African Journal of Pharmacy and Pharmacology Vol. 6(7), pp. 464-467, 22 February, 2012
Available online at http://www.academicjournals.org/AJPP
DOI: 10.5897/AJPP11.429
ISSN 1996-0816 ©2012 Academic Journals

*Full Length Research Paper*

# Curative effects by different chemotherapeutic measures pertaining to Methotrexate on unruptured ectopic pregnancy

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Accepted 24 January, 2012

**The aim of this study was to investigate curative effects by different chemotherapeutic measures involving the use of Methotrexate (MTX) on unruptured ectopic pregnancy. Between January 2001 and April 2004, a total of 164 patients with unruptured ectopic pregnancy were treated. They were randomly divided into four groups. In Group I, 50 mg/m$^2$ of MTX was administered 3 times every two days, intravenous (IV) drip, and citrovor-um factor (C.F) was intramuscularly injected 3 times every two days; in Group II, 50 mg/m$^2$ of MTX was singly injected into different sides of buttock muscle, separately; to Groups III and IV, treatment protocols given were the same as those given to Groups I and II, respectively, with the addition of 150 mg of mifepristone orally administered. The success rate in Group I was 73.17% (30/41) versus 92.68% (38/41) in Group II, and that in Group III was 75.61% (31/41) versus 87.80% (36/41) in Group IV. The difference between Groups I and II, and that between Groups III and IV both demonstrated manifest statistical significance ($p$<0.01) while neither of the difference between Groups I and III, or that between Groups II and IV showed statistical significance ($p$>0.05). 50 mg/m$^2$ of MTX by single IM has better efficacy than that by divided IV drip plus safety scheme of citrovor-um factor (C.F). The addition of mifepristone can not improve the curative effect but can only lead to the aggravation of toxic side reactions.**

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

## INTRODUCTION

Recent years have seen the increasing incidence rate of ectopic pregnancy (Rabischong et al., 2010; Cleland et al., 2010; Martyn and Kerkhoff, 2008). At present, treatment of ectopic pregnancy mainly takes two forms, surgical or conservative therapy (Ehrenberg-Buchner et al., 2009; Obeidat et al., 2010; Zakaria et al., 2011). When a patient does not present clinical symptoms (such as abdominal pain, intravaginal hemorrhage, etc.) with the blood level of β-hormone human chorionic gonadotropin (β-HCG) <3,000 IU/L, conservative treatment by using drugs to kill embryo will be favorable (Kraemer et al., 2009; Nadisauskiene et al., 2007).

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Among different drugs used in conservative treatment, MTX has been widely accepted by virtue of its good efficacy (Stovall et al., 1991). Based on the use of MTX in treatment of ectopic pregnancy, we analyzed the clinical data of 164 cases in our hospital, and compared different curative effects by four different chemotherapeutic measures involving the use of MTX in conservative treatment.

## PATIENTS AND METHODS

Between January 2008 and April 2011, a total of 164 patients with unruptured ectopic pregnancy were admitted to the First Affiliated Hospital of Harbin University, China. The diagnosis was based on case history, the blood level of β-HCG, pelvic and vaginal B mode ultrasonic examination and gynecologic examination. The indication criteria for conservative treatment were as follows: (1) Young and

**Table 1.** The observations of indexes in four groups ($\overline{X}$±S).

| Group | Duration of amenorrhea (days) | β-HCG before treatment (IU/L) | Diameter of ectopic mass after 7-day treatment (cm) | Decrease rate of β-HCG after 7-day treatment (%)[a] |
|---|---|---|---|---|
| I | 43.27±8.21 | 3251.23±241.18 | 3.13±2.43 | 52.80±12.80[b,d] |
| II | 41.78±6.57 | 3012.28±214.43 | 3.46±2.60 | 66.10±10.28[e] |
| III | 46.38±13.18 | 2892.46±0189.23 | 3.25±2.56 | 53.94±13. 66[b] |
| IV | 44.28±9.22 | 3123.85±238.26 | 3.06±2.37 | 61.36±9.08 |
| p Values | >0.05 | >0.05 | >0.05 | |

[a], The decrease rate of β-HCG = (β-HCG value before treatment - HCG value after treatment )/β-HCG value before treatment; [b], $P$<0.01 between Groups I and II; [c], $P$<0.01 between Groups III and IV; [d], $p$>0.05 between Groups I and III; [e], $p$>0.05 between Groups II and IV.

looking forward to have a future gestation; (2) Stable life sign and no apparent intra-abdominal hemorrhage; (3) Ectopic pregnancy mass ≤3.5 cm by B mode ultrasonic examination and β-HCG<3000 IU/L with normal hepatic and renal functions (Quilligan and Zuspan, 1990).

164 patients were randomly divided into four groups: I, II, III and IV with 41 cases in each group. Comparisons of the average ages, durations of amenorrhea, values of β-HCG, and diameters of adnexal masses among the four groups displayed no statistical significance ($p$>0.05). In Group I, 50 mg/m$^2$ of MTX diluted in 500 ml of 5% glucose was administered by intravenous (IV) drip every two days, three times in total. From the day of the second time on, 6 mg of CF was intramuscularly injected for anti-resistance every two days, three times totally. In Group II, MTX 50 mg/m$^2$ was singly injected to different sides of buttock muscle, separately, and the second course began one week later, respectively; Group III was treated with the same method as Group I, with the addition of 25 mg mifepristone (orally, two times every day for three consecutive days). Group IV was treated with the same method as Group II, with the addition of 25 mg mifepristone (orally, two times every day for three consecutive days). β-HCG and blood routine of four groups were rechecked every 3 days, and transvaginal ultrasonograms and hepatic and renal functions were rechecked every week to detect toxic side effects caused by chemotherapeutic drugs.

#### Criteria of cure

After 2-week conservative treatment, clinical symptoms disappeared; β-HCG was dropped to a normal level; the diameter of ectopic pregnancy mass was decreased by more than 0.5 cm and gestational sac was decreased by more than 50% in diameter or even totally disappeared.

#### Criteria of failure

Conservative treatment had to be taken over by surgical treatment due to intra-abdominal hemorrhage induced by the occurrence of abdominal pain or intensified abdominal pain after treatment; β-HCG did not present obvious decrease, or present continuous increase; ectopic pregnancy mass failed to exhibit diminishing tendency (Rose, 1999).

#### Toxic side effects of drug treatment

Scale division of toxic side effects was based on the criteria enacted by WHO concerning acute and sub-acute scales of cytotoxic drugs (Postovsky and Ben Arush, 2005).

#### Statistical analysis

$\chi^2$ tests were carried out. $p$<0.05 was considered to indicate a statistically significant difference, and $p$<0.01 was considered to indicate a manifest significant difference.

## RESULTS

### Comparisons of curative effects among groups

The success rates in Groups I, II, III and IV were 73.17% (30/41), 92.68% (38/41), 75.61% (31/41) and 87.80% (36/41), and the failure rates in four groups were 26.83% (11/41), 7.32% (3/41), 24.39% (10/41) and 12.20% (5/41), respectively. All the cases which failed to respond to conservative treatment underwent surgical treatment.

Of the success cases among four groups, the differences in durations of amenorrhea, values of β-HCG before treatment and the changes in diameters of pregnancy masses after 7-day treatment displayed no statistical significance ($p$>0.05). Both differences in the decrease rate of β-HCG after 7-day treatment between Groups I and II, and between Groups III and IV demonstrated manifest statistical significance ($p$<0.01) while neither of the difference in success rate between Groups I and III, or that between Groups II and IV showed statistical significance (Table 1).

### Comparisons of toxic side reactions

As shown in Table 2, the difference of gastrointestinal reaction in different groups showed no significantly statistics ($p$>0.05). However, the hepatic function damage, bone marrow depression, dental ulcer among different groups showed significance ($p$<0.05).

## DISCUSSION

In recent years, the incidence rate of ectopic pregnancy has shown an obvious increasing tendency (Hoover et al., 2010; Trabert et al., 2011). In the past decade, with the

**Table 2.** Toxic side reactions after MTX treatment in four groups (case).

| Group | Gastrointestinal reaction | Hepatic function damage | Bone marrow depression | Dental ulcer |
|---|---|---|---|---|
| I | 7 | 1 | 0 | 0 |
| II | 8 | 3 | 1 | 1 |
| III | 8 | 2 | 2 | 1 |
| IV | 8 | 4 | 2 | 1 |
| *p* Value | >0.05 | <0.05 | <0.05 | <0.05 |

All side reactions disappeared rapidly after drug withdrawal or during the period of follow-up.

the improved sensitivity of β-HCG measurement, most ectopic pregnancy cases can be detected at early stage, and accordingly some development in treatment method has been obtained (Doubilet and Benson, 2011; Kriplani et al., 2011). As non-surgical method (drug treatment) for treatment of ectopic pregnancy can maximally protect the patient's ability to have birth (Okorie, 2010), it is particularly fit for those young patients who are looking forward to having a baby.

The forms of drug treatment may take systemic administration, local administration and drug combination. According to large sample surveys, systemic administration can roughly get same success rate in comparison with local administration (Fylstra, 1998). Though systemic administration can lead to nonscheduled toxic side reactions, systemic administration is more favorable in selecting drug treatment method as it is more convenient to carry out while the conduct of local administration needs more technical skills and specific equipments (Fylstra, 1998). Drugs which can be used for drug treatment including Methotrexate (MTX), prostaglandin (PG), mifepristone (RU486), potassium chloride, hypertonic glucose, trichosanthin, etc., among which MTX is the most commonly used drug with most curative effect (van Esch et al., 2011; Hamed et al., 2012). In our study, four groups of ectopic pregnancy patients were randomly treated with different chemotherapeutic protocols with drugs for the purposes of the observation and comparisons of their different curative effects.

## Mechanisms of drugs

1. MTX is a kind of anti-metabolite as well as antifolate. It can bind with dihydrofolate reductase to impede the synthesis of C.F, and thus to interfere with the synthesis of DNA. As trophocytes are quite susceptible to MTX, their growth retardation after MTX treatment can cause growth of the embryo to cease and the embryo to be absorbed. But the retention of MTX in hepatic, renal, pleural or peritoneal fluid can last for several weeks with slow evacuation, which can lead to some toxic side effects. Though the addition of C.F can alleviate the damages induced by MTX to normal tissues, it can weaken the efficacy of MTX for ectopic embryo at the same time (van Esch et al., 2011; Hamed et al., 2012). This can be used to explain the phenomenon that the success rate in Group I was lower than that in Group II in our study.

2. Mifepristone. Mifepristone is a kind of synthetic steroid. Its structure resembles that of noethisterone, and it has antiprogesterone, antiglucocorticoid and slight anti-androgen characteristics. As mifepristone has affinity to endometrial progesterone receptor five times higher than progesterone, it can succeed in binding with decidual progesterone receptor over progesterone and thus block progesterone activity to stop pregnancy (Grossman, 2006; Veena, 2011).

According to Pansky et al. (1991), due to the content of progesterone receptors in fallopian tubes is far less than that in endometrium, only mifepristone (total dose of 2700 mg) with high density could compete with internal progestogen in binding with intrabubal progesterone receptors to result in necrosis and absorption of ectopic pregnancy foci because of the loss of progestogen support. Theoretically, the same dose of mifepristone in medical abortion for early intrauterine pregnancy has a very limited impact on treatment of ectopic pregnancy. This might be used to explanations the phenomenon that the addition of mifepristone failed to improve the curative rate of MTX chemotherapy in our study. As MTX and mifepristone have different mechanisms in embryo-killing, there are controversies concerning the curative effect of their combined application (Gazvani et al., 1998; Li and Quan, 2004). In our study, the addition of mifepristone aggravated toxic side reactions. Thus, whether their combined application can improve the curative effect and how to abate its toxic side effects need further studies to explore.

In summary, in treatment of ectopic pregnancy, 50 $mg/m^2$ of MTX by single IM has better efficacy than that by divided IV drip. Though it had brought about relative increase of side reactions, such reactions returned to normal after drug withdrawal or during the course of follow-up. Furthermore, the addition of mifepritone can aggravate toxic side effects without improvement of the curative effect. This study is intended to provide theoretical basis for the selection of the appropriate treatment

protocol for ectopic pregnancy. And concerning this topic, further explorations are still needed.

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