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European Journal of Obstetrics & Gynecology
and Reproductive Biology 70 (1996) 213–214

OBSTETRICS & GYNECOLOGY

Case report

# Late complications after systemic methotrexate treatment of unruptured ectopic pregnancies: a report of three cases

F. Zullo[a,*], M. Pellicano[b], C. Di Carlo[b], R. De Stefano[b], P. Mastrantonio[a], C. Nappi[b]

[a]*Department of Gynecologic and Pediatric Sciences, Reggio Calabria University, Catanzaro, Italy*
[b]*Department of Obstetrics and Gynecology, Federico II University, Naples, Italy*

Received 27 February 1996; revised 11 July 1996; accepted 29 July 1996

**Abstract**

*Background:* The use of methotrexate (MTX) by systemic administration in the treatment of unruptured ectopic pregnancy has been reported as a safe and effective method. *Cases:* We report three cases (one hematosalpinx and two pelvic hematocoeles) of complications after the use of MTX in the treatment of unruptured ectopic pregnancies. All three cases came to our observation for pelvic pain, abnormal bleeding and a pelvic mass after an interval of 3–5 months, subsequent to the disappearance of symptoms and normalization of serum human chorionic gonadotropin β-subunit (β-hCG) levels. *Conclusions:* These findings suggest that: (a) such complications should be considered before selecting the mode of treatment for ectopic pregnancy; and (b) that an early ultrasonographic control should be performed after MTX treatment even when the decline in β-hCG levels suggests a successful resolution. This would permit an early diagnosis of these late complications. Copyright © 1996 Elsevier Science Ireland Ltd

*Keywords:* Ectopic pregnancy; Hematosalpinx; Pelvic hematocoele; Methotrexate; Complications

## 1. Introduction

In the past decade the management of ectopic pregnancy has changed significantly. This is largely due to the capability to diagnose the condition early by using serial serum β-hCG measurements and transvaginal ultrasonography. Early diagnosis has also permitted a wider utilization of conservative treatment. While a laparoscopic conservative surgical approach is the most widely adopted treatment modality, systemic administration of methotrexate (MTX) is being increasingly used in unruptured ectopic pregnancies. Several studies have reported the effectiveness and safety of MTX treatment [1–3], but this approach is not completely free of complications [4–6].

The purpose of this paper is to report three cases of long term complications following MTX treatment of ectopic pregnancy.

## 2. Case reports

### 2.1. Case 1

A 28 year old woman with a 3 years history of infertility was referred to our service because of a retrouterine pelvic mass diagnosed ultrasonographically. This 8 cm mass showed a dishomogeneous echogenic pattern. The patient's only current complaint was of mild pelvic pain. Six months earlier she had been found to have an unruptured right tubal pregnancy (with no fluid in the pouch of Douglas) by US. Her β-hCG level was 1.870 mIU/ml. She had been treated

* Corresponding author, Via Michetti, 10, 80137 Naples, Italy. Tel.: +39 81 7462909; fax: +39 81 7462903.


*PII* S0301-2115(95)02573-0

in a peripheral hospital with a single dose of MTX 50 mg/m$^2$ [7]. The serum $\beta$-hCG levels were monitored subsequently and declined to less than 5.0 mIU/ml over a span of 4 weeks and she was completely symptoms-free. We performed a laparoscopy which demonstrated a large retrouterine pelvic hematocoele involving both tubes and ovaries. These structures were carefully dissected free and all visceral adhesions were removed. Clots were aspirated by means of a 10 mm cannula. Subsequent chromopertubation revealed occlusion of the right tube at the level of the ampulla and a right salpingectomy was performed. The histopathologic examination of capsula and content of the mass revealed blood clots with hemosiderin and an organized classic inflammatory and fibrous capsule.

### 2.2. Case 2

A 26 year old woman with secundary infertility of 4 years duration was referred to our service because of abnormal vaginal bleeding, pelvic pain and a pelvic mass. Four months before she had been treated elsewhere by means of a course of MTX and citrovorum factor for an unruptured ectopic pregnancy in the left tube ultrasonographically diagnosed without any other abnormal pelvic finding (6 weeks and 5 days gestational age; $\beta$-hCG serum level of 1015 mIU/ml). The treatment schedule was: MTX (1 mg/kg body weight) alternating with folinic acid (0.1 mg/kg) both administrated intramuscularly on a daily basis and each for four doses. The serum $\beta$-hCG level had dropped to less than 10 mIU/ml in 4 weeks.

At laparoscopy, performed for the investigation of the mass, a large hematosalpinx was found in a pelvis completely obliterated by adhesions. After extensive adhesiolysis the left tube was laparoscopically removed. The histopathological examination confirmed the diagnosis of hematosalpinx.

### 2.3. Case 3

A 32 year old woman with a 5 years primary infertility came back to our service complaining of pelvic pain and irregular menstruations. Her WBC count was 12 000/mc and the ultrasonographic findings were suggestive of a pelvic abscess. Four months earlier, we had treated her with a single i.m. dose of 50 mg of MTX for an unruptured ectopic pregnancy, diagnosed by means of transvaginal ultrasonography. The initial serum $\beta$-hCG level was 1500 mIU/ml and had declined to less than 5 mIU/ml in 4 weeks with the disappearance of any symptom. At readmission the ultrasonographic examination showed a complex retrouterine mass of about 10 cm in diameter.

The laparoscopic examination revealed a pelvic hematocoele, and the mass, composed of blood clots and of an external capsule, was completely removed.

## 3. Discussion

These three cases demonstrate the possibility of long term silent complications associated with MTX treatment of ectopic pregnancy. This type of treatment, notwithstanding the relevant reports of safety and effectiveness [1–3], should still be considered experimental in cases of ectopic pregnancy associated with a serum $\beta$-hCG level greater than 1000 mIU/ml.

The occurrence of tubal damage after MTX treatment has been described before [4,5]. However, at present, the real incidence of reproductive impairment after this type of treatment is still unknown. Stovall et al. [3] reported a relatively low incidence of tubal blockage at hysterosalpingography. However, a pelvic hematocoele may occur notwithstanding open tubes at hysterosalpingography. Therefore, adverse effects and complications of MTX treatment of ectopic pregnancy, such as hematosalpinx and pelvic hematocoele, should be taken into account when considering medical versus surgical treatment of the condition [8], and further studies are needed to evaluate the exact incidence. Furthermore, we suggest that an early ultrasonographic control should be performed in all patients treated with MTX with an apparently successful result at the time of $\beta$-hCG disappearance and 1 month later, to permit an early diagnosis of these complications.

We conclude that the actual incidence of such complications should be correctly evaluated in a large multicenter prospective trial of systemic MTX in the treatment of ectopic pregnancy. Meanwhile, an early ultrasonographic control is highly advisable after MTX treatment, even when the decline in serum $\beta$-hCG levels suggests a successful resolution.

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