Study of individualization therapy for 61 patients with cesarean scar pregnancy

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Summary

Objective: To investigate the clinical value of the individualization therapy for cesarean scar pregnancy (CSP). *Materials and Methods:* According to the individual characteristics of the CSP in 61 patients admitted and treated by the People's Hospital of Yuyao City, China between March 2010 and February 2013, methotrexate (MTX) with leucovorin (CF) or uterine artery chemotherapy embolization (UACE) were used to kill the embryos, stanch, and prevent bleeding. Guided by hysteroscopy or B ultrasound, uterine curettage was carried out under the surveillance of laparoscopy if necessary. *Results:* Fifty-four cases of patients were treated by UACE. MTX with CF was used in seven cases. Uterine curettage was performed in 44 cases under the guidance of hysteroscopy. Six cases were under the surveillance of the B ultrasound and both hysteroscopic guidance and B ultrasound surveillance were used in seven cases. The lesions disappeared in two cases after transabdominal excision and two cases after UACE. All of the 61 patients were cured without hysterectomy. *Conclusion:* Selection of individualization treatment programs according to the characteristics of the disease could improve the efficacy and prognosis of patients with CSP. The appropriate timing to perform curettage was five to seven days after embryo killing in order to reduce bleeding and shorten the course of the disease.

Key words: Pregnancy; Cesarean scar; Ultrasonic classification; Individualization therapy; Uterine curettage timing.

Introduction

Cesarean scar pregnancy (CSP) indicates the ectopic pregnancy with embryo implanting in the scar for the uterine incision of the previous cesarean [1], which is a potential long-term serious complications after cesarean. The cesarean rate in China is high [2], accordingly, the incidence of the CSP is increasing year by year. The CSP has become the new critical emergency in obstetrics and gynecology and could be a serious threat to the physiological and psychological health of the majority of young women. With the increased awareness of the CSP and the development of diagnostic imaging technology, misdiagnoses are significantly reduced. However, the appropriate treatment is still in the exploratory stage due to the variation of the disease features in patients with CSP, especially establishing the treatment plan of killing and eliminating pregnancy lesions, reducing trauma and bleeding, preserving individual fertility suitable for the individual characteristics of the disease is still the hot issue to be urgently solved. In this study, the retrospective analysis was used to study the clinical data of the 61 patients with CSP, the clinical value of the individualization therapy for the CSP in order to provide the basis for further improving the curative effect of patients with CSP.

Materials and Methods

Subjects

Sixty-one patients with CSP were admitted and treated by People's Hospital of Yuyao City during March 2010 and February 2013, the ratio to the total number of hospital deliveries in the same period of last year was 1:222 (61/13552), accounting 3.14% (61/1943) of the ectopic pregnancies treated by the hospital in the same period of last year. The ages of the 61 patients were between 23 and 40 (32 ± 4) years , pregnant times including the current were two to seven (4.0 ± 1.2) months, times of having babies were one to two (1.2 ± 0.4). A clear history of menopause was found in all the 61 cases, and the time of the menopause was between 32 and 105 (55 ± 18) days. Forty cases (66%) were found to have vaginal bleeding, including seven cases of bleeding after medical abortion and four cases of bleeding after artificial abortion. Nine cases (14.8%) had abdominal pains. The time of the cesarean from the previous one was 0.33-14 (5.8 ± 3.7) years. Fifty-two cases experienced cesarean for one time and nine cases two times. One case developed CSP again. The hematic β-human chorionic gonadotropin (β-HCG) level was 85 to 310,473 (42,191 ± 55,272) IU / l when the patients were admitted. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Yuyao People's Hospital. Written informed consent was obtained from all participants.

Diagnostic basis

1) Patients with the history of cesarean and clinical manifestations such as menopause, vaginal bleeding, and elevated hematic β-HCG level. 2) In line with the transvaginal ultrasound imaging changes of the CSP according to the literature [3, 4], the ultrasound of the CSP was typed as endogenous (type I) with lesion protruding into the uterine cavity and the exogenous (type II) with lesion protruding into the serosa [5]. 3) Magnetic resonance imaging (MRI) was used to examine the relationship of the lesion site and the cesarean scar when the ultrasound examination could not determine the relationship between the lesion and cesarean scar [6, 7]. 4) Histopathological examination was used to observe the specimens of the lesion clearance.

Treatment

Embryo killing: drug therapy included methotrexate (MTX) with leucovorin (CF) (MTX+CF program) was chosen to treat the

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Table 1. — *Comparison of the partial clinical characteristics of type I and type II patients ($\bar{\chi} \pm s$)*

Type	n	Early abortion history [n (%)]	Mean diameter of the mass (cm)	Thickness of surface muscle layer (mm)	Amount of bleeding (ml) in uterine curettage
Type I	54	6(11)	2.4±1.3	2.7±1.0	63±93
Type II	7	5(71)	4.3±1.2	1.6±0.5	183±310
$\chi 2$ or *t* value		11.445	-3.612	2.916	-0.948
P value		0.001	0.001	0.005	0.386

Note: Two cases of type I with lesions disappearance after embryo killing and one case of the type II after direct transabdominal excision were not included in the number of total cases in the comparison of the amount of bleeding in uterine curettage. Approximate t test was used for comparison between groups due to the heterogeneity of variance.

patients with hematic β-HCG < 5,000 IU/l. Interventional therapy by uterine artery embolization (uterine artery chemoembolization,) was selected to treat the patients with hematic β-HCG ≥ 5,000 IU/l [8]. The total dosage of the MTX perfusion by bilateral uterine arteries was 100 mg for the patients with hematic β-HCG levels between 5,000 and 10,000 IU/l. For the patients with hematic β-HCG levels > 10,000 IU/l, MTX was increased by 50 mg for each additional 10,000 IU/l of β-HCG levels. The maximum infusion dose was 300 mg. Gelatin sponge particles were used to perform bilateral uterine arteries embolization (UAE) after perfusion.

Lesion clearance: uterine curettage was performed under the guidance of hysteroscopy and the surveillance of the B ultrasound for the type I lesions with the thickness of the surface muscle layer ≥ two mm. Uterine curettage was performed under the guidance of the hysteroscopy and the surveillance of laparoscopy for the type II lesions with the thickness of the surface muscle layer < two mm or mass diameter < four cm with less blood supply [10]. Lesion excision through abdomen and uterine repair were used for the patients with mass diameter ≥ four cm with rich blood supply or concurrent bleeding in the uterine curettage. According to the differences of the time between the embryo killing after the UACE or MTX+CF programs ending, the uterine curettage within seven days (≤ 7d) group and uterine curettage after seven days (> 7d) group were divided to compare the indexes relevant to the treatment.

Hemostasis: emergent UACE or UAE hemostasis were used to patients with concurrent more bleeding (≥ 200ml) at the time of admission or before the uterine curettage [11], the Foley catheter sacculus uterine hemostasis was used for the patients with bleeding volume ≥ 50 ml with uterine curettage.

Follow-up

Hematic β-HCG level was detected one week after leaving hospital until the β-HCG turning negative (<5 IU/l). The time of β-HCG turning negative was observed after the treatment of embryo killing. The re-examination by B ultrasound was performed one for two to three weeks to observe the healing of the uterine scars after leaving hospital. The time of menstruating again were followed-up by telephone after lesion clearance.

Statistical analysis

Statistical analysis was performed using SPSS19.0 statistical package. The comparison of the measurement data among different groups with homologous variance was performed using t test, and data with heterogenous variance using approximate t test. The enumeration data among groups were compared using corrected fourfold table χ^2 test. A $p < 0.05$ was considered to have statistical significance.

Results

Results and differences of classification by ultrasound

According to the vaginal ultrasound imaging, combined with the MRI examination findings if necessary, 54 patients were diagnosed with type I and seven patients with type II. The results of comparing the drugs or artificial abortion rates in the earlier period, the mean diameter of the gestational sac or the mass, the muscle layer thickness of the lesion surface, and the amount of blooding in uterine curettage were shown in Table 1.

As shown in Table 1, compared with type I, more patients had a history of early miscarriage, the mass mean diameter was larger and the surface muscle layer was thinner in type II, which indicated that the difference was statistical significance ($p < 0.01$). The amount of the blood loss was also larger, but the difference did not have statistical significance ($p > 0.05$).

Overall results of treatment

Fifty-four cases (88.5%) experienced embryo killing by UACE, including five cases that experienced embryo killing by emergent UACE had concurrent hemorrhea with β-HCG > 5,000 IU/l when admitted. Of the 54 cases, 40 cases were performed with uterine curettage guided by hysteroscopy, six cases were performed with uterine curettage under the surveillance of B ultrasound, and five cases were performed with uterine curettage both guided by hysteroscopy and under the surveillance of B ultrasound. One case (patient with type II) with mass diameter of 4.8 cm with rich blood supply had a directly performed lesion excision through the abdomen with uterine repair. The lesions disappeared without curettage in two cases. Ten cases were performed using a Foley catheter sacculus uterine hemostasis for the patients with large amount of bleeding (50 - 400 ml). Seven cases experienced embryo killing by MTX+CF program, including four cases that were performed uterine curettage under the guidance of hysteroscopy, two cases under the surveillance of laparoscopy, and one case (patients with type II) with concurrent hemorrhea (800 ml) when uterine curettage was performed with lesion excision through abdomen and with uterine repair. After the 61 patients were cured and discharged, there were no postoperative infections, hysterec-

Table 2. — *Comparison of different therapy results in different uterine curettage timing ($\bar{\chi} \pm s$)*

Groups	n	β-HCG before uterine curettage (IU/l)	Surgery duration (min)	Amount of intra-operative bleeding (ml)	Hospital stay (d)	Medical costs (RMB)	Time for turning negative of β-HCG (d)
≤ 7d	22	8,673 ± 24,227	14 ± 7	43 ± 53	13±6	13405±3405	18±7
> 7d	35	2,830 ± 3,115	17 ± 7	74 ± 108	27±12	14898±3281	31±11
T value		1.125	-1.597	-1.468	-5.862	-1.649	-5.486
p value		0.273	0.116	0.148	0.000	0.105	0.000

Note: 1) Four cases, including one case was performed by turning to transabdominal surgery during uterine curettage complicating with massive haemorrhage and one case was directly performed via transabdominal excision and two cases with lesions disappearance after UACE were not counted in the number of total cases. 2) The four indexes including hematic β-HCG before uterine curettage, blood loss during surgery, hospital stay, and turning negative time of the hematic β-HCG after embryo killing were analyzed by approximate t test due to the heterogeneity of variance.

tomy and complications such as uterine perforation with curettage, severe MTX toxicity, syndrome after artery embolization, and non-targeted vessel embolization after embryo killing, lesion clearance, and hemostasis. The overall time in hospital was seven to 55 (22 ± 13) days and medical expenses were 6,921 to 22,811 (14,241 ± 3,442) RMB, which were approximately in line with the data reported in the literature [12].

Result comparisons of the different timing for uterine curettage

The result comparisons of the relevant treatment for the uterine curettage within seven days (≤ 7d) group and after seven days (> 7d) group are shown in Table 2. As shown in the differences of the hematic β-HCG levels, timing for uterine curettage, blood loss amount during the operation, and medical expenses between the two groups before the curettage had no statistical significance ($p > 0.05$), while the hospital time and turning negative time of the hematic β-HCG for the uterine curettage within seven days group were shorter than that of the uterine curettage after seven days group, the difference had statistical significance ($p < 0.01$).

Pathological examination

The lesion clearance specimens of the 59 cases were sent for pathological examination, and all were diagnosed as degenerated with necrotic villus or placental tissues.

Follow-up results

The time of hematic β-HCG turning negative was 12 to 59 (27 ± 12) days after the end of the UACE or MTX+CF treatment program of the 61 patients. The first time of menstruation of the 51 cases (51/59, 86%) followed-up by telephone was 15 to 60 (34 ± 6) days after the operation. The healing of the uterine scars was re-examined by B ultrasound for three to seven days after the complete end of the second menstruation after leaving hospital [13]. Forty-seven patients (77%) were detected with good healing (scar thickness ≥ five mm), and 14 patients (23%) were detected with poor healing (scar thickness < five mm).

Discussion

Clinical significance of the ultrasonic type for the CSP lesions

According to the imaging findings, the CSP lesions were divided to be type I (endogenous) and type II (exogenous), the manifestations of the patients treated by abortion and uterine curettage due to misdiagnosing as intrauterine pregnancy were also type II. According to the observation in this study, compared with type I, more patients had a history of early miscarriage and uterine curettage, the gestational sac or the mass were larger, and the surface muscle layer was thinner in type II, which indicated that the difference was statistically significant ($p < 0.01$). The amount of bleeding was also large. Uterine curettage was substituted to abdominal incision due to the hemorrhea during uterine curettage in patients with type II. These results indicated that uterine curettage under the guidance of the hysteroscopy or the surveillance of B ultrasound was feasible for patients with type I, while it was better to perform uterine curettage under the guidance of the hysteroscopy and the surveillance of the laparoscopy for patients with type II in order to avoid uterine perforation or rupture, and the Foley catheter sacculus uterine hemostasis was used after the surgery. For type II patients with too large masses, rich blood supply and very thin surface muscle layer, it was better to directly perform lesion excision through abdomen and uterine repair. Therefore, the ultrasonic type of the CSP lesions in patients provided to be significant in effectively selecting lesion clearance surgery. Following the aforementioned principle, there were no uterine perforation occurring with lesion clearance surgery in this study, and the majority (77%) of the patients had good scar healing.

Clinical value of individualized treatment

The aim of the CSP treatment was to select the appropriate methods to kill embryos, clear pregnancy lesions, reduce the amount of bleeding, and preserve fertility. Currently, the main treatment methods included drugs, uterine curettage after killing the embryos by UACE, lesion clearance under the surveillance of the hysteroscopy or laparoscopy, lesion excision through abdomen used with uterine repair, and hysterectomy [14]. However, there was no standardized solu-

tion for the treatment of CSP. In this study, MTX+CF program was chosen to kill embryos for the patients with hematic β-HCG < 5,000 IU/l when admission, and UACE was selected to kill embryos or stop bleeding for the patients with hematic β-HCG ≥ 5,000 IU/l when admitted. Uterine curettage was performed under the guidance of the hysteroscopy or under the surveillance of the B ultrasound for the type I patients with thickness of the surface muscle layer ≥ two mm. Uterine curettage was performed under the guidance of the hysteroscopy or under the surveillance of laparoscopy for type II patients with thickness of the surface muscle layer < two mm, mass diameter ≥ four cm, and less blood supply. Lesion excision through abdomen and uterine repair were performed for the patients with a mass diameter ≥ four cm and rich blood supply or with concurrent hemorrhea during uterine curettage. Emergent UACE or UAE hemostasis was used for the patients had hemorrhea when admitted or before uterine curettage, and the Foley catheter sacculus uterine hemostasis was used for patients with large amount of bleeding. Following the principle of individual treatment mentioned above, there were no serious complications and hysterectomy cases, achieving the desired therapeutic effect. Therefore, the method of selecting individual embryo killing, lesion clearance, and method to stop bleeding according to the comprehensive factors such as hematic β-HCG levels, location, size, blood supply, the surface muscle layer thickness of the lesions, and vaginal bleeding for the CSP patients when admitted, had practical value in the improvement of the CSP curative effect and prognosis, which was consistent with the findings reported by Zhang *et al.* [15].

Rational for the application of interventional therapy

The vascular interventional therapy for CSP included MTX infusion chemotherapy and embolization. The drug directly entered and gathered locally in the pregnancy lesions when infused MTX through uterine artery. After first extracting the drugs by the lesions, the local drug concentration and bioavailability were higher than systemic administration, the toxicity was mild, and the infused dose for could surpass 1 mg/kg or 50 mg/m^2 of the systemic administration for one time. The maximum infusion dose reached 300 mg and there were no serious toxicities. The use of UAE following MTX infusion could play a dual role in embryo killing with chemotherapy killing and anti-ischemic damage. UAE could also quickly control bleeding and reduce the risk of bleeding in lesion clearance. According to the literature [16], the interventional therapy had advantages in reducing the amount of bleeding, reduce the hysterectomy rates, and shorten the hospital stays. In this study, embryo killing and hemostasis by UACE were used in the majority (88.5%) of the patients, and the desired therapeutic effect was achieved. Therefore, the interventional therapy was suitable for the embryo killing of the CSP patients with hematic β-HCG ≥ 5,000 IU/l, acute hemostasis of the concurrent vaginal hemorrhea, and the bleeding prevention of the high-risk patients with uterine curettage. According to the individualized treatment principle, the rational use of interventional therapy was the key measure of the standard treatment for CSP. However, there are complications such as certain femoral artery puncture injuries and infection, syndrome after embolism, and non-targeted vessel embolism in the interventional therapy. The long-term effects of the UAE on ovarian function also could not be ignored.

Timing selection of uterine curettage

The timing for uterine curettage after killing embryos by intervention therapy or drug had not reached consensus, mainly related to factors such as embryonic necrosis after the embryo killing treatment, the decline rate of the hematic β-HCG, and blood supply of the lesions [17]. At present, it was believed that gelatin sponge particles were absorbed normally in seven to 21 days after embolization, so that the recanalization of the blood vessel could be realized. In addition, embryo killing by MTX could act more completely after three to four days, when the embryo is necrotized [18]. Uterine curettage could be performed 24-120 hours after UAE according to the literature [19]. In this study, the timing of the embryo killing was divided into within seven days group and after seven days group. The results showed that the differences of the hematic β-HCG levels, timing for uterine curettage, blood loss amount during the operation, and medical expenses between the two groups before the curettage had no statistical significance ($p > 0.05$), while the hospital time and turning negative time of the β-HCG for the curettage within seven days group were shorter than that of the curettage after seven days group, and the difference had statistical significance ($p < 0.01$). Therefore, considering the factors such as reducing the difficulty and bleeding in the uterine curettage, five to seven days after embryo killing treatment was the appropriate timing for uterine curettage, which enabled complete removal of the lesion, reducing bleeding, and shortening the course of the disease and duration of hospitalization. Premature uterine curettage timing might increase the amount of bleeding and the rate of residual lesions.

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