

Low-dose methotrexate administration in the management of cervical pregnancy

Servikal gebeliğin tedavisinde düşük doz metotreksat tedavisi

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Abstract

Objective: Cervical pregnancy is a rare form of ectopic pregnancy. There is the risk of hysterectomy when this type of ectopic pregnancy is managed with surgery. An established form of conservative treatment is the administration of methotrexate (MTX). We demonstrate the effectiveness of a low-dose MTX regimen.

Materials and Methods: Case analysis of cervical pregnancies at a tertiary referral center at an University Hospital. Six patients presented with cervical or isthmocervical pregnancies. Low-dose of MTX was administered intravenously. Secondary surgical intervention was carried out when needed. The main outcome measures were to preserve childbearing capacity using conservative treatment partly followed by curettage for cervical pregnancy

Results: Six patients received conservative treatment with MTX in a low-dose regimen. During the course of conservative treatment with MTX, three patients underwent curettage. One of these patients also received an intra-amniotic administration in addition to systemic administration of MTX.

Conclusions: Systemic low-dose methotrexate treatment is an effective form of primary treatment, with a low rate of side effects.

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Key words: Cervical pregnancy, methotrexate, low-dose regime

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Özet

Amaç: Servikal gebelik dış gebeliklerin nadir görülen bir formudur. Cerrahi yapılmaya çalışıldığında histerektomi riski doğar. uygun görülen tedavi metotreksat (MTX) verilmesidir. Biz düşük doz MTX in etkinliğini araştırdık.

Gereç ve Yöntemler: Üçüncü derece bakım hizmeti veren Üniversite hastanesindeki servikal gebelik vakalarının analizi. altı vaka servikal veya servikoistmik gebelik nedeniyle müracaat etti. düşük doz MTX intravenöz olarak uygulandı. ikincil cerrahi girişim gerektiğinde yapıldı. Ana hedef, hastanın çocuk doğurma kapasitesinin korunması idi.

Bulgular: Bu 6 hastaya düşük doz MTX tedavisi verildi. Bu süre içinde hastalardan 3 ü küretaja gitti. Hastalardan bir tanesi ise ek olarak intra-amniyotik MTX tedavisi aldı.

Sonuç: Sistemik düşük doz MTX tedavisi, düşük yan etki profili ile servikal gebeliklerin birinci basamak tedavisinde etkindirler.

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Anahtar kelimeler: Servikal gebelik, metotreksat, düşük doz rejimi

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Introduction

Cervical pregnancy is a rare event occurring in one in 1,000-95,000 pregnancies. Less than 1% of ectopic pregnancies are cervical pregnancies (1). In 1978, Raskin published the first report of a cervical pregnancy diagnosed using ultrasound (2). The etiology of cervical pregnancy is still unknown but factors that make it more probable appear to include surgically caused mucosal defects following dilatation and curettage (3, 4) or cesarean sections (5) as well as methods of artificial fertilization such as in vitro fertilization and embryo transfer (6). The diagnosis is established using endovaginal ultrasonography when there is positive evidence of hCG. Early diagnosis of cervical pregnancy with a low hCG titer suggests good chances for success with a conservative approach. Cervical ectopic pregnancies are especially feared due to associated

life-threatening hemorrhage. Surgical procedures involve increased risks, and systemic administration of methotrexate (MTX) is therefore an established form of conservative treatment in cervical pregnancies. Farabow et al. introduced MTX treatment for cervical pregnancies in 1983 (7). A study by Kung and Chang showed that there was a 91% success rate in preserving the uterus when conservative MTX treatment was used (8). The chemotherapeutic agent can be administered in various forms and with various dosage schemes. In the present study, we investigated systemic administration of MTX using a low-dose regimen according to Schäfer et al. (9).

Material and Methods

In a case analysis, all cervical and isthmocervical pregnancies treated at the Department of Gynecology at Erlangen University

Hospital from January 2003 to August 2008 were studied (Table I).

Patient selection

The patients were referred to our department by their family physicians on the basis of a suspected ectopic pregnancy. Following a gynecological examination, the initial step was to determine the serum hCG concentration. Using 3D ultrasonography, the localization of the pregnancy was determined (Figure 1, Figure 2).

A cervical pregnancy was diagnosed with ultrasound when the following criteria were met:

- Presence of a gestational sac below the inner closed cervix or insertion of the uterine artery (10-12).
- Absence of an amniotic cavity in the uterus, with a small hourglass-shaped uterus (10-12).
- Absence of what is known as the “sliding sign.” This sign appears when gentle pressure is applied to the cervix with the endovaginal ultrasound probe and the gestational sac of the abortus slides against the endocervical canal. This is not observed in an implanted cervical pregnancy (13).
- Evidence of blood flow around the gestational sac on color Doppler, serving as a sign of implantation (13, 14).

The ultrasound 3D examinations were carried out using the Voluson Expert 750 ultrasound scanner (GE Medical Systems, Solingen, Germany) equipped with a 7.5-MHz transvaginal transducer. The following criteria led to the inclusion of MTX treatment:

- Ultrasound evidence of cervical or isthmocervical pregnancy with a gestational age \leq 12 weeks
- Positive evidence of serum hCG
- Normal blood count and normal liver and kidney function
- Patient consent following the provision of detailed information

The following criteria led to the exclusion of MTX therapy:

- Clinically unstable patients with heavy vaginal bleeding and/or severe lower abdominal complaints
- Advanced gestational age ($>$ 12 weeks)
- Presence of contraindications to MTX such as leukocytopenia or thrombocytopenia, anemia, or renal or hepatic function disturbances
- Refusal of conservative treatment by the patient

MTX regimen

After a diagnosis of cervical or isthmocervical pregnancy had been established, all six patients received a single intravenous bolus of 30 mg or 50 mg methotrexate (9), depending on the hCG concentration. The higher 50 mg dose of MTX was selected in patients with high hCG values (\geq 12.000 mIU/mL). The cut off

of 12.000 mIU/ml was chosen because of long-standing experience in our department also in the conservative management of tubal ectopic pregnancies. After 4-10 days following MTX treatment another ultrasound and hCG levels were performed. If the hCG values were increasing or there was an hCG plateau, and in patients with a persistent viable pregnancy, the intravenous MTX bolus was repeated at a dosage dependent on the hCG level. The hCG concentration was further monitored until it became undetectable. Before each dose of the chemotherapeutic agent, a complete blood count was taken, and electrolytes and hepatic and renal values were assessed.

Surgical regimen

When there was a persistent gestational sac or heavy vaginal bleeding during MTX treatment, curettage was carried out with suction curettage, or with blunt curettes with the patient under general anesthesia.

Results

This case analysis included six patients. An intracervical pregnancy was diagnosed in five patients (Figure 2) and an isthmocervical pregnancy in one (Figure 1). The mean maternal age was 29 ± 5.42 years (range 22-40 years). The median gestational age at presentation was 44.5 days (range 39-63 days); five patients had pregnancies with a gestational age $<$ 9 weeks and one patient had a pregnancy with a gestational age \geq 9 weeks. The initial hCG values ranged from 1,300 mIU/mL to 149,431 mIU/mL (median 10,684 mIU/ml). The pregnancies were initially viable in four cases. There were various ultrasound findings in the six cases; details are given in Table 2.

After receiving information and providing consent, six patients underwent primary outpatient treatment with MTX as an intravenous bolus of either 30 mg or 50 mg, depending on the hCG concentration. All six patients received a further dose of MTX due to an insufficient decline in the hCG level or a persistence of embryonic cardiac activity. Five out of the six patients received a third dose of the chemotherapeutic agent during the course of treatment. The courses of the hCG levels during MTX treatment are shown in Table 2.

Exclusively conservative treatment with MTX according to the low-dose scheme was successful in three patients. Surgical treatment had to be carried out after the initial MTX therapy in three patients. Due to heavy vaginal bleeding, one patient underwent suction curettage. Another underwent hysteroscopy and cervical curettage due to a persistent and constantly large

Table 1. Characteristics of the group of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Age	27	40	29	22	28	28
Gravida/para	IV/I	I/0	II/0	II/0	III/I	II/I
History of treatment for sterility	Yes	Yes	No	No	No	No
History of extrauterine pregnancy	2	0	0	0	0	0
History of miscarriage/abruptio	0	0	1	1	1	0
Previous uterine surgery	0	0	1 curettage	1 curettage	1 curettage, 1 cesarean section	0

Table 2. Overview of patients and treatments.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Type of pregnancy	Cryotransfer	Embryo transfer	Spontaneous	Spontaneous	Spontaneous	Spontaneous
Location	Intracervical	Intracervical	Intracervical	Intracervical	Isthmocervical, in the area of the section scar	Intracervical
Gestational week at presentation	6+2	6+2	5+4	9+0	6+3	7+1
hCG (mIU/mL) at diagnosis	1,300	1,741	10,990	149,431	10,378	13,895
Yolk sac	Visible	Not visible	Visible	Not visible	Visible	n.d.
Chorionic cavity	Visible	Visible	Visible	Not visible	Visible	n.d.
Embryonic structure	Visible	Not visible	Not visible	Visible	Visible	Visible
Fetal cardiac activity	Positive	Negative	Negative	Positive	Positive	Positive
Treatment	30 mg MTX	30 mg MTX	30 mg MTX	50 mg MTX	30 mg MTX	50 mg MTX
hCG (mIU/mL)/day	3,583/7	1,663/6	12,687/4	78,428/10	29,081/7	23,392/8
Fetal cardiac activity	Negative	Negative	Negative	Positive	Positive	Positive
Treatment	30 mg MTX	30 mg MTX	50 mg MTX	50 mg MTX	50 mg MTX	50 mg MTX
hCG (mIU/mL)/day	2,172/14	1,269/16	4,358/18	75,057/17	16,308/16	3,305/22
Fetal cardiac activity	Negative	Negative	Negative	Positive	Negative	Negative
Treatment	30 mg MTX	30 mg MTX	30 mg MTX	50 mg MTX	50 mg MTX	
Invasive treatment/ day			Hysteroscopy Cervical curettage/60	Intrafetal KCl, intra-amniotic MTX instillation/25 Suction curettage/ 151		Suction curettage/22
Side effects of MTX	None	None	None	Nausea, vomiting	Nausea	None
N.d., not done or not described; KCl, potassium chloride; MTX, methotrexate; hCG, human chorionic gonadotropin						

amniotic cavity. One patient also underwent suction curettage following feticide using intrafetal 20% KCl instillation and intra-amniotic MTX administration (50 mg) during a course with persistent vaginal bleeding.

The curettage procedures were all carried out on an outpatient basis without any complications. One patient had symptoms after two MTX doses, consisting of headache, vertigo and coordination disturbances. After a neurological work-up, tension headache unconnected with the MTX administration was diagnosed. Subsequent administrations of the chemotherapeutic agent were well tolerated by the patient. Two patients reported mild nausea, with vomiting in one case.

Discussion

MTX administration is widely used as a form of conservative treatment in ectopic pregnancies. A large number of treatment methods have been developed in recent years. In addition to chemotherapy, they include placement of a Foley catheter (15), curettage and local prostaglandin injection (16), and arterial embolization (17). The aim of all these methods is to avoid hysterectomy and preserve childbearing capacity.

Because of the rarity of cervical pregnancies no prospective, randomized, controlled studies exist which evaluate the efficacy of the different therapeutic regimens of MTX treatment.

Our case analysis showed that patients treated with low dose systemic administration of MTX tended to respond satisfactorily. Neither the rate of decline in hCG nor ultrasonographic criteria are capable of definitely predicting successful treatment for cervical pregnancy. Despite this, there has been discussion on whether the initial value for the hCG concentration and the form in which the chemotherapeutic agent is administered might not be regarded as offering the most important positive predictive values for successful conservative treatment (18).

The present case analysis shows that, during MTX treatment, additional surgical intervention was still necessary when there were high initial hCG values of >10.500 mIU/mL (see cases 3, 4 and 6, Table2). We agree with Hung et al. (19), that patients with risk factors like gestational age of ≥ 9 weeks, serum hCG titer of ≥ 10.000 mIU/ml and fetal cardiac activity have an increased risk of an unsatisfactory result of primary MTX treatment (19).

In our case analysis, conservative treatment was completed successfully in three of the six women who were treated with MTX primarily. Two of these cases involved viable pregnancies. Evidence of embryonic cardiac activity has been regarded in several studies as an exclusion criterion for MTX administration, or as requiring further intervention in addition to MTX, such as intra-amniotic administration of potassium chloride (12, 20). In a retrospective study by Kung and Chang including 62 patients, the need for a surgical procedure in addition to MTX treatment was

significantly higher in patients with viable cervical pregnancies than in nonviable cervical pregnancies (8). Among the four patients in the present group with viable pregnancies, an additional surgical intervention was not required in two. In the patients in whom a surgical procedure was necessary, this was carried out on an outpatient basis without any complications. These patients were always hemodynamically stable so that no blood transfusions, cervical tamponade or hysterectomy were necessary. It is often mentioned that the weakness of MTX treatment is the inability to predict the occurrence of massive bleeding (21, 22) which we cannot confirm using MTX in the low-dose regimen.

Yitzhak et al. preferred a step-by-step conservative approach, with an initial intramuscular MTX dose followed by intra-arterial administration (23). Leeman and Wendland also used this approach, in combination with intra-amniotic potassium chloride administration, if the gestational age was more than 9 weeks and/or fetal heart activity was found (12). In one case (patient 4) in the present group also, intravenous MTX administration alone was not sufficient, so that intra-amniotic MTX administration had to follow after intrafetal potassium chloride application. In our opinion, embryonic cardiac activity alone is no contraindication for the low dose MTX regimen. However, the existence of several poor prognostic factors such as advanced gestational age, a very high initial hCG concentration and persisting cardiac activity after MTX administration (case 4) can necessitate other adjuvant therapy.

There are many protocols for MTX administration, which differ both in the form of application (intramuscular, intravenous, or intra-amniotic) and in the dosage (with single-dose versus multiple-dose regimens). Multiple-dose regimens can include up to four doses per week (24). The form of systemic administration most often mentioned in the literature is 50 mg/m² or 1 mg/kg intramuscular. Hung et al. and Schäfer et al. demonstrated that the administration of a higher dose of MTX appeared not to offer a better therapeutic response than a lower dose (19, 9). Systemic MTX is at least as successful as local injections (9, 25) and is the least invasive method of treating cervical pregnancy. Pharmacokinetics of MTX has not shown any advantage of local application over its systemic administration (26). Taking into account the results of the in vitro studies of Schäfer et al. (27), and due to the results of the different MTX dose regimes which ranged from 20 mg to 50 mg (9), we prefer 30 mg or 50 mg MTX as an intravenous bolus initially as a single dose, depending on the hCG concentration. The advantage of this low-dose scheme is that only mild side effects occur, although an average of three MTX doses were necessary for a successful treatment. All of the side effects which were observed in the present group of patients -nausea in two cases, one with vomiting- are classed to grade 1 out of 4 grades due to the Common Toxicity Criteria of the National Cancer Institutes. Other side effects associated with systemic MTX therapy including stomatitis, diarrhea, elevated liver enzymes and bone marrow depression were not observed in this group. Repeated systemic administration of MTX is needed due to the agent's short half-life of 10 hours. The patients have to be informed that the medical treatment sometimes requires time and patience.

It is notable that five of the six patients had a history including a cervical and/or uterine surgical procedure or treatment for sterility (Table 1). The etiology of cervical pregnancy is not known, but on the basis of this observation in this group of patients,

iatrogenic cervical pathologies appear to have an influence on the frequency of cervical pregnancy. Earlier literature reviews by Parente et al. (10) and Shinagawa et al. (3) also pointed out this connection. In these reports, 25 of 31 patients and 18 of 19 patients, respectively, with cervical pregnancy had previously undergone curettage (10, 3).

Following a cervical pregnancy, it is recommended to patients that they should only become pregnant again after 6 months at the earliest (28). No teratogenic effects have yet been observed after MTX treatment. In a retrospective study investigating the efficacy of MTX in the treatment of cervical pregnancies, no evidence that fertility was affected in these patients was found (8). Follow-up consultations in the present group showed that two of the six women had in the meantime given birth to one child and one woman had given birth to twins and to another child.

In summary, systematic low-dose MTX therapy is a successful form of conservative treatment, with hardly any side effects, that can also be carried out in cervical pregnancies with embryonic cardiac activity. If surgical intervention is necessary despite this, the present data show that the course following prior treatment with MTX can be expected to be free of complications. This management approach can make a considerable contribution to the preservation of childbearing capacity. Prospective and randomized studies are necessary in order to confirm these data and establish a standard protocol for MTX administration in patients with cervical pregnancies.

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