Systemic methotrexate treatment in early unruptured ectopic pregnancy

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Summary

Ectopic pregnancy is one of the most common and dangerous complications of the early pregnancy period. Until now diagnosis has been late because major symptoms occur after tubal rupture and so only demolitive surgery has been possible. At present, with the appearance of ultrasound in obstetrics an earlier diagnosis of this pathology can be made before tubal rupture so medical treatment has become possible.

We treated a series of twelve patients with early ectopic pregnancy (9 tubal and 3 with no localized site of implantation) with intramuscular 0.5 mg/kg methotrexate and oral 0.1 mg/kg of folic acid (Citrovorum Factor) on alternate days, in the attempt to reduce hospitalization and obtain more effective and safer medical management. We observed a fall in serum ß-HCG levels after one cycle of treatment in 11 out of 12 patients and after two cycles of therapy in the remaining case. Minimal side-effects were observed in four cases. Three pregnancies occurred after treatment before the advised interval time and ended in blighted ovum. Methotrexate systemic therapy can be considered an elective treatment and a sufficiently safe management in early unruptured ectopic pregnancy when a good clinical selection of patients is performed.

Key words: Ectopic pregnancy; Methotrexate; Early pregnancy.

Introduction

Ectopic Pregnancy (EP) is one of the most common and dramatic complications of early pregnancy. It constitues a major public health problem worldwide. In fact, sometimes, this pathology can be unrecognized and become a life-threatening condition [1, 2].

The incidence of this disease is progressively increasing all over the world and is calculated at about 1.2 percent in Italy [5]. Etiology of ectopic pregnancy includes mechanical (salpingitis, peritubal adhesions, developmental abnormalities of the tube, previous ectopic pregnancy, previous surgery on the tube, multiple previous induced abortions, tumors distorting the tube) and functional factors (external migration of the ovum, menstrual reflux, altered tubal motility and cigarette smoking) [3].

In recent years scientific knowledge has made real progress in the early diagnosis of this disease, before tubal rupture, allowing a conservative choice of the affected tube by a pharmacological approach. Methotrexate administration, by its cytolitic effect on rapidly developing tissues like trophoblastic ones, is at present, the elective therapy for this pathology [6, 10, 14].

We treated early ectopic pregnancy with systemic methotrexate administration to test the effectiveness of this therapy and to reduce or eventually avoid tubal surgery and thus preserving its function.

Material and Method

Twelve consecutive ectopic pregnancies were treated with systemic administration of methotrexate at a dosage of 0.5 mg/kg via i.m. on days 1, 3, 5, 7 and folic acid at a dosage of 0.1 mg/kg orally on days 2, 4, 6, 8, in an effort to avoid injury to cells dividing more slowly than trophoblasts, as well as to minimize drug toxicity.

All patients were normally ovulating women without endocrine pathologies who had not undergone any pelvic surgery, had had no former ectopic pregnancy and had normal hematochemical parameters. Five of the patients were primigravidae and the other seven had had another pregnancy before. Mean age of the women was 26.2 years and the mean BMI was 23.6.

The effectiveness of this chemotherapeutic association (methotrexate plus folinic acid on alternate days) was monitored every two days by ultrasound transvaginal examination, complete blood count including platelet count and liver function tests, and serum HCG titration.

Inclusive criteria for the methotrexate systemic treatment were:

1) Gestational Sac diameter less than 15 mm;
2) Serum ß-HCG titration less than 1500 mU/UI;
3) Absence of haemoperitoneum;
4) Absence of liver problems and general alterations contraindicating the use of the methotrexate.

Ultrasound transvaginal examination was carried out by an Aloka SSD-500 scanner with a 5.0 Mhz transvaginal probe. Longitudinal, parasagittal and transversal scans of the gestational sac (measuring major diameters) and the endometrium along the uterine sagittal and transversal (at the level of the tubal angles) axis were done for each patient.

Serum ß-HCG titration was performed with a RIA kit standard technique (RADIM Pomezia, Rome, Italy).

Results

Eleven of 12 patients obtained a progressive decrease of serum ß-HCG levels of nearly zero (less than 10 mUI/ml) within ten days after the onset of therapy with one cycle of treatment. Each patient was positive for serum ß-HCG titration and ultrasonographically negative

Received August 18, 1997
revised manuscript accepted for publication September 15, 1997

for intrauterine gestational sac evidence with nine of them ultrasound positive for the tubal pregnancy finding (3 ampullar and 6 infundibular tubal pregnancies). In 3 cases with serum ß-HCG positivity and no ultrasonographical presence of intrauterine pregnancy it was impossible to determine the site of implantation (see Table 1).

In only one case with unknown localization of the gestational sac (1158 mUI/ml serum ß-HCG levels at the onset of treatment), two cycles of therapy were needed. In that case the therapy was repeated after a one week discontinuation. In all the one-cycle therapy women the

Table 1. — *Ultrasound findings and Serum ß-HCG levels in treated patients.*

Patients	Serum ß-HCG levels	Implantation Site	Gest. Sac Diameter
1	1078	Ampulla	12
2	578	Infundibulum	8
3	876	Ampulla	9
4	768	Infundibulum	5
5	657	Not localized	—
6	485	Not localized	—
7	1158	Ampulla	15
8	1397	Infundibulum	13
9	1425	Infundibulum	14
10	378	Infundibulum	3
11	946	Not localized	—
12	1416	Infundibulum	15

lowering of serum ß-HCG was obtained on the sixth day of the treatment cycle while in the patient with two cycles of therapy it occurred an the fourth day of the second cycle. A drop of serum ß-HCG levels near zero occurred in this patient on the 21st day after the onset of treatment. Seven women showed presence of fetal heart beat at the ultrasound exploration. All the patients had no significant alteration in blood, renal or liver function parameters during or after therapy. All the women underwent a weekly titration of serum ß-HCG levels three times to assure a negative value of this marker.

Three pregnancies, in spite of physician advice, occurred in the patient group within four months after the end of therapy. In all these cases an ultrasonographically-assessed and histologically-confirmed blighted ovum was observed.

Conclusions

The treatment of ectopic pregnancy in the past has been exclusively demolitive surgery (salpingectomy); the chance of conservative surgery was only by plastic surgery. However, the possibility of a conservative treatment was very limited for late diagnoses which rarely occurred before tubal rupture.

After the introduction of the ultrasound technique, particularly with transvaginal probe, has made earlier diagnosis before tubal rupture possible allowing an alternative pharmacological approach to surgical treatment.

Methotrexate therapy associated with folinic acid supplementation is at present the most used pharmacological treatment with various modalities of administration (oral, systemic, endoamniotic injection laparoscopically or ultrasonographically-guided) [7, 9, 12].

The action of this drug is based on the similarity of its molecule to dihydrofolic acid which allows the methotrexate non-covalent linkage to the dehydrofolate reductase, blocking this enzyme which is crucial for the purine synthesis. Consequently, this drug prevents the synthesis of DNA via inhibition of the transformation of dihydrofolic acid to a tetrahydrofolic one, an essential cofactor of thymidilate synthetase; and, it has been shown to inhibit normal trophoblasts *in vitro* [4, 13]. Recently, a highly specific folate receptor, common to methotrexate, on the syncytiotrophoblastic layer of human molar placental tissue has been found [8]. Folic acid (Citrovorum factor) minimizes the incidence of side-effects and is generally used when prolonged treatment courses are required.

Side-effects commonly reported include leukopenia, thrombocytopenia, elevated liver enzymes and occasionally bone marrow depression and pneumonitis [4].

In our series we observed a rapid response to methotrexate treatment, except in one case, and this was possible by the early diagnosis of unruptured ectopic pregnancy. Side-effects were scarce and were limited to 4 cases of low, not well-localized pelvic pain. When an exact localization of the implantation site (3 cases in our group) was not possible to determine, the criteria for a normally thickened and incomplete decidualized endometrium together with the positivity of serum ß-HCG titration were judged sufficient to diagnose an ectopic pregnancy and start the treatment.

In addition, the finding of 3 cases of pregnancy after systemic methotrexate treatment, before the advised interval time (8 months) and ending in blighted ovum is interesting for the evaluation of possible long-term biological consequencies of the drug on the embryonal tissues. However, due to the few cases detected further observations is needed.

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