention and preventive treatment for CSP complications. The current data suggest that UAE jointed curettage has same success rate of 99.1% to 100% to other conservative treatments.[17,18] Some studies even show that curettage after embolization is safer and more effective than curettage after drug treatment.[19,20]

The surgical approach is the first option for cases with life-threatening complications, but introduction of minimally invasive approaches make surgery the first-line strategy.[5] Operative hysteroscopy or laparoscopy cannot be performed in cases with heavy bleeding or unstable vital sign.[21] As the remedy for CSP patients with confirmed or highly suspected uterine rupture or bleeding after other surgeries, laparotomy is still necessary because resection of the previous scars could help uterus heal better.[11]

Timor-Tritsch and Monteagudo[22] conducted a meta-analysis of 31 different treatment regimens for CSP and found that the highest success rate was 90.1%. In this study, the success rates of the first regimes of all the 3 treatments were >90%, indicating they were good for CSP. CSP treatment mainly depends on age, hemodynamic stability, availability of endoscopic techniques, requirements for further fertility, and follow-up feasibility using serological and ultrasound techniques.[23] Therefore, it is required to select the best personalized treatment.

It has been reported that curettage after transcatheter arterial chemoembolization with MTX is more advantageous than curettage after intravenous MTX therapy in reducing blood loss and hospital stay.[24] Vial et al[11] suggested that surgery could rapidly reduce serum β-hCG to normal level and shorten follow-up times, but it would cause greater lesions and longer hospital stay and recovery. In this study, there was no significantly different in hospital stay among patients in the 3 treatment groups. Although the blood loss was higher in surgery group, it was not significantly different from those in the other 2 groups, possibly due to fewer patients in the surgery group.

WHO defined postpartum bleeding ≥500 mL within 24 hours as postpartum hemorrhage.[7] However, with the advances in medical technologies and more rational and effective treatment selection, the amount of bleeding, hospital stay, and cost have been greatly reduced. Thus, in this study, bleeding ≥200 mL was used as the critical cutoff for hemorrhage, in consistence with that of the study in 2015.[8]

The study in 2013[7] believed that gestational age ≥8 weeks and gestational sac ≥6 cm are risk factors for CSP patients with hemorrhage after UAE curettage, because whether the embryo is alive or not, the invasion ability of villus myometrium is always present, which is consistent with the pathological findings of Einenkel et al[25] for CSP. In the 2015 study,[8] the meaningful factors for intraoperative hemorrhage include serum β-hCG >20,000 mIU/mL, gestational age >8 weeks, maximum diameter ≥5 cm, myometrial thickness ≤0.15 cm, and significant peritrophoblastic perfusion.

In this study, univariate analysis found that menolipsis time and maximum diameter in bleeding group were significantly higher than those in the control group, consistent with the above study. ROC analysis further found that the best cutoff of menolipsis time was 51 days, also consistent with that of 8 weeks in the above study. In addition, the best cutoff of maximum diameter was 27 mm, less than that in the above studies,[7,8] which may be related to grouping criteria for bleeding. It should be noted that the above study did not use ROC analysis to obtain the critical value. Thus, our cutoffs used to assess the risk factors of bleeding may be more reliable.

The OR values for menolipsis time and maximum diameter were 11.49 and 96.59, respectively, in the 2013 study,[7] and 2.1 and 7.4, respectively, in the 2015 study,[8] indicating that the maximum diameter is more important than menolipsis time for hemorrhage. Our results showed that maximum diameter is the most important risk factor for bleeding, in agreement with that the area under the ROC curve of maximum diameter is greater than that of menolipsis time. With the increase of menolipsis time and maximum diameter,

Table 2

Results of multivariate logistic regression analysis.

Factor	Regression coefficient	*P*	OR	95% CI
Menolipsis time, d	0.013	.588	1.013	0.967~1.061
Max diameter, mm	0.065	.013	1.067	1.014~1.123

95% CI = 95% confidence interval, OR = odds ratio.

the risk for bleeding might increase accordingly, and the maximum diameter is a more important risk factor.

Overall, the 3 treatment regimes in this study all had very high success rate and no significant effect on intraoperative hemorrhage. Both menolipsis time and maximum diameter of gestational sac or mass could predict the risk of intraoperative hemorrhage with the best cutoff value of 51 days and 27 mm, respectively, and the latter is more important. The above indexes can help filter patients with a high risk of intraoperative hemorrhage and select treatment options. However, the present study has shortcomings, such as small sample size and fewer cases in the surgery group. Thus, the conclusion of the study needs to be further studied with case accumulation.

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