Int J Clin Exp Med 2014;7(7):1867-1872
www.ijcem.com /ISSN:1940-5901/IJCEM0000804

Original Article

Injection of MTX for the treatment of cesarean scar pregnancy: comparison between different methods

Xiang-Hua Yin*, Shi-Zhang Yang*, Zhong-Qin Wang, Hong-Yan Jia, Min Shi

*Department of Obstetrics and Gynecology, Clinical Medical College of Yangzhou University, Yangzhou, Jiangsu 225001, China. *Equal contributors.*

Received May 15, 2014; Accepted June 26, 2014; Epub July 15, 2014; Published July 30, 2014

Abstract: The aim of this study was to analyze clinical treatment and outcome of injection MTX for Cesarean scar pregnancy (CSP). We use retrospective study to compare the time in CSP of blood chorionic gonadotropin (β-HCG) and progesterone drooped to the normal, blood flow resistance and hospitalization days. 34 patients diagnosed with CSP were reviewed in our department from 2000 to 2013, including clinical characteristics, early diagnosis, treatment methods and treatment outcome. All patients were divided into B ultrasound-guided gestational MTX inject group (Group one), local intramuscular treatment group (Group two) and uterine artery perfusion MTX group (Group three). All cases had responded well to treatment. Except three cases of local intramuscular serum β-HCG decreased slowly MTX 10 mg intramuscular again, the average serum β-HCG decline of 65% the 4th day after treatment. In intramuscular group, the average length of stay is 19 ± 2.1 days. Serum β-HCG, progesterone recovery time were 20 to 89 days, an average of 54.5 days. B ultrasound-guided group hospital stay were 15 ± 3.1 days, serum β-HCG, progesterone recovery time were 18 to 71 days, an average of 44.5 days. In Uterine artery embolization group, the average length of stay is 16 ± 2.4 days, serum β-HCG, progesterone recovery time were 20 to 70 days, an average of 45 days. Statistical data results using T-test and chi-square test analysis. Three groups of β-HCG, progesterone decreased to normal days the difference was statistically significant ($P < 0.05$), but uterine artery embolization group and ultrasound-guided group B showed no significant difference ($P > 0.05$). B ultrasound-guided gestational injection of MTX and uterine artery embolization perfusion MTX are the better ways to treat uterine scar pregnancy.

Keywords: Cesarean scar pregnancy, B ultrasound-guided, methotrexate, uterine artery embolization

Introduction

Cesarean scar pregnancy (CSP) is an ectopic pregnancy implanted in the myometrium at the site of a previous cesarean section scar [1]. Since sac grown in lower segment of uterine where the scar in there, the muscular is thin here, surrounding by rich blood supply, when abortion it is often difficult to control bleeding. With the increased use of cesarean section and comprehensive use of more accurate imaging methods such as tansvaginal ultrasound, three-dimensional ultrasound, and magnetic resonance imaging (MRI), the blastocyst invasion at uterine incision scar myometrium in the early can be discovered. However, the serious complications of a cesarean scar pregnancy, including uterine scar rupture and internal hemorrhage, occur most often in the first trimester if the pregnancy is allowed to continue [2]. As a result, this inevitably leads to loss of the patient's fertility and significant long-term adverse effects on her health and quality of life [3-5]. There is no consensus about the method of choice for managing CSP. An understanding of the diagnosis and therapy of cesarean scar pregnancy and the differential diagnosis is important because it is relationship to a specific treatment choice, the exact choice of treatment can be a huge benefit to the patient. In this study, we retrospectively analysis and summary of the treat methods, results and treatment experience in 34 cases of CSP patient who admitted to hospital in the past 10 years in the Department of Obstetrics and Gynecology, Yangzhou University Teaching Hospital, which aims to provide the necessary treatment guidance for CSP patient in Clinical work.

Table 1. Clinical manifestations of 32 patients with CSP

Clinical manifestations	n (%)
Menopausal history	34 (100)
Abdominal pain	23 (67.65)
Uterus enlarged	27 (79.41)
Irregular vaginal bleeding	21 (61.76)

Table 2. Cesarean section history: comparison of 32 women of CSP

Gestation time after cesarean section	n (%)	Cesarean section times	n (%)
< 2	22 (67.05)	1	26 (76.47)
2-4	9 (26.47)	2	8 (23.53)
≥ 5	3 (8.82)	3	0 (0)
No.	34 (100)	-	34 (100)

Clinical data

Basic Information

34 CSP patients in January 2000 to December 2013 in our hospital, aged 20 to 38 years, mean 29 years. All cases of menopause time are 41 to 92 days, average (66.5 ± 13.1) days. 21 (61.76%, 21/34) cases had a small amount of vaginal bleeding after menopause and non-vaginal bleeding are 13 (38.24%, 13/34) cases. Serum β-HCG 21540.20~60161.14 U/L, mean (40850.67 ± 2249.23) U/L. Progesterone increased 25.07-134.47 nmol, average 79.77 ± 16.9. All cases caesarean methods are uterine lower segment transverse incision. The onset time to latest cesarean section time is 4 months to 5 years, average (5.33 ± 0.32) years and patients are not associated with chronic diseases (**Tables 1**-**3**).

Diagnosis standards of ultrasonography

(1) The empty uterine cavity without contacting with gestational sac; (2) The cervical canal was empty; (3) The gestational sac was located at the anterior wall of the uterine isthmus with or without cardiac activity; (4) The fluff implantation site myometrial blood stream are rich, presenting a low-speed low resistance flow rate curve; (5) Absence of or a defect in the myometrial layer between the bladder and the sac. All patients in this study were prompted uterine scar pregnancy by transvaginal B-ultrasound, gestational sac located in the anterior uterine lower segment caesarean section scar. Five cases gestational sac diameter are 1.1~4 cm in the lower uterine segment anterior see hybrid echo area, both in line with the above diagnostic criteria.

Methods

All patients completed necessary laboratory tests to exclude surgical contraindications. Then we get patients and family members agree and sign special treatment and surgical consent by communicate to patients and their families before surgery. The B ultrasound-guided gestational sac injection MTX group 22 (65.71%, 22/34) cases were treated with a bracket needle which can be fixed to the B ultrasound in our hospital Reproductive Center by vaginal fornix puncture gestational sac aspiration germ before inject MTX 50~80 mg (1 mg/kg). Sac puncture were implemented by path through the cervix as possible as to reach the sac in order to reduce injuries and bleeding during operation. To facilitate the operation, long needle were used, MTX at a dose of 50 mg dissolved in 2 to 3 ml of water for injection were slowly injected after sucked into portion cyst fluid recognized in the sac, then the patients obtained bed rest and were observed vaginal bleeding, no complications occurred during puncture.

Eight (23.53%, 8/34) cases were treated with local intramuscular, by MTX 10 mg injected into gluteus maximus per time, then the progesterone and serum β-hCG value changes every time were observed, if the progesterone or serum β-hCG value drop dissatisfied the patient would be given MTX injections again. We monitor blood β-hCG and progesterone value at the fourth day, seventh day and fourteenth of postoperative, when blood β-HCG dropped to 100 U/L, if necessary, B-monitored curettage was been done for the patients.

After routine disinfection and shop towels at the right inguinal, 4 (11.76%, 4/34) cases were treated by femoral artery puncture under the introduction of the catheter sheath uterine artery embolization perfusion MTX with Seldinger technique. In this method, 4, 5 F Cobra catheter were chosen as guidance by going through the two sides of the common iliac artery, internal iliac artery to the uterine artery

Table 3. General information of each group

Group	Gravity and parity	Age (y)	Gestational age (w)	Vaginal bleeding (ml)	Pregnancy tissue exhaust time (h)	Hospital-ization (d)	No.
Group one	G3P1	28.45 ± 3.9	9 ± 5.9	105.33 ± 5.81*	48.73 ± 5.88	18 ± 5.81*	22
Group two	G2P1	26.30 ± 4.39	8 ± 3.1	139 ± 4.83*	80.73 ± 6.32	25 ± 6.61*	8
Group three	G2P1	29.50 ± 3.55	9.5 ± 6.0	99 ± 2.88*	39.42 ± 7.63	15 ± 4.88*	4
P Value		0.462	0.391	0.042	0.031	0.021	

Group one: B ultrasound-guided gestational sac MTX inject; Group two: Local intramuscular treatment; Group three: uterine artery perfusion MTX. *There was no significant difference in mean age, gestational age, gravid discharge time ($P > 0.05$). Intrapartum bleeding, hospitalization have some difference ($P < 0.05$).

Table 4. β-hCG and progesterone value changes after treatment in 4th, 7th and 14th days

	β-hCG (U/L)			Progesterone (nmol/L)		
	Group one	Group two	Group three	Group one	Group two	Group three
Untreated	40154.17 ± 2249.23	32810.67 ± 1549.41	30250.61 ± 1247.16	128.6 ± 40.6	115.2 ± 31.4	137.2 ± 59.3
4th	2531.56 ± 1249.23	30561.67 ± 1429.51	20120.61 ± 1247.16	113.6 ± 32.6	108.1 ± 32.8	95.3 ± 31.4
7th	1167.29 ± 849.23	22610.68 ± 1149.41	1250.61 ± 247.16	76.4 ± 23.7	92.08 ± 21.4	61.5 ± 21.3
14th	143.29 ± 59.41	281.97 ± 49.62	120.61 ± 47.16	20.1 ± 25.4	38.2 ± 10.6	19.8 ± 31.4
P Value		< 0.05			> 0.05	

Table 5. Blood flow resistance (RI) of the lesion in each group

	Untreated	Treated
Group one	0.49 ± 0.20	0.91 ± 0.32
Group two	0.5 ± 0.10	0.61 ± 0.25
Group three	0.5 ± 0.20	0.95 ± 0.41
P Value	0.788	0.653

to make uterine artery angiography but we should confirm catheter within the uterine artery. In this situation some cases can be seen of intrauterine hemorrhage. After angiography, MTX (total in the 60~200 mg) were primed through both sides of the uterine arterial then suspension of 125 mg of gelatin sponge rubber and diluted contrast agent was injected into uterine artery slowly under fluoroscopic monitoring embolization until the uterus contrast staining disappeared. If necessary, supplemented with gelatin sponge embolization, and finally the internal iliac artery angiography should been done to confirm the uterine artery branches disappear. After the intervention perfusion MTX, we monitor blood β-hCG and progesterone value at the fourth day, seventh day and fourteenth of postoperative. If the blood β-hCG and progesterone decreased rapidly and the ultrasound imaging figure embryos no longer enlargement, curettage was been done for necessary patients under ultrasound guidance after operation 3~7 day. All patients were given folic acid detoxification treatment when necessary.

Postoperative observed indicators and follow-up

Cure: The main indicator is pregnancy termination that the serum β-hCG, progesterone decreased rapidly and even to the normal lever, ultrasound embryos imaging figure is no longer increasing or disappearance and menstruation returned to normal within six months. All patients had no serious adverse reactions after MTX chemotherapy and curettage bleeding less than 20 ml.

Therapeutically effective: Serum β-hCG decreased but did not reach to normal levels and scar mass unchanged even need supplement MTX injection in gestational sac or intramuscular.

Treatment failures: Serum β-hCG continue to increase or increase again after fall. Scar mass increase required additional surgery, or hemorrhage after interventional postoperative. Check the blood β-HCG, progesterone and blood routine at the fourth day, seventh day and fourteenth of postoperative for all patients during hospitalization. Vaginal B-understand checked again to observe both gestational sac diameter variation and the surrounding blood supply. Every week to check blood β-HCG and B-until

Table 6. Curettage cases in each group after treatment

Curettage	Group one		Group two		Group three		*P* Value
	Complete abortion (%)	Incomplete abortion (%)	Complete abortion (%)	Incomplete abortion (%)	Complete abortion (%)	Incomplete abortion (%)	
Need curettage	0 (0)	1 (3)	1 (12.5)	0 (0)	2 (50)	0 (0)	> 0.05
Unneeded curettage	19 (86.4)	2 (9)	5 (62.5)	2 (25)	0 (0)	2 (50)	

Table 7. Follow-up results

	First month (n, %)	Second month (n, %)	Third month (n, %)
Group one	17 (70.8)	5 (55.6)	0
Group two	4 (16.7)	3 (33.3)	1 (100)
Group three	3 (12.5)	1 (11.1)	0
Total	24 (100)	9 (100)	1 (100)

until to the normal after discharge and the follow up time is 3 to 6 months.

Results

All cases have responded well to treatment. Except three cases of local intramuscular the serum β-HCG decreased slowly and they got MTX 10 mg intramuscular again. On the forth day of the postoperation by detecting the blood β-HCG lever we find that the group one and group three fell by an average of 65% and the group two β-HCG lever decreased average approximately 59% (**Table 4**) and we continue review the blood β-HCG and vaginal ultrasound to observe the outcome at the 7th day and 14th day. Group one incomplete abortion three cases one of them got curettage under the guidance of B ultrasound. Group two incomplete abortion two cases and group three only one case both of them got curettage (**Table 6**).

In group one, the hospital stay are 15 ± 3.1 days. Serum β-HCG, progesterone recovery time are 18 to 71 days, an average of 44.5 days. In group two, the average length of hospital stay is 19 ± 2.1 days. Serum β-HCG, progesterone recovery time were 20 to 89 days, an average of 54.5 days. In group three, the average length of hospital stay is 16 ± 2.4 days. Serum β-HCG, progesterone recovery time are 20 to 70 days, an average of 45 days. Three groups patients both were followed up to the blood β-HCG down to normal. Statistical data results using T-test and *Chi-square test* analysis, according $\alpha < 0.05$ inspection standards, there difference at amount of vaginal bleeding, hospital stay and blood β-HCG dropped to normal days have statistically significant ($P < 0.05$) in three groups but there is no significant difference between group one and group three ($P > 0.05$) (**Table 4**). All patients were discharged by satisfied with the β-HCG decrease, weekly reviewed of blood β-HCG and transvaginal ultrasound after discharge. The blood flow resistance (RI) in the lesion showed no statistically significant ($P > 0.05$) (**Table 5**). Three months later, all patients were cured (**Table 7**).

Discussion

The risk of uterine rupture may be highest for the women with a previous cesarean section combined with a previous abnormal implantation of the placenta to the thin cesarean section such as a cesarean scar pregnancy [6]. Uterine rupture has previously been reported in patients who have undergone a prior cesarean section, it usually occurs at a frequency of between 0.3% and 1.7% [7] and the patients are 16.98 times more likely to experience uterine rupture than those with an unscarred uterus [8]. The second issue related to a subsequent pregnancy after a prior cesarean scar pregnancy is placenta accrete or increte. When the placenta is implanted over the scar of a previous cesarean delivery, the risk of placenta accrete is increased by 4.5 fold [9-11].

Implantation of a pregnancy within a caesarean fibrous tissue scar is considered to be the rarest form of ectopic pregnancy and a life-threatening condition [12]. The exact etiology remains unclear and most evidence suggests that damage to the endometrium and myometrium is the primary reason for its occurrence. Many theories for explaining its occurrence, the most reasonable one seems to be that the conceptus enters the myometrium through a microscopic dehiscent tract or defect in the cesarean section scar [13]. Another mechanism for intramural implantation is IVF and embryo transfer, even in the absence of any previous uterine surgery [14, 15]. This may be created throughout a trauma of a previous caesarean section,

any other uterine surgery, or following manual removal of the placenta.

Lin et al [16] drive a conclusion that collagen-binding VEGF may be a pragmatic solution for the treatment of severe uterine damages through the experiment of remodeling of scarred rat uterus. There is no agreement on the best approach of treatment for CSP. Some authors support the surgical alternative [17]. Such as, elective laparotomy with excision of the gestational mass reduces the risk of recurrence and shortens the follow-up period. However, a large wound, long recovery and hospitalization time, together with the possibility of postoperative adhesions that might affect fertility have to be considered [18, 19]. An invasive approach including diagnostic hysteroscopy followed by operative laparoscopy to treat an unruptured ectopic cesarean scar pregnancy has been described. Abviously, if late diagnosis with intraperitoneal hemorrhage and rupture occurs, immediately laparotomy should be performed.

In general, expectant management is not routinely recommended, but for patients who are young or have fertility requirements and reluctant to accept the surgical treatment, conservative treatment is of great significance. In this study, 34 patients were divided into three groups, group one 22 cases, group two 8 cases and group three 4 cases. On the forth day of the postoperation by detecting the blood β-HCG lever we find that the group one and group three fell by an average of 65% and the group two β-HCG lever decreased average approximately 59% and we continue review the blood β-HCG and vaginal ultrasound to observe the outcome at the 7th day and 14th day. All patients were follow up three months, there difference at amount of vaginal bleeding, hospital stay and blood β-HCG dropped to normal days have statistically significant ($P < 0.05$) in three groups but there is no significant difference between group one and group three ($P > 0.05$). All patients were discharged by satisfied with the β-HCG decrease and weekly were reviewed of blood β-HCG and transvaginal ultrasound after discharge. All patients were follow-up 1-3 months after discharge until they were cured.

As gestational sac drug injection with the B-understand guidance making direct contact with the drug and the gestational sac it kills sac and trophoblasts at 100%. With the uterine artery direct administration after embolization, the drug can directly into the embryonic vessels with higher biological activity of the free drug concentration, and the drug potency can be increased by 2 to 22 times. Maurer et al [20] reported that through the artery infusion, the drug concentration in the target organ systemic is chemotherapy's as 9 to 68 times, the drug in uterus up to the peak instantly. After uterine artery embolization, the target organ blood flow rapidly reduce, making the drug concentration in target organs remain longer than other parts 13 to 15 times higher. The first target organ extraction and first-pass metabolism reduce the toxicity of chemotherapy drugs significantly compared with intravenous administration.

Although conservative treatment is necessary, the immediately laparotomy should be done if the pregnancy found abdominal bleeding or uterus rupture occurs. The hysteroscopy and diagnostic curettage or laparoscopy surgery in the uterus scar ectopic pregnancy can also be applied [21]. In this study, although there is no case of surgery, laparotomy or laparoscopic, however, some studies considered if drug have no use in early scar pregnancy about three months the surgical treatment is feasible [22]. Blind curettage is contraindicated, because it may cause uterine perforation and bleeding, and severe patients maybe require hysterectomy which can cause the patients reproductive function loss. So early and correct diagnosis and treatment have important implication in clinical practice.

Drug therapy can reduce the blood β-HCG lever, reducing the risk of bleeding during treatment, is the basis treatment of this disease, therefore it is extremely important. MTX is the most commonly drug, but there is a major problem plagued clinicians that is systemic administration use of MTX for patients with high β-HCG the efficacy is poor. In some instances, assisted interventions, such as local excision or curettage pregnancy tissue is necessary, and bilateral uterine artery embolization to reduce bleeding has been further promoted [23, 24].

This study shows that groups one and three had significantly effect in CSP treatment more than local intramuscular injection. We believe that B ultrasound-guided gestational sac injection of MXT and uterine artery embolization of

MTX perfusion are better treatment methods for uterine scar pregnancy.

Acknowledgements

We thank the pathologists for their expert technical work and helpful suggestions.

Disclosure of conflict of interest

None.

Address correspondence to: Xianghua Yin, Department of Obstetrics and Gynecology, Clinical Medical College of Yangzhou University, 98 W Nantong Rd, Yangzhou, Jiangsu 225001, China. Tel: 1381582-7460; Fax: 87373012; E-mail: yinxh1965@126.com

References

[1] Fadhlaoui A, Khrouf M, Khémiri K, Nouira K, Chaker A, Zhioua F. Successful conservative treatment of a cesarean scar pregnancy with systemically administered methotrexate and subsequent dilatation and curettage: a case report. Case Rep Obstet Gynecol 2012; 2012: 248-564.

[2] Marcus S, Cheng E, Goff B. Extrauterine pregnancy resulting from early uterine rupture. Obstet Gynecol 1999; 94: 804-805.

[3] Maymon R, Halperin R, Mendlovic S, Schneider D, Herman A. Ectopic pregnancies in a Caesarean scar: Review of the medical approach to an iatrogenic complication. Hum Reprod Update 2004; 10: 515-523.

[4] Ash A, Smith A, Maxwell D. Caesarean scar pregnancy. BJOG 2007; 114: 253-263.

[5] Rotas MA, Haberman S, Levgur M. Cesarean scar ectopic pregnancies: Etiology, diagnosis, and management. Obstet Gynecol 2006; 107: 1373-1381.

[6] Seow KM, Cheng WC, Chuang J, Lee C, Tsai YL, Hwang JL. Methotrexate for cesarean scar pregnancy after in vitro fertilization and embryo transfer. A case report. J Reprod Med 2000; 45: 754-757.

[7] Leung AS, Leung EK, Paul RH. Uterine rupture after previous caesarean delivery. Maternal and fetal consequences. Am J Obstet Gynecol 1993; 169: 945-950.

[8] Gregory KD, Korst LM, Cane P, Platt LD, Kahn K. Vaginal birth after cesarean and uterine rupture rates in California. Obstet Gynecol 1999; 94: 985-989.

[9] Miller DA, Chollet JA, Goodwin TM. Clinical risk factors for placenta previa-placenta accreta. Am J Obstet Gynecol 1997; 177: 210-214.

[10] Chazotte C, Cohen WR. Catastrophic complications of previous cesarean section. Am J Obstet Gynecol 1990; 163: 738-742.

[11] Chattophadhyay SK, Kharif H, Sher eeni MM. Placenta praevia and accreta after caesarean section. Eur J Obstet Gynecol Reprod Biol 1993; 52: 151-156.

[12] Fylstra DL. Ectopic pregnancy within a cesarean scar: a review. Obstet Gynecol Surv 2002; 57: 537-543.

[13] Gobin PA, Bassil S, Donnez J. An ectopic pregnancy developing in a previous Cesarean section scar. Fertil Steril 1997; 67: 398-400.

[14] Hamilton CJ, Legarth J, Jaroudi KA. Intramural pregnancy after in vitro fertilization and embryo transfer. Fertil Steril 1992; 57: 215-217.

[15] Cheng PJ, Chueh HY, Soong YK. Sonographic diagnosis of a uterine defect in a pregnancy at 6 weeks gestation with a history of curettage. Ultrasound Obstet Gynecol 2003; 21: 501-503.

[16] Lin N, Li X, Song T, Wang J, Meng K, Yang J, Hou X, Dai J, Hu Y. The effect of collagen-binding vascular endothelial growth factor on the remodeling of scarred rat uterus following full-thickness injury. Biomaterials 2012; 33: 1801-1807.

[17] Seow KM, Huang LW, Lin YH, Lin MY, Tsai YL, Hwang JL. A cesarean scar pregnancy: issues in management. Ultrasound Obstet Gynecol 2004; 23: 247-53.

[18] Vial Y, Petignat P, Hohlfeld P. Pregnancy in a cesarean scar. Ultrasound Obstet Gynecol 2000; 16: 592-593.

[19] Wang CJ, Chao AS, Yuen LT, Wang CW, Soong YK, Lee CL. Endoscopic management of cesarean scar pregnancy. Fertil Steril 2006; 85: 494, e1-4.

[20] Maurer CA, Borner M, Buchler MW. Regional chemotherapy of gastre-intestinal cancer. Dig Surg 1977; 14: 9-22.

[21] Lee CL, Wang CJ, Chao A, Yen CF, Soong YK. Case Report: Laproscopic management of an ectopic pregnancy in a previous caesarean section scar. Hum Reprod 1999; 14: 1234-1236.

[22] Jurkovic D, Hillaby K, Woelfer B, Lawrence A, Salim R, Elson CJ. Firsttrimester diagnosis and management of pregnancies implanted into the lower uterine segment cesarean section scar. Ultrasound Obstet Gynecol 2003; 21: 220-227.

[23] Pascual MA, Ruiz J, Tresserra F, Sanuy C, Grases PJ, Tur R, Barri PN. Cervical ectopic twin pregnany and conservative treatment. Hum Reprod 2001; 16: 584-586.

[24] Chuang J, Seow KM, Cheng WC, Tsai YL, Hwang JL. Conservative treatment of ectopic pregnancy in a caesarean section scar. Br J Obstet Gynecol 2003; 110: 869-870.