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Subsequent reproduction and obstetric outcome after methotrexate treatment of cervical pregnancy: a review of original literature and international collaborative follow-up

Fu-Tsai Kung[1,3], Shiuh-Young Chang[1], Yung-Chieh Tsai[1], Fu-Ren Hwang[1], Te-Yao Hsu[1] and Yung-Kuei Soong[2]

[1]Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Kaohsiung and [2]Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, Chang Gung Medical School, Linkou Medical Center, Taipei, Taiwan, Republic of China

[3]To whom correspondence should be addressed at: Department of Obstetrics and Gynecology, Chang Gung Memorial Hospital, 123 Ta Pei Road, Niao Sung Hsiang, Kaohsiung Hsien, Taiwan, Republic of China

The case reports of 22 patients with cervical pregnancies treated by methotrexate (MTX) administration and published in English literature between 1983 and 1995 were reviewed, by either original paper review or follow-up under international collaboration, to determine the subsequent reproductive performance and obstetric outcomes. Out of 22 cases, 18 (78%) MTX chemotherapy attempts succeeded with complete remission and four (22%) failed. Of the 13 women who wished to conceive and could be followed for at least 3 years, nine succeeded in having live births without congenital malformations, one spontaneously aborted and three suffered infertility. In general, MTX chemotherapy alone or combined with adjuvant methods such as subsequent cervical curettage or cervical tamponade, or intracervical potassium chloride injection, appears to be a convenient and effective method for the treatment of the majority of cervical pregnancies before 12 weeks gestation, and has not been shown to have detrimental effects on subsequent reproductive capacities, obstetric outcomes and progeny health for those cases with successful preservation of the uteri.

Key words: cervical pregnancy/methotrexate/reproduction

Introduction

Cervical pregnancy, a rare form of ectopic pregnancy, results from the passage of a blastocyst through the uterine cavity and its subsequent implantation and growth within the endocervical canal. Cervical pregnancy is extremely difficult to manage and generally results in either spontaneous abortion or a surgical attempt at evacuation, both of which might be combined with life-threatening bleeding. Before 1979, the occurrence of cervical pregnancy made most women sterile because an unavoidable hysterectomy to save the life of the patient was mandatory in ~90% of cases (Bachus *et al*., 1990). After the advent of ultrasound, ultrasonic criteria were developed (Raskin, 1978; Hofmann *et al.*, 1987) to diagnose cervical pregnancy precisely by imaging. Timor-Tritsch *et al*. (1994) reported that the diagnosis of a viable cervical pregnancy could be made if ultrasonography could identify the placenta and chorionic sac containing a live fetus below the internal os, the empty uterine cavity and the barrel-shaped cervix with a significantly dilated cervical canal. These criteria are especially useful when an intracervical gestational sac is established, and the likelihood of a cervical pregnancy over the first trimester is thus dramatically decreased (Barham and Raine, 1989; Yankowitz *et al*., 1990). With this new ability to make an early diagnosis of cervical pregnancy, various conservative surgical techniques, such as cervical curettage followed by intracervical balloon tamponade or cervical cerclage, angio-embolization of feeding arteries and bilateral ligation of hypogastric arteries, could be performed in an effort to avoid total hysterectomy and preserve fertility potential (Bachus *et al*., 1990; Frates *et al.*, 1994; Meerssche *et al*., 1995). The more conservative method of methotrexate (MTX) administration, a non-surgical and minimally invasive approach to eradicate trophoblasts within the endocervix, is now a viable treatment option. Meerssche *et al.* (1995) proposed an algorithm for the management of cervical pregnancy of <12 gestational weeks. There were two arms in the algorithm. One underwent surgical curettage followed by a cervical tamponing technique, and the other received MTX therapy. MTX therapy in combination with high-resolution ultrasound and rapid quantification of serum human chorionic gonadotrophin is a milestone in the shift in treatment modality away from surgical approaches toward non-invasive therapy. MTX therapy may provide a favourable prognosis and is rapidly becoming the method of choice in the majority of cases of cervical pregnancy.

The main concern expressed by patients of childbearing age after MTX treatment for cervical pregnancy is for their prospects of a successful pregnancy in the future. Here we examine the subsequent reproductive performance, obstetric outcomes and birth health of patients with a prior cervical pregnancy treated by MTX alone or in combination with adjuvant procedures. The main purposes of this study were to determine the efficiency of chemotherapy with MTX in treating cervical pregnancy and maintenance of fertility potential, and to provide reassurance of the normality of the children subsequently born to mothers receiving MTX therapy.

Materials and methods

Case reports of cervical pregnancy treated by MTX, which had been published in English literature during the period 1983–1995 and could be retrieved using the CD-PLUS MEDLINE OVID system (OVID Technologies Inc., NY, USA), were screened for this international

collaborative study. We reviewed subsequent reproductive performance in patients who had had prior cervical pregnancies of various gestational length and had received chemotherapy with MTX administration via local and/or systemic administration as the primary treatment modality. Factors that were considered in assessing the reproductive status of the patients after cervical pregnancy included the desire for pregnancy, the diagnosis of infertility, the obstetric outcome of the first conception following the cervical pregnancy, the mode of delivery and the presence or absence of birth defects in the live-born children. Those case reports that totally or partially lacked information on subsequent gestations were supplemented by direct correspondence with the authors, who were requested to complete a questionnaire. Cases were excluded from the study if an adequate response to the questionnaire was not obtained. MTX management of cervical pregnancy was defined as treatment by MTX alone or concomitantly with one or two of the following procedures: cervical curettage, cervical packing or tamponade, angio-embolization, intra-amniotic potassium chloride injection and other antitrophoblastic chemotherapeutic drug administration.

Results

Our literature search produced a total of 37 case reports of patients with cervical pregnancies whose management included MTX chemotherapy, reported in 26 publications. Eight of these case reports contained information regarding subsequent reproductive function and obstetric outcomes (Farabow *et al*., 1983; Cheng *et al*., 1986; Wolcott *et al*., 1988; Bakri and Badawi, 1990; Yankowitz *et al*., 1990; Dall *et al*., 1994; Mantalenakis *et al.*, 1995; Zohav *et al*., 1995). In the remaining 29 cases, which had incomplete information on subsequent reproductive function and obstetric outcomes (in 18 separate reports), questionnaires were sent to the 18 corresponding authors by registered mail. A total of nine questionnaire responses were obtained. Analysis of the questionnaire data showed that 14 cervical pregnancy cases met our study criteria. Thus, a total of 22 (the original eight plus 14) cases, which could be traced from the diagnosis of cervical pregnancy to subsequent gestation after cervical pregnancy, formed the study database. Table I lists the patient characteristics, concomitant therapeutic procedures and reproductive and obstetric outcomes in detail.

Of 22 MTX treatments with or without other concomitant procedures, 18 (78%) succeeded in complete remission and four (22%) treatments failed. Among the 18 patients with complete remission, six (whose pregnancies had gestational ages varying between 6 weeks and 8 weeks 4 days) received MTX administration only and the other 12 required concomitant adjuvant therapeutic procedures either during or after MTX treatment (Table I). The concomitant procedures for those 12 patients included cervical curettage in five cases, intra-amniotic potassium chloride injection in two cases, vaginal packing in one case, the combination of dilatation and curettage and tamponade in one case, embolization of the uterine artery in one case, the combination of embolization and dilatation and evacuation in one case and simultaneous chemotherapy with actinomycin D and cyclophosphamide in one case. Among the four patients whose MTX attempts failed, three lost reproductive function because of the need for a hysterectomy (Farabow *et al*., 1983; Cheng *et al*., 1986; Dall *et al*., 1994) and one preserved the uterus after a major operation including bilateral ligation of the internal iliac arteries and hysterotomy (Wolcott *et al*., 1988).

Of the 19 women whose uteri were preserved following treatment, 18 indicated the desire to conceive in the future after cervical pregnancies, while one woman was undecided (Miyamura *et al*., 1993). Only 16 of these patients were followed for at least 3 years after their cervical pregnancy. Among the 16 women who received follow-up, two did not want to conceive yet (Timor-Tritsch *et al*., 1994), one conceived despite not wanting a pregnancy and received an elective termination (Palti *et al*., 1989) and 13 earnestly wanted to conceive.

Of the 13 women who wished to conceive, nine succeeded in having live births, including six viable singletons (Wolcott *et al*., 1988; Kim *et al*., 1989; Roussis *et al*., 1992; Kung *et al*., 1995; Mantalenakis *et al*., 1995; Zohav *et al*., 1995), one term twin (Timor-Tritsch *et al.*, 1994), one live twin (Frates *et al*., 1994) and one preterm healthy delivery (Bakri and Badawi, 1990). One patient spontaneously aborted at 8 weeks of gestation (Yankowitz *et al*., 1990), and the remaining three patients suffered infertility (Balasch *et al*., 1994; Frates *et al*., 1994) and failed to conceive even after an attempt at in-vitro fertilization in one case (Frates *et al*., 1994). Neither repetitive cervical pregnancy nor other forms of ectopic pregnancy occurred.

Concerning the obstetric management and outcomes of the nine wanted pregnancies which were carried to live births, four deliveries were via the vaginal route, four were via Caesarean section and another one was unknown. No patient was found to have cervical incompetence during pregnancy, although a singleton preterm delivery occurred at 32 weeks gestation (Bakri and Badawi, 1990). None of the infants was found to have either minor or major anomalies or neonatal morbidity or mortality. One case of placenta increta (Kim *et al*., 1989) requiring a Caesarean hysterectomy occurred among the nine deliveries.

The therapeutic doses and protocols of MTX administration varied with the reports. Generally speaking, a schedule of 0.5–1.0 mg/kg every other day for 5–7 days with folinic acid rescue i.m. (Farabow *et al*., 1983; Kim *et al*., 1989; Palti *et al*., 1989; Yankowitz *et al*., 1990; Roussis *et al*., 1992; Balasch *et al*., 1994; Kung *et al*., 1995) and/or a single injection of 12.5–50.0 mg intracervically or intra-amniotically (Timor-Tritsch *et al.*, 1994; Mantalenakis *et al*., 1995) was commonly used. The route of MTX administration was systemic and/or intra-amniotic injection or a combination of the two, depending on the choice of the investigator. However, there was a significant clinical implication that MTX treatment appeared to be more effective and convenient if MTX was administered locally through intracervical or intra-amniotic injection under initial ultrasonic guidance, with or without a subsequent sequential systemic injection for those cases of a viable cervical pregnancy with fetal cardiac activity (Palti *et al*., 1989; Timor-Tritsch *et al.*, 1994; Mantalenakis *et al*., 1995).

The mean time interval between elimination of the cervical pregnancy by MTX and the awareness of subsequent conception was 8 months, as averaged from the sum of five available

Table I. Patient characteristics, concomitant therapeutic procedures, and reproductive and obstetric outcomes of cervical pregnancies managed by methotrexate

Reference	No. of cases	Gestation (weeks) (FHB)	Concomitant procedure(s)	Result	Fertility desire	Pregnancy	Obstetric outcome	Congenital anomaly	Comments
Farabow *et al.* (1983)	1	20 (?)	Laparotomy	Hysterectomy	?				Failure
Cheng *et al.* (1986)	1	9^{+} (?)	D&C, packing	Hysterectomy	(+)				Failure
Wolcott *et al.* (1988)	1	12 (+)	Iliac artery ligation, hysterotomy, tamponade	Major surgery	(+)	(+)	2785 g (C/S)	–	Failure; uterus preserved
Palti *et al.* (1989)	1	9 (+)	Curettage	Remission	(+)	(+)	D&C (elective)		
Kim *et al.* (1989)	1	12 (–)	Curettage	Remission	(+)	(+)	3500 g (C/S)	–	Caesarean hysterectomy (placenta increta)
Yankowitz *et al.* (1990)	1	9 (–)	Packing	Remission	(+)	(+)	Abortion (spontaneous)		
Bakri and Badawi (1990)	1	6 (–)	Actinomycin D and cyclophosphamide	Remission	(+)	(+)	1900 g (preterm, V/D)	–	
Roussis *et al.* (1992)	1	5 (–)	Curettage	Remission	(+)	(+)	3920 g (V/D)	–	
Miyamura *et al.* (1993)	1	5 (+)	Curettage	Remission	(–)				Divorced woman
Timor-Tritsch *et al.* (1994)	5								
	(i)	8^{+} (+)	–	Remission	(+)	(–)			Not prepared for pregnancy
	(ii)	6^{+} (+)	–	Remission	(+)	(–)			Not prepared for pregnancy
	(iii)	6^{+} (+)	–	Remission	(+)	(+)	Twin (term)	–	
	(iv)	7^{+} (+)	Curettage	Remission	(+)	?			Loss of follow-up
	(v)	6^{+} (+)	–	Remission	(+)	?			Loss of follow-up
Dall *et al.* (1994)	1	9 (?)	Prostaglandin (IA), D&C, tamponade	Hysterectomy	?				Failure
Frates *et al.* (1994), Ginsburg *et al.* (1994)	3								
	(i)	6^{+} (+)	Embolization, D&E	Remission	(+)	(–)			History of Asherman's syndrome, infertility
	(ii)	6^{+} (+)	KCl (IA)	Remission	(+)	(–)			IVF failure after cervical pregnancy
	(iii)	5^{+} (?)	Embolization	Remission	(+)	(+)	Twin (live, C/S)	–	IVF babies after cervical pregnancy
Balasch *et al.* (1994)	1	7^{+} (?)	–	Remission	(+)	(–)			Infertility before and after cervical pregnancy
Zohav *et al.* (1995)	1	6 (?)	–	Remission	(+)	(+)	3540 g (V/D)	–	
Mantalenakis *et al.* (1995)	1	12^{+} (+)	D&C, tamponade	Remission	(+)	(+)	3080 g (V/D)	–	
Kung *et al.* (1995)	1	10 (+)	KCl (IA)	Remission	(+)	(+)	3500 g (C/S)	–	

C/S = Caesarean section; D&C = dilatation and curettage; D&E = dilatation and evacuation; FHB = fetal heart beat; IA = intra-amniotic injection; V/D = vaginal delivery; (+) = yes; (–) = no; (?) = unknown, uncertain or not available.

data sources, including 8 months from Yankowitz *et al.* (1990), 10 months from Bakri and Badawi (1990), 12 months from Zohav *et al.* (1994), 5 months from Mantalenakis *et al.* (1995) and 6 months from Kung *et al.* (1995).

Failure of MTX therapy occurred in four patients. One failure occurred at 20 weeks gestation (Farabow *et al*., 1983), one at 12 weeks gestation (Wolcott *et al*., 1988) and the other two at 9 weeks gestation (Cheng *et al*., 1986; Dall *et al*., 1994). The first patient eventually underwent hysterectomy during the second laparotomy because of an unresectable cervical mass, which was misdiagnosed as malignant gestational trophoblastic disease unresponsive to chemotherapy. The second patient had successful preservation of the uterus after a major operation with a combination of iliac artery ligation, hysterotomy and intracervical balloon tamponade following failure of the initial management with MTX. The remaining two patients both required an emergency hysterectomy because of uncontrollable bleeding from the cervix. The uncontrollable bleeding occurred during evacuation and curettage in the third patient and at follow-up after the completion of MTX therapy in the fourth patient.

Discussion

Previously, reports of patients with cervical pregnancies treated with MTX were mostly considered as case reports because of their rarity with an incidence ranging from 1 in 2400 to 1 in 50 000 pregnancies (Parente *et al.*, 1983). This made difficult an adequate overall assessment of the efficacy of MTX therapy and an evaluation of subsequent reproductive potential following cervical pregnancy. This retrospective study has used international cooperation to follow and describe reproductive performance and the perinatal outcome of the first conception after MTX treatment of cervical pregnancy during the period from 1983, when Farabow *et al.* (1983) introduced MTX treatment of cervical pregnancy, to 1995. The preliminary result of this study reveals a significant chemotherapeutic effectiveness of MTX therapy alone or in combination with adjuvant therapy, and an apparent lack of detrimental effects on subsequent reproductive function and pregnancy outcomes in patients after MTX treatment of cervical pregnancy with a gestational age younger than the first trimester.

Successful MTX therapy was achieved in 18 out of 22 cases. However, 12 cases required the use of adjuvant therapies in addition to MTX administration. MTX therapy can be a good treatment choice for cervical pregnancy, and combination with less invasive surgical procedures is mandatory under some circumstances. In patients with a viable cervical pregnancy, initial intra-amniotic injection of MTX to cease fetal cardiac activity was more effective than systemic MTX administration only, and would be likely to minimize the potential risk of MTX treatment failure.

Four attempts at MTX treatment failed. A total hysterectomy to remove the entire uterus and the diseased cervix was required in two patients because uncontrollable haemorrhaging occurred. In our opinion, MTX, via either systemic or local administration, effectively destroyed the aberrant trophoblasts within the endocervical canal in those patients who had non-viable cervical pregnancies. However, after trophoblast shedding, either spontaneously or manually, rapid and massive bleeding from the uninvolutional and atonic cervix could occur unexpectedly.

MTX, a cytotoxic drug, has been thought to have a potential mutagenic activity on animal and human gametes and also teratogenic effects on concepti. Out of a total of 11 post-cervical pregnancy concepti in this study, nine developed to live births without any congenital defects, one ended in elective abortion because of an unwanted intrauterine pregnancy and one (9%) had a spontaneous abortion of unknown cause at 9 weeks gestation. According to this observation, patients experiencing MTX administration are not likely to be at increased risk of fetal anomalies or spontaneous abortion in later conceptions. Actually, total doses of MTX used during the entire treatment course of cervical pregnancy were not high when compared with those used for treating gestational trophoblastic tumours (Rustin *et al.*, 1984). Furthermore, on the basis of previous data on patients with unruptured tubal pregnancies, MTX therapy, when compared with salpingostomy via laparoscopy or laparotomy, has not impaired subsequent reproductive performance (Stovall *et al*., 1990; Pansk *et al*., 1993; Darai *et al*., 1996). MTX was administered in a sequential way or via a single injection. The relatively low dose and short exposure duration of MTX minimize its potential systemic side-effects and any possible hazardous inducement of follicular growth in the ovaries.

The possible loss of adequate anatomical patency and hospitable mucus production of the cervix, resulting from trophoblast invasion and its sequelae after eradication, may be implicated in disruption in the outflow of resumptive menses and transport of spermatozoa in the reproductive tract. However, results from this study indicated that a combination of return of normal menstruation in all patients and achievement of 11 intrauterine pregnancies among 14 patients who either wished to conceive (13 cases) or had an unwanted conception (one case) showed that cervical function was restored without impairment. Balasch *et al*. (1994) performed hysteroscopies to examine the cervix and found the endocervical canal to be normal 1 week after complete eradication of the trophoblasts. Thus, it appears that when a sufficient portion of the cervix is preserved, cervical function is more likely to recover. On the basis of follow-up data available on five pregnancies, the mean time interval between elimination of disease and diagnosis of subsequent conception was 8 months, with the shortest period being 5 months. We suggest a minimum 8 month follow-up period before attempting subsequent pregnancy following cervical pregnancy so as to ensure adequate functional recovery of the cervix.

The incidence of infertility after MTX treatment for cervical pregnancy, excluding those patients receiving a hysterectomy, was 23% (three out of 13 who wished to conceive). Actually, infertility problems had been anticipated in all three cases before the cervical pregnancy occurred. On the basis of this result, we might speculate that a prior cervical pregnancy with MTX treatment does not impair subsequent reproductive function and that the risk of infertility after MTX therapy does

not generally increase. However, a larger study population will be needed to prove this hypothesis.

The two obstetric complications that occurred in our study group of patients were one placenta increta and one singleton preterm birth in subsequent parturition. In reviewing the history of these two cases, we were unable to find any significant clinical link between complications and MTX treatment, and we believe their occurrence was independent of MTX management.

In conclusion, the MTX regimen has been shown to be a convenient and effective method of therapy for cervical pregnancy, particularly before 12 weeks gestation. The majority of uteri were totally preserved without functional impairment of the cervix after MTX therapy alone or when combined with adjuvant procedures. Patients who are treated successfully with MTX are likely to recover normal reproductive function and to have good pregnancy outcomes in the future and do not appear to have an increased risk of congenital anomalies in their live births.

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