The treatment of cervical pregnancy with ultrasound-guided local methotrexate injection

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Abstract

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OBJECTIVES: Cervical pregnancy (CP) is a rare type of ectopic pregnancy. Methotrexate (MTX) appears to be the first-line therapy for clinically stable women; however, there is still no consensus on the most appropriate treatment for this abnormal pregnancy. The aim of the present study was to investigate the efficacy of a single local MTX injection under transvaginal ultrasound guidance for the initial treatment of CP and to assess the post-treatment fertility.

METHODS: We retrospectively reviewed 15 CP patients treated with local MTX injection under transvaginal ultrasonography. In all patients, the serum human chorionic gonadotropin (hCG) levels were monitored and the gestational sac was evaluated after the treatment using ultrasonography. Magnetic resonance imaging was performed as necessary. The patients' clinical characteristics and clinical course after treatment, the efficacy of treatment, and the post-treatment fertility in patients desiring subsequent pregnancies were evaluated.

RESULTS: The median estimated gestational age at the time of the injection was 6w2d (range, 5w5d-11w0d). All 15 patients were successfully treated without the need for blood transfusions or surgical procedures; however, 3 patients required an additional local MTX injection due to a poor decline in the serum hCG level, and 1 patient required uterine artery embolization due to

persistent vaginal bleeding and an enlarging treated sac with contrast-enhanced blood vessels. The mean time required for hCG normalization was 43.8 days (95% confidence interval [CI], 33.3−54.3 days). Menses resumed after 68.4 days (95% CI, 51.9-84.9 days). Seven out of 10 women desiring subsequent pregnancies after the treatment had uneventful parturitions.

CONCLUSIONS: A single, ultrasound-guided, local MTX injection appears to be effective for the treatment of CP without the need for concomitant procedures or surgical interventions. Additionally, this conservative technique both preserves fertility and allows for the possibility of subsequent uneventful parturitions.

Introduction:

Cervical pregnancy (CP) is a rare ectopic pregnancy in which the trophoblast develops in the cervical glands and the fibrous cervical wall [1]. The incidence of CP is estimated to be approximately 1 in 8,628 to 10,000 deliveries [2, 3], and CP accounts for fewer than 1 in 455 ectopic pregnancies (0.2%) [4]. CP is considered to be associated with in vitro fertilization (IVF) or a history of prior curettage [5]. In an analysis of 3,145 transfer cycles after IVF, 1 patient out of a total of 825 pregnancies (0.1%) and 27 ectopic pregnancies (3.7%) that developed after IVF was diagnosed with CP [5]. Because the most common symptom of CP is painless vaginal bleeding, which may lead to massive haemorrhage, it is necessary to identify and manage CP at an early stage [1].

Various medical and surgical treatments for CP have been reported in the past, and there are still no standard protocols for treating CP. Methotrexate (MTX) seems to be the first-line therapy for clinically stable women and has been systemically administered or locally injected in case reports or case series [1]. In 2001, we successfully preserved an intrauterine gestation in a patient with a simultaneous cervical pregnancy through the use of an ultrasound-guided local MTX injection into the cervical gestation [6]. Since then, we have applied a

single local MTX injection as the initial treatment for CPs and cesarean scar pregnancies [7]. Previous articles suggested that local MTX injection may be effective as an initial treatment for CP; however, concomitant procedures or surgical interventions were used in combination with local MTX injection in most studies [8-13]. The efficacy of a single local MTX injection without concomitant procedures for treating CP has not been reported, and the prognosis of patients has been unclear. Here, we examined the efficacy of a single local MTX injection under transvaginal ultrasound guidance to treat CP and assessed post-treatment fertility.

Methods:

We retrospectively reviewed 15 CP patients treated at Kumamoto University Hospital between May 2007 and October 2015. The diagnosis was based on the patient's medical history, a clinical examination, the serum human chorionic gonadotropin (hCG) levels, transvaginal ultrasonography, and magnetic resonance imaging (MRI). The serum levels of intact hCG were measured using automated electrochemiluminescence immunoassays (TOSOH, Tokyo, Japan). Ultrasound examinations were performed using a 5−7.5 MHz mechanical sector probe (Mochida, Tokyo, Japan) with the following criteria used to establish the diagnosis: 1) a gestational sac in the cervical gland or trophoblastic invasion into the cervical glands if an entire gestational sac is not located in the cervix; 2) a yolk sac, a fetus or cardiac activity identified in the gestational sac; 3) the presence of flowing blood around the gestational sac detected by a Doppler study; and 4) the absence of a sliding sign that indicates an abortion. In patients with history of previous caesarean delivery, we excluded a diagnosis of caesarean scar pregnancy by reference to the previously reported criteria for the diagnosis [7]. MRI was performed as an adjunct to ultrasonography when the implantation site remained obscure or when the clinical course was eventful [14].

After diagnosis, a patient's baseline blood count and liver and kidney status were assessed, followed by treatment with a local ultrasound-guided transvaginal injection of 50 mg of MTX dissolved in 2 ml of distilled water. A 21-gauge percutaneous transhepatic cholangiography needle (Hakko, Tokyo, Japan) was attached to a transvaginal probe, and the needle was introduced into the gestational sac via the vaginal fornix under transvaginal ultrasound guidance. When the amniotic sac was large enough to allow aspiration, amniotic fluid was first aspirated. Next, a total of 50 mg of MTX was injected into the gestational sac and the stroma of the uterine cervix surrounding it. In cases where the flow around the gestational sac could be visualized by color Doppler, MTX was administered into the region of flow. The procedure was performed in an operating room under general anesthesia to prevent patient movement and to prepare for potential serious bleeding. We used the same procedure on clinically stable CP patients with or without fetal cardiac activity and with any initial hCG level.

The treatment date was defined as day 0, and the serum hCG levels were monitored until they became negative. The ratios of the serum hCG levels to those on day 0 were evaluated in every 1 to 3 days during the first 2 weeks

after the treatment. An additional local MTX injection was administered on weekdays when the serum hCG levels on day 5 exceeded the previous value. The gestational sac was also observed by ultrasonography until the sac completely resolved. During the follow-up period, the mean time required for hCG normalization, the duration until menses resumed, the treatment success rate, and the subsequent parturition rate in patients desiring pregnancy were analyzed.

All CP patients were numbered in order of admission. Descriptive statistics are presented as median (range), percentages, or mean (95% confidence interval [CI]). This study was approved by Kumamoto University Hospital Review Board, and all of the patients signed an informed consent form for participation in the study.

Results:

Clinical characteristics

Fifteen patients were diagnosed with CP at our institution during the study period. The characteristics of the patients are summarized in Table 1. All patients were referred to our hospital by their primary physicians. The median age of the patients at the time of diagnosis was 32 years old (range, 23−42 years old). Nine patients were nulliparous (60.0%), and 2 patients had experienced a previous cesarean delivery (13.3%). Eight of the patients had a history of uterine curettage (53.3%). Twelve pregnancies were spontaneously conceived, and 3 pregnancies were conceived through IVF-ET (patients 12, 13 and 15). One patient had a septate uterus, and 1 patient had myoma in the posterior wall of the uterine cervix (patients 5 and 12, respectively).

Twelve patients presented with vaginal bleeding (80.0%). Fetal cardiac activity was present in 6 patients at presentation (40.0%). MRI was performed as an adjunct to ultrasonography for 3 patients because ultrasonographic study showed uncharacteristic findings of CP (patient 5, 9, and 14). After the diagnosis of CP, all 15 patients were treated with a transvaginal ultrasonography-guided local MTX injection as the initial therapy. The median estimated gestational age

at the time of the injection was 6w2d (range, 5w5d−11w0d). The median serum hCG level at initial treatment was 11,565 mIU/ml (range, 2,323−100,578 mIU/ml).

The pattern of hCG level resolution and need for additional treatments

The changes in the serum hCG ratio in all of the CP patients during the first 2 weeks after MTX injection are presented in Figure 1. The hCG levels increased over the levels observed on day 0 after the local MTX injection in 8 patients (patients 2, 3, 4, 6, 10, 11, 13, and 14). Of these patients, the hCG levels on day 5 exceeded the previous value in three patients; therefore, an additional local MTX injection into the uterine cervix in the presence of color flow by a Doppler imaging was required on day 5 in patient 3 and on day 7 in patients 4 and 11. The hCG levels in all patients were reduced by more than 50% within 2 weeks.

One patient required uterine artery embolization after local MTX injection

A 35-year-old Japanese woman (gravida 1, para 0), who had undergone 2 uterine curettages after a diagnosis of hydatidiform mole at the age of 33 years,

was referred to Kumamoto University Hospital because of a suspicion of CP at the 8w1d of pregnancy (patient 9). The patient's serum hCG level was 100,578 mIU/ml. Transvaginal ultrasonography revealed that there was a gestational sac with a yolk sac without a fetus in the uterine cavity; however, the chorion frondosum with blood flow invaded into the stroma of the uterine cervix (Fig. 2A). MRI showed an enlarged lesion with dilated vessels in the uterine cervix that was connected to the gestational sac in the uterine cavity (Fig. 2B). These findings led to a diagnosis of cervical pregnancy. On the same day as the examination, 50 mg of methotrexate was injected into the stroma of the uterine cervix under ultrasonographic guidance, and the serum hCG levels continuously decreases thereafter. However, the patient's vaginal bleeding continued, and she started to complain of abdominal pain. Her cervical mass with color flow by a Doppler study gradually enlarged on ultrasonography, although the hCG levels had declined to 23.9 mIU/ml on day 54. MRI on day 55 showed an irregular lesion of 6×6×7.5 cm in the cervix, with high intensity on T1-weighted images and low intensity on T2-weighted images (Fig. 2C). Dynamic contrast-enhanced MRI revealed shadows of blood vessels with an early enhanced area in the mass (Fig. 2D), and three-dimensional aortography showed bilateral dilated

peripheral uterine arteries (Fig. 2E). The patient underwent uterine artery embolization (UAE) on day 56 because of continued vaginal bleeding and the presence of shadows of blood vessels with an early enhanced area in the enlarging cervical mass. The vaginal bleeding subsequently disappeared, and the treated sac was spontaneously discharged on day 94 (Fig. 2F).

The patient spontaneously conceived and had an uneventful pregnancy. She vaginally delivered a 3,150 g newborn at 39 weeks of gestation, 16 months after the local MTX injection.

Outcome after treatment and following parturition

Of all 15 CP patients, 11 patients were successfully treated by a single local MTX injection, while 3 patients required an additional MTX injection due to a poor decline in the hCG levels, and 1 patient required UAE due to persistent vaginal bleeding and the enlargement of the treated sac with blood flow. There was little blood loss during local MTX injection in all patients. No patient required systemic MTX injection, curettage, surgical treatment, or a blood transfusion. No adverse effects related to the MTX treatments were observed. The outcomes of all patients are summarized in Table 1. The mean time required for hCG

normalization was 43.8 days (95% CI, 33.3-54.3 days), and menstruation resumed after 68.4 days (95% CI, 51.9−84.9 days). The median observation period after the treatment was 63 months (range, 2−104 months).

Twelve patients were followed-up for more than 6 months after the treatment, and 10 of these 12 patients desired subsequent pregnancies. Seven of the 10 patients had uneventful parturition during the follow-up period (Table 2). Of the 7 patients, one patient underwent an IVF procedure after the resection of a cervical myoma (patient 12), and all 7 patients delivered at term 27.2 months (95% CI: 8.8-45.6 months) after the treatment. Of the remaining 3 patients, one patient spontaneously aborted at 8 weeks of gestation (patient 1), and one patient was treated by laparoscopic surgery after the diagnosis of tubal pregnancy (patient 4). The rate of parturition in women desiring to conceive after CP treatment was 70%.

Discussion:

Our results indicate that a single ultrasound-guided MTX injection was effective for the treatment of CP without the need for concomitant procedures or surgical interventions. In addition, this conservative technique preserves the fertility and enables the possibility of subsequent uneventful parturition.

The limitations of our study include small study population, lack of a control group, and retrospective design. Accordingly, further studies are necessary to establish the efficacy of this therapy.

MTX has been systemically (intramuscular injection) or locally administrated for the treatment of CP. The systemic administration of MTX alone does not appear to be effective for CP patients [15]. The systemic administration seems to be more effective if local injections of KCL or UAE are also combined [16-18] (table 3). In 1994, Timor-Tritsch et al. first reported that single ultrasound-guided transvaginal local injection of MTX was effective for 5 CP patients, and only one patient subsequently required curettage due to a poor decline in the hCG levels [8]. Since then, 5 reports including more than 5 cases have been published about patients initially treated with local MTX injection, although concomitant treatments were used with local MTX injection in all of

these reports (Table 4) [9-13]. MTX was transabdominally injected in one study; however, the needle was inserted through the bladder in 3 patients [10]. Therefore, the transvaginal injection of MTX under ultrasound guidance appears to be safe for the treatment of CP patients. There is currently no consensus regarding the appropriate dose of MTX for local injection to treat CP. MTX was used in total doses of 25 to 70 mg or 1 mg/kg in previous studies. In the present study, MTX was administered at a fixed total dose of 50 mg, similar to that used in other articles in which single local MTX injections were effective for patients with cesarean scar pregnancy [7, 19]. No adverse effects related to MTX therapy were observed in any of our patients.

The need for a concomitant procedure with local MTX injection, such as cervical curettage, systemic MTX administration, or local KCL injection, remains controversial. Routine cervical curettage seems to be associated with a possibility of cervical bleeding. Two articles adopted local KCL injection concomitant with local MTX injection if fetal cardiac activity was present [12, 13]. However, the fetal heartbeats in all 6 of our CP patients who initially showed a heartbeat disappeared after a single local MTX injection, and these patients could be uneventfully treated with single local MTX injection alone in the present

study. Another study also reported prompt arrest of fetal heartbeats following a single local MTX injection without KCL injection in 5 patients [8]. Further studies are necessary to verify the need for concomitant local KCL injection.

The methods used to evaluate the effects of local MTX injection have also not been unified. Additional treatments such as cervical curettage or systemic MTX administration were required for CP patients whose hCG levels did not decline smoothly in 4 previous studies; however, the indications for and the timing of the additional treatment were different in each study. We previously reported that the hCG concentration tended to increase within 6 days after a local MTX injection for patients with cesarean scar pregnancy [7]. Similar phenomenon was observed in patients with ectopic pregnancy treated with a single intramuscular MTX injection and in patients with cesarean scar pregnancy [20-22]. In the present study, the hCG levels temporarily increased over the levels observed on day 0 after the local MTX injection in 5 of the 11 patients who did not require additional treatments, suggesting that this characteristic pattern of changes in the serum hCG concentration may not necessarily reflect a poor outcome. Our results indicate that patients whose hCG levels on day 5 do not exceed the previous value can be observed without any additional intervention

after single local MTX injection. This finding may serve as a useful reference for clinical practice. A single local MTX injection appears to be of limited effectiveness for every CP patients. Cervical tamponades were necessary for 5 CP patients with postoperative cervical bleeding in 2 previous articles [11, 12]. One patient in the present study whose serum hCG level was 100,578 mIU/ml also required UAE for postoperative vaginal bleeding. It will be necessary to establish standard protocols for this treatment strategy.

As CP is most likely to be diagnosed in women who are undergoing fertility treatment, the preservation of fertility after CP treatment is significantly important. In 61 CP patients initially treated with systemic MTX administration, 6 required hysterectomy (table 3). On the other hand, our review indicates that none of the 86 CP patients, including our 15 patients, required hysterectomy following local MTX injection, and more than 20 women subsequently had uneventful parturition (Table 4). On the other hand, 6 patients Local MTX injection may be considered as the first-line treatment for CP patients who desire future fertility.

In conclusion, a single ultrasound-guided local MTX injection appears to be effective for the treatment of CP without the need for concomitant procedures

or surgical interventions, although it will be necessary to establish the indications and protocols for this therapy. Additionally, this conservative technique both preserves fertility and allows for the possibility of subsequent uneventful parturitions.

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Figure legends

Figure 1: Changes in the human chorionic gonadotropin (hCG) ratios from the hCG level on day 0 during the first 2 weeks after local methotrexate (MTX) injection for cervical pregnancy.

An additional local MTX injection was required on day 5 in patient 3 and on day 7 in patients 4 and 11 because their hCG levels on day 5 exceeded the previous value. The hCG levels in all patients were reduced by more than 50% within 2 weeks.

Fig. 1

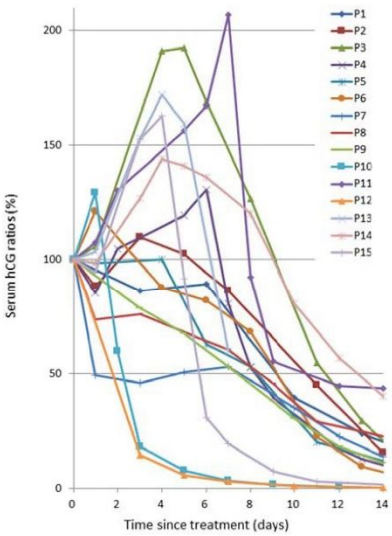

Figure 2: The serial findings of transvaginal ultrasonography (TUS) and magnetic resonance imaging (MRI) during the course of treatment for the patient who required uterine artery embolization after local MTX injection. (A) TUS showed that the chorion frondosum invaded into the stroma of the uterine cervix before the treatment (Arrows). (B) Sagittal T2-weighted MRI showed an enlarged mass with high intensity in the uterine cervix connected to the gestational sac in the uterine cavity before the treatment (Arrows). (C) Sagittal T2-weighted MRI showed an irregular lesion with low intensity in the uterine cervix on day 55. (D) Transverse dynamic contrast-enhanced MRI showed shadows of blood vessels with an early enhanced area in the mass on day 55 (Arrows). (E) Three-dimensional magnetic resonance aortography showed bilateral dilated peripheral uterine arteries on day 55 (Arrows). (F) TUS showed that there was no remaining tissue observed in the uterine cervix on day 94. U: uterus; B: bladder.

Fig. 2

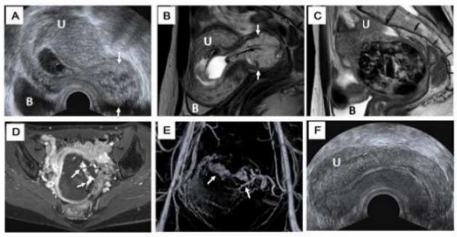

Table 1: Characteristics and outcome of the patients with cervical pregnancy treated with local MTX injection

Variable	Value
Age (yr)*	32 (23-42)
Nulliparous**	9 (60.0%)
Prior uterine curettages**	8 (53.3%)
Estimated gestational age*	6w2d (5w5d-11w0d)
Bleeding at presentation**	12 (80.0%)
Fetal cardiac activity**	6 (40.0%)
Serum hCG concentration before treatment (mIU/ml)*	11,565 (2,323-100,578)
Time to hCG normalization (days)*	43.8 (33.3-54.3)
Time to resumption of menses (days)*	68.4 (51.9-84.9)
Observational period after treatment (months)**	63 (2-104)
Parturition rate in women who desired pregnancy (%)	70

*Data presented as median (range). **Date presented as n (%).

Table 2: Parturition after the treatment of cervical pregnancy

Patient	Mode of delivery (Indication for C/S)	Birth weight of new born (gram)	Gestation age at delivery (weeks)	Time between treatment and delivery (months)
3	Vaginal*	2,470	37	83
7	Cesarean (Previous C/S)	2,986	38	21
8	Vaginal*	3,066	39	14
9	Vaginal	3,150	39	16
10	Cesarean (CPD)	2,890	41	26
11	Vaginal	3,418	40	16
12	Cesarean (Post-myomectomy)	2,645	38	15

*Delivery at an outside hospital, CPD: Cephalopelvic disproportion

Table 3: Outcomes for CP patients treated with systemic MTX administration

	Source	Year	No	Dose of MTX (mg)	Concomitant procedure	Required additional treatment	The proportion of women that did not require any additional treatment (%) (95% confidence interval)	Subsequent parturition
1	Kung et al [16]	1997	16	–	Curettage (3) Local KCL injection (2) Vaginal packing (1) D&C and tamponade (1) UAE (1) UAE, D&C, and chemotherapy (1)	Hysterectomy (4)	75.0 (47.6-92.7)	5 term and 1 preterm deliveries
2	Verma et al [17]	2009	19	50-75 mg/m^2	Local KCL injection if cardiac activity is present (15)	4 (UAE, D&C, transvaginal ligation of the uterine artery brunch, blood transfusion, tamponade with Foley catheter)	78.9 (54.4-93.9)	1 term delivery
3	Shrestha et al [15]	2011	11	50 mg	–	Hysterectomy (2) Curettage (9) Hysteroscopic electrocoagulation followed by gauze packing (3) Uterine aspiration (1)	18.1 (2.2-51.7)	–
4	Zakaria et al [18]	2011	15	1 mg/kg	UAE (6) UAE and local KCL injection (4)	1 (Blood transfusion and UAE followed by vaginal packing)	93.3 (68.0-99.8)	1 term and 1 preterm deliveries

D&C: dilation and curettage, UAE: uterine artery embolization

Table 4: Serum hCG concentrations, treatments, and outcomes in CP patients treated with local MTX injection

	Source	Year	No	Mean initial hCG concentration (mIU/ml)	Mode	Dose of MTX (mg)	Concomitant procedure	Required additional treatment	Indication for additional treatment	The proportion of women that did not require any additional treatment (%) (95% confidence interval)	Subsequent parturition
1	Timor-Tritsch et al [8]	1994	5	20,536 (2,040-40,214)	TV	25 or 50	–	Cervical curettage (1)	Poor decline in the hCG levels	80.0 (28.3-99.4)	1 twin pregnancy (unknown outcome)
2	Hassiakos et al [9]	2005	6	NA (4,100-10,500)	TV	70	D&C (6)	–	–	100 (54.0-100)	–
3	Mesogitis et al [10]	2005	9	10,732 (6,500-31,105)	TA	25	Cervical curettage (9)	Second local MTX injection (2)	Persistent fetal cardiac activity	77.7 (39.9-97.1)	–
4	Grimbizis et al [11]	2006	5	14,144 (1,440-36,800)	TV	25	Systemic MTX injection (5)	Cervical curettage (4) Cervical tamponade (2)	Poor decline in the hCG levels Bleeding	20.0 (0.5-71.6)	1 term delivery
5	Jeng et al [12]	2007	38	38,948 (2,765-103,256)	TV	50	Local KCL injection if cardiac activity is present (22)	Systematic MTX injection (2) Cervical tamponade (3)	Poor decline in the hCG levels Bleeding	86.8 (71.9-95.5)	15 term and 1 preterm deliveries
6	Junior et al [13]	2014	8	20,723 (3,013-71,199)	TV	1 mg/kg	Local KCL injection (8)	Systematic MTX administration (3)	Poor decline in the hCG levels	62.5 (24.4-91.4)	2 term deliveries including 1 previa
	Present study	2016	15	22,898 (2,323-100,578)	TV	50	–	Second local MTX injection (3) Uterine artery embolization (1)	Poor decline in the hCG levels Bleeding	73.3 (44.8-92.2)	7 term deliveries

D&C: dilation and curettage, KCL: potassium chloride, NA: not available, TA: transabdominal, TV: transvaginal