

Outcome of high-intensity focused ultrasound and uterine artery embolization in the treatment and management of cesarean scar pregnancy

A retrospective study

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Abstract

The aim of the study was to compare the efficacy and safety between high-intensity focused ultrasound (HIFU) treatment and uterine artery embolization (UAE) treatment; we retrospectively analyzed 152 cases with cesarean scar pregnancy (CSP). Based on our inclusion and exclusion criteria, 152 patients (average age, 31.8 ± 4.6 years old) with CSP were eligible for the HIFU group (85 patients) or the UAE group (77 patients). All patients in 2 groups received the treatment with suction curettage under hysteroscopy prior to HIFU or UAE treatment and followed up for 12 months. The assessment criteria of treatment efficacy included the success rate, intraoperative blood loss, duration of vaginal bleeding, normal menstrual function recovery time, time for β -human chorionic gonadotrophin (β -HCG) back to normal level, duration of hospital stays, and other adverse effects. Following up for 12 months, the HIFU group was of less intraoperative blood loss (76.38 ± 22.89 vs 114.42 ± 30.34 mL, $P = .02$), shorter duration of postoperative vaginal bleeding (11.28 ± 3.65 vs 15.77 ± 7.24 days, $P = .01$) and lower adverse effects rate comparing to the UAE group. However, the HIFU group have longer time for the β -HCG recovery to the normal level (35.28 ± 9.86 vs 29.91 ± 7.29 , $P = .03$). Additionally, there were no significantly statistic differences between the 2 groups in baseline characteristics, success rate, and average time of gestational sac disappeared and menstrual recovery and hospital stay. Thus, we concluded that the method of both HIFU and UAE combined with suction curettage under hysteroscopy is safe and effective in the management of CSP. Meanwhile, HIFU is a better therapy option than UAE for those women who are seeking complete relieve of symptom to gain fertility.

Abbreviations: β -HCG = β -human chorionic gonadotrophin, CSP = cesarean scar pregnancy, HIFU = high-intensity focused ultrasound, UAE = uterine artery embolization.

Keywords: cesarean scar pregnancy, high-intensity focused ultrasound, suction curettage, uterine artery embolization

1. Introduction

Cesarean scar pregnancy (CSP) is a rare type of ectopic pregnancy, characterizing by the empty uterus and cervical canal. Gestational sac (GS) commonly implants in anterior uterine wall with diminished myometrium between sac and bladder.^[1] Recently, with the prevalence of cesarean section worldwide, increasingly CSP cases were reported. Considering the severe complications of CSP, such as uterine rupture, catastrophic postpartum hemorrhage, and even death, many researches focus on the early diagnosis and management. Based on specific features of CSP, diagnosis was commonly made by ultrasonography, magnetic

resonance imaging (MRI), and laparoscopy. However, there is still no consensus guideline for the management of CSP.^[2] More than 30 therapeutic options for CSP have been reported and most of them are mainly based on individual and case series rather than randomized controlled trials.

As a minimally invasive treatment, uterine artery embolization (UAE) followed by suction curettage has been reviewed as a key strategy with a high success rate for CSP.^[3,4] However, the side effects of UAE such as fever, infertility, infection, and ovarian dysfunction are still presented.^[5] High-intensity focused ultrasound (HIFU), a noninvasive technique, was approved by the U. S. Food and Drug Administration (FDA) and modified in 2004.^[6,7] The application of HIFU converting focused acoustic energy into thermal energy at target tissue is mainly focus on ablating uterine fibroids and adenomyosis.^[8,9] So far, several researches of HIFU used in management of CSP have been reported and manifested that HIFU combined with or without supplement treatment was safe in treating CSP patients.^[10,11]

To figure out the better therapeutic option for CSP patients, in this study, we compared the clinical efficacy, feasibility, health recovery, and safety between HIFU and UAE.

2. Materials and methods

2.1. Patient population and characteristics of the study group

This study was a retrospective analysis of a prospectively collected database. Consecutive patients (N=152) with definite

Editor: Daryle Wane.

The authors have no funding and conflicts of interest to disclose.

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Medicine (2017) 96:30(e7687)

Received: 5 April 2017 / Received in final form: 10 July 2017 / Accepted: 13 July 2017

<http://dx.doi.org/10.1097/MD.0000000000007687>

Table 1**Inclusion and exclusion criteria for enrolled patients in our cohort.**

Inclusion criteria	History of cesarean section delivery
	Early clinical manifestations of pregnancy
	Positive amenorrhea, the urine pregnancy, and serum β -HCG
	Diagnosis of CSP or confirmed by MRI or laparoscopy according to diagnostic criteria recommended. ^[2,12]
	Vital signs were stable, desire to retain the uterus
Exclusion criteria	Gestational age less than 10 weeks
	Patients with severe internal and external diseases
	Abnormal coagulation and pelvic inflammatory
	Receive other treatment before HIFU or UAE
	Clinical data incomplete and lost following up
	Unable to cooperate or tolerate for an hour HIFU treatment in a prone position

β -HCG = β -human chorionic gonadotrophin, CSP = cesarean scar pregnancy, HIFU = high-intensity focused ultrasound, MRI = magnetic resonance imaging, UAE = uterine artery embolization.

CSP receiving conservative treatment were enrolled in our institution between September 2014 and January 2016, and all patients were equally eligible for both treatments based on our inclusion and exclusion criteria given in Table 1. A typical case confirmed by ultrasound was provided in Fig. 1. Out of 152 patients, 85 patients chose HIFU treatment (set as the HIFU group), 67 patients treated with UAE (set as the UAE group). All patients were followed with suction curettage under the hysteroscopy and followed up for 18 months. The research protocol was approved by the ethics committee and institutional review board of the Tangshan Maternity and Child health care Hospital and each patient was given informed consent.

2.2. Ultrasound-guided HIFU ablation

Ultrasound-guide HIFU procedure was performed by 2 experienced ultrasonic physicians using the Haifu JC-200 focused ultrasound tumor therapeutic system (Chongqing Haifu Tech Co., Ltd., Chongqing, China), equipped with a 3.75-MHz diagnostic ultrasound probe (My-Lab70, Esaote, Italy) for real-time sonographic monitoring during HIFU treatment. All patients were required to complete all preoperative preparations before HIFU treatment, including physical and laboratory examination, specific skin preparation, and bowel preparation. The measurement of gestational sac size and blood flow by color Doppler ultrasound before ablation could help to preliminarily assess the treatment

parameters including focal point, ablation range, therapeutic acoustic power, firing time, and number of treatment sessions.

Patients (N=85) underwent HIFU procedure as previously described.^[11,13] Briefly, the procedure was performed under deep sedation, a urinary catheter was inserted in each patient to control the bladder volume. Select the sagittal view of ultrasound scanning model, real-time monitoring the treatment response and adjusting the treatment parameters accordingly. The gestational sac was divided into sections with 3 mm separation. Then, the ablation proceeded from the innermost section to the section outside the entire mass was covered, using 350 to 400W acoustic output power and repeated this process section-by-section. The end-point of the HIFU sonication was disappeared of the pregnancy tissue blood flow signal or grayscale changes in the target tissue observed on the color Doppler ultrasound. Contrast enhanced ultrasound (SonoVue, Bracco, Italy) was used to evaluate the blood perfusion in the pregnancy tissue and then suction curettage under hysteroscopy was proceeded few days later.^[14]

2.3. UAE technique

The protocol of UAE was previously described in detail.^[15] In brief, patients (N=67) were placed in a supine position under local anesthesia, and right femoral artery catheterization was routinely performed. Uterine angiography was used to locate the position of caesarean scar lesion, uterine artery, and the potential sites of bleeding. The uterine arteries were blocked with absorbable gelatin sponge power. Gelatin sponges could be completely absorbed and facilitate re-canalization of the uterine artery, thereby preserving patients' fertility. The results of UAE were the stasis of blood flow or occlusion of the uterine artery observed by angiography (Fig. 2). Patients received suction curettage under hysteroscopy after an average of 4 days later.

2.4. Evaluation of therapeutic effects and follow-up

Clinical success of those 2 protocols was determined as control of bleeding and complete recovery with preserve fertility, without repeated embolization and surgical intervention and without any severe complication. After the treatment of HIFU and UAE, patients were closely observed and checked for several possible complication, such as gastrointestinal perforation, skin burn, abdominal pain, uterine rupture, and uncontrolled hemorrhage. Serum β -HCG levels were measured before intervention, 7 days after treatment and every week until complete recovery. Transvaginal ultrasound examination was

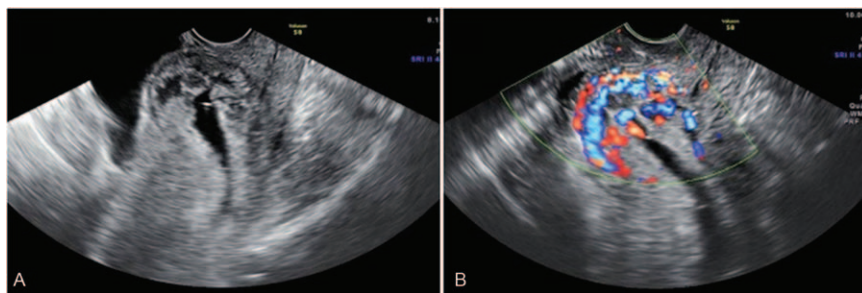


Figure 1. Ultrasound reveals an obvious enlargement of the previous cesarean section cicatrix and found a mixed mass attached to the cicatrice with a very thin myometrium (A). Color Doppler ultrasonic displays a mixed mass surrounded by the abundant color bloodflow signal (B).

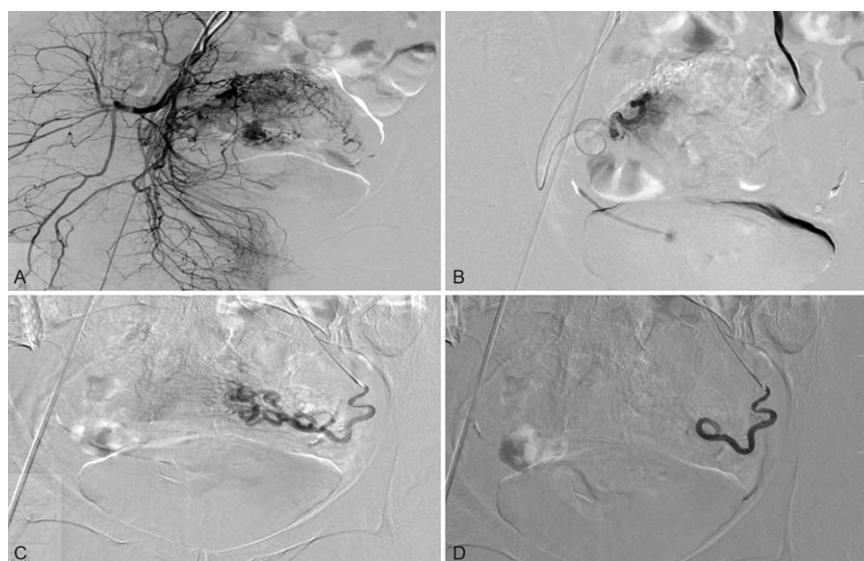


Figure 2. Uterine angiography and uterine arteries chemoembolization of patients with caesarean scar pregnancy during the UAE procedure. The angiogram of the internal iliac artery before embolization shows the gestational sac surrounded by numerous artery branches (A, C). The angiogram of the internal iliac artery after embolization demonstrates the occlusion of the bilateral uterine arteries, and loss of blood supply of gestational sac (B, D). UAE=uterine artery embolization.

managed every 2 weeks to monitor the condition of pregnancy remnants. Blood loss during HIFU, UAE, and suction curettage counted through the amount and weight of medical gauze. The hospitalization time and cost of each patients were also recorded.

There is no patient lost during 18 months follow-up. Serum β -HCG levels, ultrasound examination, condition of menstruation recovery and repeat pregnancy, the time of vaginal bleeding, and other adverse effects were followed up.

2.5. Statistical analysis

Continuous variables were summarized as the mean \pm standard deviation if normally distributed, and discrete variables were described as counts with percentages. Comparisons between the 2 groups were analyzed by the t test for continuous variables and the chi-square test for categorical data. Statistical analyses were performed with SPSS version 20.0 (SPSS, Inc, Chicago, IL). Two-

tailed *P*-values were calculated and difference were considered significant when *P*-value < .05.

3. Results

3.1. Patient characteristics

The subjects (N=152) included patients treated with HIFU (HIFU group, N=85) and patients received UAE treatment (UAE group, N=67). Both groups combined with suction curettage under hysteroscopic guidance. The baseline clinical characteristics of study population are summarized in Table 2.

The average age of the patients was 32.37 ± 4.35 years old and the average gestational age was 51.28 ± 9.1 days. The median interval from the last cesarean section to CSP was 56.72 ± 34.93 months. In addition, the average diameter of the sac was 36.56 ± 21.19 mm and the baseline median serum β -HCG was 37789.62 ± 25794.23 mIU/mL. There is no obviously statistic differences in

Table 2
Demographic data at baseline.

Characteristics	All patients (N=152)	HIFU group (N=85)	UAE group (N=67)	P
Age, Y	32.37 ± 4.35	32.87 ± 4.64	31.74 ± 3.69	.25
Ga, D	51.28 ± 9.19	50.58 ± 9.02	52.18 ± 9.53	.54
Time, M	56.72 ± 34.93	54.92 ± 35.73	59.01 ± 39.57	.69
PNP, N				
1	18	6	12	
2	5	3	2	
DS, mm	36.56 ± 21.19	39.18 ± 21.61	33.23 ± 20.69	.34
Serum β -HCG, mIU/mL	37789.62 ± 25794.23	39574.27 ± 23872.27	35517.91 ± 28462.19	.58
SCS, N				
Abdominal pain	37	21	16	.91
Painless vaginal bleeding	12	8	4	.43
Nausea, vomiting, and bleeding	5	4	1	.39

β -HCG = β -human chorionic gonadotrophin, DS=diameter of the sac, Ga=gestational age, HIFU = high-intensity focused ultrasound, PCP = previous caesarean, SCS=subjective clinical symptom, Time = time from the last CS, UAE = uterine artery embolization.

Table 3**Comparison of clinical outcomes and follow-up between the 2 groups.**

Characteristics	HIFU group (N=85)	UAE group (N=67)	P
Successful rate, %	90.58%	88.06%	.27
Intraoperative blood loss, mL	76.38 ± 22.89	114.42 ± 30.38	.02*
Time for β -HCG reduction to normal level, days	35.28 ± 9.86	29.91 ± 7.29	.03*
Gestational sac disappeared, wk	6.12 ± 1.84	5.28 ± 1.99	.81
Hospital stay, days	7.68 ± 1.45	8.55 ± 2.21	.32
Menstrual recovery to normal, days	37.82 ± 7.54	34.86 ± 6.09	.72
No. with disordered menses	10	15	.08
No. with fertile, n, %	5	3	.70
Adverse effects			
Abdominal or pelvic pain, n	3	8	.06
Fever, n	6	13	.02*
Lower limb pain or numbness, n	3	9	.03*
Duration of vaginal bleeding, days	11.28 ± 3.65	15.77 ± 7.24	.01*
Hematuria, n	1	0	.67

β -HCG = β -human chorionic gonadotrophin, HIFU = high-intensity focused ultrasound, UAE = uterine artery embolization.

*Means the difference was statistically significant.

age, gestational age, previous caesarean pregnancies, diameter of the sac, baseline serum β -HCG, and time from the last cesarean section.

3.2. Comparison of clinical outcomes between HIFU ablation and UAE

Both treatments demonstrated high success rates and had no significantly statistical difference. In the HIFU group, 76 patients (89.4%) underwent only 1 HIFU session, 9 patients (10.6%) underwent 2 HIFU sessions, the median treatment time was 92 minutes and the median HIFU sonication time was 58.2 (33–189) min, and all ablations were successfully performed. During HIFU treatment, the main complaints were lower abdominal or lumbosacral pain, which was relieved within 1 week without any special treatment and no skin burning or vaginal bleeding was observed. After HIFU treatment, no patients presented fever symptom. For the UAE group, the main complaints were lower abdominal pain and high fever, and 3 patients were of severe fever and treated with medication. For the 26 patients presented with high fever, the highest temperature reached to 38.9°C; the fever lasted for average 3 to 4 days and subsided within 1 week.

Clinical outcomes and follow-up of all patients with CSP are summarized in Table 3. All 152 patients received uterine curettage under hysteroscopic guidance, and the average of intraoperative blood loss during curettage in the HIFU group was lower than the UAE group (76.38 ± 22.89 vs 114.42 ± 30.38 mL, $P = .02$). However, the average duration of vaginal bleeding in the HIFU group was longer than the UAE group (11.28 ± 3.65 vs 15.77 ± 7.24 days, $P = .01$). The level of serum β -HCG did not drop remarkably after HIFU ablation, but decreased rapidly after 1 week later. However, in the UAE group, serum β -HCG declined rapidly after embolization and continued to drop after section curettage. The average time for the serum β -HCG level reduction to the normal level in the HIFU group was longer than the UAE group (35.28 ± 9.86 vs 29.91 ± 7.29 days, $P = .03$). Table 3 showed that there were no statistical differences in the average time of gestational sac disappeared, the average time for menstrual recovery and hospital stay between the 2 groups ($P < .05$ for all).

For these patients, 128 patients (84.21%, 68 of HIFU group, 60 of UAE group) were diagnosed as CSP without recurrence during the follow-up time. Also, 19 patients (12.5%, 13 of HIFU

group, 6 of UAE group) were diagnosed with CSP for the second time, and 5 patients (3.29%, 4 of HIFU group, 1 of UAE group) were diagnosed with CSP for the third time. There was no statistical difference between the HIFU group and the UAE group (P -value = .25).

3.3. The assessment of adverse effects

Adverse effects were also the main markers of prognostic evaluations. In line, 37 patients with CSP accompanied with abdominal pain, 12 patients complained of painless vaginal bleeding, and 5 patients with nausea, vomiting, and bleeding. Table 3 and Fig. 3 showed no significant statistically difference in the symptom of lower abdominal pain or pelvic pain and hematuria between the HIFU group and the UAE group. However, the HIFU group had slightly shorter duration of vaginal bleeding, and fewer symptom of fever and lower limb pain or numbness than the UAE group.

4. Discussion

CSP accompanied with uterine rupture and uncontrolled hemorrhage is a rare diagnosis of ectopic pregnancy. Considering of an ever-growing population of patients with CSP in recent years, particularly in China, early diagnosis and better manage-

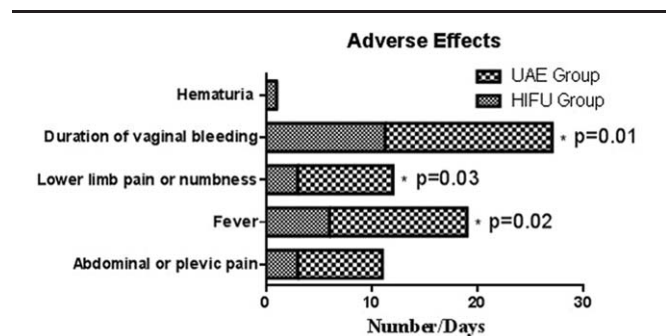


Figure 3. No significant difference in the symptom of lower abdominal pain or pelvic pain and hematuria between the HIFU group and the UAE group detected, but the HIFU group was of a tendency of shorter duration of vaginal bleeding, and fewer symptom of fever and lower limb pain or numbness. HIFU=high-intensity focused ultrasound, UAE=uterine artery embolization.

ment strategies were urgently needed.^[16] In light of no clear etiology and no consensus guideline for the management of CSP, there is a clear need to make individual treatment strategy and improve procedure with higher efficiency.

The objection of the treatment for CSP is to eliminate the embryo or fetus, expel the pregnancy tissue, decrease bleeding risk, and preserve the uterus to maintain reproductive function. The main principle of the management and treatment of patients with CSP is early detection by ultrasonography or MRI to determine the localization of the CSP and prevention of severe complications. However, due to villus implanting in the muscular layer and lacking of effective shrinkage, it is dangerous to perform curettage directly, because it could cause blood vessels rupture and catastrophic hemorrhage. Methotrexate provides a noninvasive, low cost, and reproductive function treatment, but serious bleeding and low success rate are inevitably occurred.^[17,18]

By obstructing of the uterine arteries and blocking the blood supply to the embryo, UAE can cause the death of the embryo and prevent excessive bleeding from embryo abruption and uterine curettage. Consistent with previous studies,^[17-19] the methods in present study of UAE followed by curettage is an effective and safe treatment for CSP with a low risk of heavy bleeding and hysterectomy. By transferring low energy ultrasound waves into instantaneous high temperature, HIFU can destroy small blood vessels, coagulate necrosis of targeted tissue around CSP lesions, and decrease the risk of hemorrhage in the later procedure of suction curettage. HIFU ablation was regarded as a safe technique to treat various diseases, such as uterine myoma, adenomyosis and malignant tumors.^[20-24] In addition, HIFU also were applied in patients with CSP.^[10,11]

Our study showed that there is no statistically significant difference in the baseline clinical characteristics, average time for gestational sac disappeared and serum β -HCG level reduction to normal level, normal menstruation recovery, and hospital stay between the HIFU group and the UAE group. Thus, the results demonstrated that HIFU combined with suction curettage was as effective as UAE followed by suction curettage in the management of CSP. Interestingly, less intraoperative blood loss and shorter duration of vaginal bleeding, which destroyed nutrient vessels and achieved satisfactory hemostatic effect, especially for the small vessels with a diameter less than 2mm,^[25] was observed in patients with the HIFU group when compared with the UAE group. As for larger vessels, the temperature of local tissue was taken away by rich blood flow during HIFU ablation. Therefore, HIFU ablation has no damage to the large vessels and prevents the occurrence of intraoperative blood loss and postoperative vaginal bleeding more directly and effectively.

During the follow-up period, the improvement of health quality of patients and the safety assessment of HIFU and UAE treatment for CSP were recorded. The results confirmed that both HIFU and UAE are safe and promising therapy option in the management of CSP patients. Complications of HIFU treatment have been reported according to the experience of treatment of uterine fibroid, including skin burns, fever, urinary tract infection, injuries of bowel and nerves, pelvic pain, and distension-radiating pain into the lower limbs.^[6,26,27]

In the present study, during the follow-up period, common complaints of HIFU ablation patients were lower abdominal pain and low-grade fever, which were subsided in 7 days with no treatment. Only 1 patient complained with mild hematuria, and recovered after oral administration of hemostatic drugs and anti-

infection treatment. Nine patients had dark red bloody secretions 2 weeks after HIFU ablation. However, all included patient returned to normal menstruation after 2 months follow-up. The adverse effects of UAE included high fever, mild lower limb pain, or numbness and longer duration of vaginal bleeding. These adverse effects were considered as post-embolization syndrome after the UAE procedure. In addition, 3 patients complained of acute lower abdominal pain and pelvic inflammation with a high fever after the curettage, and experienced a long period of vaginal bleeding. All patients of UAE group resumed menstruation, whereas 9 patients have less menstrual capacity than prior to treatment; 7 patients have longer menstrual periods, potentially resulted from excessive curettage. Five patients in the HIFU group and 3 in the UAE group had conceived during the follow-up. It demonstrated that HIFU treatment have less adverse and more effect than the UAE group. HIFU combined with suction curettage considered as an effective way as UAE followed by suction curettage in the management of CSP. Furthermore, compared with the UAE group, the HIFU group proved its features of noninvasive therapy with lower adverse effects and more comprehensive recovery.

5. Conclusions

Although both HIFU and UAE combined with suction curettage can effectively manage patients with CSP, HIFU results in a significantly lower adverse effects and better quality of life improvement than UAE during the long-term follow-up. For female patients who are searching for definitive symptom release and future children bearing plans, HIFU treatment is a better therapeutic option than UAE treatment.

5.1. Limitations

Limitations to our study included a relatively small sample size owing to stringent inclusion criteria and long-term follow-up. Additionally, patients with gestational age larger than 10 weeks were not included in this study. As a retrospective analysis, several unexpected factors could influence the results. Thus, further prospective, multicenter randomized controlled trials were necessary to evaluate and compare HIFU with UAE followed by suction curettage under hysteroscopy.

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