THE USE OF INTRAVENOUS METHOTREXATE IN THE TREATMENT OF ECTOPIC PREGNANCY

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Summary

Between January 1996 and December 2001, at the Department of Gynecology, Perinatology and Human Reproduction of the University of Florence, 49 ectopic pregnancies were submitted to medical treatment. The treatment schedule consisted of the administration of 100 mg of intravenous methotrexate (MTX). The patients included in this study fulfilled the following requisites: gestational period <8 weeks; diameter of the ectopic gestational sac <4 cm; serum level of human chorionic beta-gonadotropin (β-hCG)<5000 IU/ml; absence of clinical and ultrasound signs of tube rupture with initial hemoperitoneum; hematochemical tests compatible with chemotherapic treatment.

All patients were followed with a dosage of serum β-hCG repeated every 2-3 days after chemotherapy and with an ultrasound every 3-4 days. In case of documented success of treatment the patient was hospitalized for no more than 3 days after administration of the drug. In 1 case therapy took place in a day-hospital regimen.

Medical treatment was effective in 35 patients out of 49 (71.4%) and led to negative β-hCG in a median time of 11 days, with a range between 2 and 48 days. In the 14 non-responsive cases (28.6%), after a mean time of 6 days we proceeded to a traditional surgical approach or laparoscopy. In none of the cases did we find significant pharmacological toxicity, while in 9 patients (18.3%), severe painful symptoms appeared immediately after treatment, but resolved within 24 hours.

Our results are interesting and in agreement with other experiences found in the literature. In our opinion, the advisability of a second administration in case of slow response, the comparison with an analogous intramuscular treatment, a more precise definition of the eligibility criteria, long-term follow-up of the patients, especially in case of subsequent pregnancies should all be further considered.

Key words: **Ectopic pregnancy, methotrexate, pregnancy.**

INTRODUCTION

The incidence of ectopic pregnancy is 41 cases out of 100,000 women, or 1 case in 64-241 births. If we consider the relationship to the number of diagnosed pregnancies, we find that in the last 20 years the incidence of ectopic pregnancies has doubled, going from 4.5 cases to the present 10 cases per 1000 pregnancies [1].

In 12-18% of the cases a subsequent pregnancy will be another ectopic pregnancy in the same tube or in the contralateral one while 50% of the women who have had an ectopic pregnancy will have a full-term pregnancy, independently of the type of treatment given (conservative or not) [2-4]. This fact has justified less aggressive and not necessarily surgical approach to the problem [5]. The particular sensitivity of the trophoblastic tissue to methotrexate (MTX) has in fact allowed the programming of a pharmacological treatment of ectopic pregnancy for carefully selected cases. Most of the studies found in literature call for local intralesional or systemic intramuscular

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(i.m.) administration of MTX [6]. Recent studies have demonstrated its non-invasiveness, high efficiency and absence of systemic toxicity in a low single-dose treatment [7-9].

The treatment of choice for ectopic pregnancy is, therefore, as we have mentioned, conservative, medical or surgical. The cost/benefit ratio favors medical over surgical treatment. Although cases with human chorionic beta-gonadotropin (β-hCG) inferior to 1000 mUI/ml have 75% spontaneous regression, medical treatment accelerates the process, reducing the costs of diagnostic controls [10,11].

The aim of this study is to describe the protocol in use at the Department of Gynecology, Perinatology, and Human Reproduction of the University of Florence on medical treatment of ectopic pregnancy, consisting in the systemic intravenous (i.v.) administration of MTX and to report the results of the relative clinical-diagnostic experience in the period between January 1996 and December 2001.

PATIENTS AND METHODS

Starting in January 1996, at the Department of Gynecology, Perinatology, and Human Reproduction of the University of Florence a treatment protocol for ectopic pregnancy was designed, involving the use of i.v. MTX 100 mg in a single administration [12,13]. Intravenous administration was chosen in an attempt to allow a greater concentration of the drug to reach the target organ, even if for a shorter period, and to limit the side effects correlated with i.m. administration.

The diagnosis of ectopic pregnancy was made by measuring serum β-hCG levels and transvaginal ultrasound (TVU) evaluation. At the onset of treatment, a serum specimen was taken for the β-hCG dosage, which was repeated after 2 and 7 days.

Table 1 lists the exclusion criteria from medical treatment.

TABLE 1 - *Exclusion criteria from medical treatment of ectopic pregnancy.*

- tubal rupture with massive hemoperitoneum (with or without acute abdomen);
- β-hCG level >5000 mUI/ml;
- adnexal mass diameter >4 cm;
- gestational period >8 weeks;
- previous homo- or contralateral tubal pregnancy;
- positive history of tubal pathology (sactosalpinx);
- failure of conservative surgical therapy;
- hypersensitivity to the drug;
- white blood cells <3000/l and/or platelets <100,000/l;
- severe kidney and/or liver failure;
- patient unwillingness to have conservative treatment.

The response to therapy was evaluated at 2, 4, and 7 days after treatment with a dosage of serum β-hCG, ultrasonic control after 4 days and clinical examination (symptoms, body temperature, pulse, arterial pressure). Therapy success was defined as a >30% decrease of β-hCG after 48 hours. Decreased β-hCG is not seen before 48 hours (only 30% of cases treated with salpingectomy have a decrease after 24 hours) [14].

Therapy failure was defined as increased or stable levels or worsening of symptoms (evolution of pregnancy). In case of failure of medical therapy, patients underwent surgery but only as a necessity.

RESULTS

Forty-nine women with evolutive ectopic pregnancy were submitted to MTX medical treatment. Their median age was 32.8 years (range: 23-43 years). Twenty-four (48.9%) women were in their first pregnancy; of the remaining 25, 5 (10.2%) had a history of previous ectopic pregnancy, all had been treated surgically. The left tube was involved in 25 (51%) of the patients and the right one in the remaining 24 (49%).

Thirty-five (71.4%) patients had a complete response and 14 an unsuccessful response (28.6%) who then underwent traditional laparotomy (9 cases, 64.3%) or operative laparoscopy (5 cases, 35.7%).

No significant pharmacological toxicity was found in any case, while 9 patients (18.3%) had grade I side effects: nausea and vomiting limited to a couple of days with spontaneous resolution in 5 cases (55.5%), abdominal pain controlled with a mild analgesic in 3 patients (33.3%) and one case with headache and extrasystole (11.2%).

In the group of 35 patients who responded to treatment, β-hCG monitoring, performed with serial controls, in 10 cases (28.6%) revealed stable levels on day 2 after MTX administration and a subsequent reduction until negativation; in 25 cases (71.4%) there was an immediate lowering of β-hCG from the 2nd day. Negativation of hormonal levels was obtained in a mean time of 11 days, (range 2 - 48 days). Of the 14 non-responders who underwent surgery after a median of 6 days (range: 2-21 days), 9 (64.3%) were characterized by a constant increase in β-hCG levels, and 5 (35.7%), instead, by an initial reduction followed by an increase until plateau.

Patients were hospitalized for only 3 days after administration of the medication in cases of documented efficacy of treatment; the overall median hospital stay was 8.4 days, (range 1 - 20 days). In 1 case treatment was performed in a day-hospital regimen.

DISCUSSION

Until a few years ago, ectopic pregnancy therapy consisted essentially of surgery. In spite of the

introduction of new therapeutic possibilities, in cases complicated by tubal rupture with acute hemoperitoneum, surgery still represents the only way of saving the woman's life if promptly performed by laparotomy. Waiting in such cases is much riskier than the operation, which is justified when the β-hCG level is inferior to 1000 mIU/ml and continues to decline, when the diameter of the adnexal formation is less than 2 cm and the hemoperitoneum is less than 50 ml with a stable clinical condition, in which case there are good probabilities of a spontaneous resolution and reabsorption of the ectopic pregnancy [15].

On the other hand, the remarkable development of therapy, especially in the last few years, has allowed greater fulfillment of the following objectives:

- eliminate the ectopic pregnancy;
- maintain, as much as possible, fertility;
- limit the risks of a relapse;
- reduce therapeutic morbidity as much as possible.

Thus, over the years, therapy has changed from a radical (salpingectomy) to a conservative (salpingotomy) operation. At any rate, the probability of a new ectopic pregnancy in the same tube or in the other one is independent of the type of treatment performed, which justifies the search for a less aggressive approach.

Recently, an even more conservative treatment with medical therapy has been introduced, consisting of local injections of potassium chloride (KCl) in the gestational sac under ultrasonic guidance associated with salpingocentesis and MTX [16], prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) or hyperosmolar glucose [17] administration, and in systemic treatment with MTX or, more recently, with other substances (mifepristone, etoposide, actinomycin D and anti-hCG monoclonal antibodies). These new diagnostic and therapeutic strategies have radically modified the outcome of ectopic pregnancy, reducing its mortality and morbidity despite the increase in incidence [18].

The aim of pharmacological treatment of ectopic pregnancy is to block the development of the trophoblast: MTX, a folic acid antagonist, is the drug of choice in the therapy of gestational trophoblastc disease. Its mechanism of action consists in the inhibition of the dihydrofolate reductase, an enzyme implicated in the conversion of dyhydrofolic acid into tetrahydrofolic acid; in this way the incorporation of the purine and pyrimidine bases in DNA is prevented, with the consequent inhibition of cell proliferation [19].

MTX is generally completely absorbed when administered parenterally. After i.m. injection, peak serum concentrations occur in 30 to 60 minutes. After i.v. administration, the initial volume of distribution is approximately 0.18 l/kg (18% of body weight) and steady-state volume of distribution is approximately 0.4 to 0.8 l/kg (40% to 80% of body weight). MTX competes with reduced folates for active transport across cell membranes by means of a single carrier-mediated active transport process. At serum concentrations greater than 100 μM, passive diffusion becomes a major pathway by which effective intracellular concentrations can be achieved. MTX in serum is approximately 50% protein bound. Laboratory studies demonstrate that it may be displaced from plasma albumin by various compounds, including sulfonamides, salicylates, tetracyclines, chloramphenicol, and phenytoin. MTX does not penetrate the blood-cerebrospinal fluid (CSF) barrier in therapeutic amounts when given orally or parenterally. High CSF concentrations of the drug may be attained by intrathecal administration.

After absorption, MTX undergoes hepatic and intracellular metabolism to polyglutamated forms which can be converted back to MTX by hydrolase enzymes. These polyglutamates act as inhibitors of dihydrofolate reductase and thymidylate synthetase. Small amounts of MTX polyglutamates may remain in tissues for extended periods. The retention and prolonged drug action of these active metabolites vary among different cells, tissues, and tumors. A small amount of metabolism to 7-hydroxy-MTX may occur at doses commonly prescribed. The aqueous solubility of 7-hydroxy-MTX is 3- to 5-fold lower than the parent compound. The terminal half-life reported for MTX is approximately 3 to 10 hours for patients receiving less than 30 mg/m^2. For patients receiving high doses of MTX, the terminal half-life is 8 to 15 hours.

Renal excretion is the primary route of elimination and is dependent upon dosage and route of administration. With i.v. administration, 80% to 90% of the administered dose is excreted unchanged in the urine within 24 hours. There is limited biliary excretion amounting to 10% or less of the administered dose. Enterohepatic recirculation of MTX has been proposed. Renal excretion occurs by glomerular filtration and active tubular secretion. Impaired renal function, as well as concurrent use of drugs such as weak organic acids that also undergo tubular secretion, can markedly increase MTX serum levels. An excellent correlation has been reported between MTX clearance and endogenous creatinine clearance. MTX clearance rates vary widely and are generally decreased at higher doses. Delayed drug clearance has been identified as one of the major factors responsible for MTX toxicity. It has been postulated that the toxicity of MTX for normal tissues is more dependent upon the duration of exposure to the drug rather than the peak level achieved. When a patient has delayed drug elimination due to compromised renal function, third space effusion, or other causes, MTX serum concentrations may remain elevated for prolonged periods. The potential for toxicity from high dose regimens or delayed excretion is reduced by the administration of leucovorin calcium during the final phase of MTX plasma elimination.

Pharmacokinetic monitoring of MTX serum concentrations may help identify those patients at high risk for MTX toxicity and aid in proper adjustment of leucovorin dosing [20].

Systemic medical treatment of ectopic pregnancy was introduced in the '60s for cases of abdominal implant forms (while local therapy was used mostly for cervical localization) [21-23], but it is only recently that new interest has developed for tubal pregnancy treatment with the administration of i.m. MTX (more rarely i.v. or oral) associated with *Citrovorum factor* (folic acid, the natural antidote of the antimetabolite) for reducing toxicity on other tissues [24,25]. In case of failure a possible second dose is foreseen [26-28].

The possibility of a spontaneous resolution of ectopic pregnancy generally occurs exclusively in patients who have low production of β-hCG [29,30]. The use of a specific and effective drug such as MTX in cases with a sure evolution has allowed not only reduction in the costs of diagnostic tests and resolution times, but has especially found in the single-dose monochemotherapeutic medical approach a valid alternative to surgical treatment in appropriately selected patients [31]. Such an approach has certainly reduced the aggressiveness of treatment and the risks correlated with a traditional or laparotomic operation [32]. We must emphasize that MTX is an extremely manageable drug and does not present significant side effects in the dosage used. This treatment could easily be peformed in an out-patient clinic, with careful patient follow-up with ultrasonic and biohumoral monitoring: if the decrease of β-hCG is <15% on the 4th and 7th day, a second administration is needed, while if it is >15%, monitoring is necessary every 15 days for the subsequent period until β-hCG serum levels are negative [33]. Intravenous MTX administration offers the advantages of reducing side effects and toxicity linked to i.m. injection, making treatment simpler to realize.

In our study, fewer women who had had surgical treatment (87.7%) were satisfied with their care than those who had had medical treatment (95.3%). The costs of medical and surgical treatment have been compared and are lower for the medical one, in terms of reduced morbidity and reduced hospitalization.

The women were asked to fill out a daily log of pain symptoms, measured on a 10-point numeric scale, and other symptoms such as nausea. They were questioned about side effects at each visit. At the last visit, they handed in their symptom log and were asked about their satisfaction with the procedure ("If you had to undergo this procedure again and had a choice, do you think you would choose surgical or medical treatment?"). Of the 35 women who had successful medical abortions, only 2 said they would choose surgical treatment if faced with the choice again; they gave as reasons that medical treatment was too painful or too long or that the uncertainty was too stressful. One of these 2 women had had previous surgical treatment. One woman said she was uncertain whether she would have medical treatment and another one did not answer the question. The 31 women who were satisfied with their experience gave the following reasons: they did not need to wait for an operation in a clinic, they wanted to avoid surgery, they were afraid of the protesters around the clinics, they wanted to be home soon with their support person, and they found that medical treatment "felt more natural" than surgery. Patient satisfaction could not be predicted on the basis of a history of previous ectopic pregnancy, patient age, or gestational age. In conclusion, patient satisfaction was high despite the long process involved. There were no serious side effects.

The amount of pain caused by medical treatment is greater than that caused by surgery. The mean amount of pain shown in this study was 5.8 on the 10-point pain scale. However, the side effects of the drug were infrequent, mild, and transient. Most of the women were satisfied and said they would choose medical over surgical treatment if faced with the same situation again. These women were highly motivated to avoid surgery; many were very grateful to have the choice of medical treatment.

Our experience confirms what has been widely reported in the literature, namely that MTX, the drug of choice for the treatment of breast cancer and choriocarcinoma, today can be successfully used in the therapy of a non neo-plastic pathology which until recently was treated exclusively with surgery [8].

We also believe that, even when β-hCG is inferior to 1000 mIU/ml and there is usually 75% spontaneous regression, medical treatment can accelerate this process, thus reducing the costs of diagnostic controls [16].

The use of MTX for medical treatment of ectopic pregnancy, and in particular as a single dose, presents different advantages which also increase patient compliance (*Table 2*) [34].

TABLE 2 - *Advantages of MTX treatment for ectopic pregnancy.*

- clinical efficacy
- minimum side effects
- quick resumption of working activity by the patien;
- high percentage of success
- maintenance of reproductive function comparable to that obtainable with conservative surgery
- favorable cost/benefit ratio compared to surgery

In our opinion, further evaluation is needed regarding the advisability of a second administration in cases of slow response, the comparison with anal-

ogous i.m. treatment [35,36], a more precise definition of eligibility criteria and long-term patient follow-up, especially for subsequent pregnancies.

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