

# Medical Treatment of Ectopic Pregnancy: A Ten-Year Review of 106 Cases at Maharaj Nakorn Chiang Mai Hospital

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**Objective:** To evaluate the effectiveness of single-dose intramuscular methotrexate in the treatment of ectopic pregnancy at Maharaj Nakorn Chiang Mai Hospital

**Material and Method:** A retrospective review of the patient records was performed on the patients with diagnosis of ectopic pregnancy and treatment with single-dose methotrexate according to the protocol of Stovall et al between 1996 and 2005. The successful treatment was defined as no need for surgical intervention.

**Results:** As many as 96 out of 106 (90.6%) were successfully treated with methotrexate, though four required a second dose. Pretreatment  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) levels were significantly lower in women who responded to single-dose therapy than either in those who required two doses or who had a failure of medical management ( $p < 0.01$ ). The mean pretreatment level of  $\beta$ -hCG was 873 mIU/ml. The median time to resolution of  $\beta$ -hCG was 21 days. In addition, all cases with failed medical treatment had adnexal masses larger than 3.5 centimeters in diameter.

**Conclusion:** In the present series, treatment of ectopic pregnancy with single-dose methotrexate was as high as 90% successful. Women with a high pretreatment  $\beta$ -hCG level and large sonographic adnexal masses had a greater probability of requiring either surgical intervention or multiple doses of methotrexate.

**Keywords:** Ectopic pregnancy, Methotrexate

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The use of methotrexate as a treatment option for ectopic pregnancy is a relatively new development. The first reported treatment of an ectopic pregnancy with methotrexate was by Tanaka et al in 1982<sup>(1)</sup>. Since that time, the use of methotrexate for the treatment of ectopic pregnancies has become common and now medical treatment of ectopic pregnancy with methotrexate (MTX) has become one of the most important developments in the management of this disorder<sup>(2)</sup>. This conservative approach to treatment has supplanted surgical therapy in most cases<sup>(2-6)</sup>. The success rate in properly selected women ranges from approximately 75%<sup>(7)</sup> to > 90%<sup>(8)</sup>. Although the highest success rates

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have been reported in settings with well-defined diagnostic and treatment protocols<sup>(8,9)</sup>, lower rates have been reported in non-research, or "actual-use", settings<sup>(7,10)</sup>. Most of the "actual-use" studies have been relatively small, with < 50 subjects<sup>(7,10)</sup>. Medical treatment of ectopic pregnancy has been established in Maharaj Nakorn Chiang Mai Hospital, Thailand since 1992, and the authors have prospectively collected into the database since 1996. However, the efficacy of this treatment in the authors' setting has never been thoroughly evaluated. Moreover, treatment of ectopic pregnancy with methotrexate has never been reported in Thailand. The purpose of the present study was to review the authors' experience with methotrexate treatment for ectopic pregnancy as an actual-use setting, at Maharaj Nakorn Chiang Mai Hospital, a

tertiary center in the northern part of Thailand over a 10-year period retrospectively.

### Material and Method

The records of the patients diagnosed with ectopic pregnancy at Maharaj Nakorn Chiang Mai Hospital between 1996 and 2005 were reviewed. The diagnostic workup for tubal ectopic pregnancy included single or serial  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) measurements, transvaginal ultrasound scanning and uterine curettage performed only as clinically indicated. The diagnosis of ectopic pregnancy was made with an algorithm, including 1) positive  $\beta$ -hCG, 2) empty uterus on ultrasound examination with adnexal masses indicating ectopic pregnancy<sup>(11)</sup>, or empty uterus without adnexal mass with poor hCG doubling time (<66% in 48 hours) and no villi on curettage specimens. Laparoscopic diagnosis was performed in only the cases in which ultrasound and  $\beta$ -hCG results were inconclusive. The inclusion criteria for methotrexate included stable hemodynamics, no desire of surgical therapy, agreement to appropriate follow-up, pretreatment  $\beta$ -hCG level < 10,000 mIU/ml, no fetal cardiac activity, the size of the ectopic pregnancy by transvaginal ultrasonography did not exceed 4 cms in diameter and normal liver function test. The patients were treated with a single-dose (50 mg/m<sup>2</sup>) intramuscular methotrexate regimen, which was described initially by Stovall et al<sup>(3)</sup>. According to this protocol,  $\beta$ -hCG levels are

measured on days 1, 4, and 7. If the  $\beta$ -hCG level fails to decline at least 15% between days 4 and 7 or at least 15% each week thereafter, then a repeated dose of methotrexate is given. In this retrospective study, a computer-generated list of records of the patients with ectopic pregnancy identified and reviewed. The patients with subsequent spontaneous abortion (products of conception identified in pathology reports from curettage) and patients with incomplete record or loss to follow-up before the resolution of the ectopic pregnancy were excluded. Successful response to methotrexate treatment was defined as the resolution of the  $\beta$ -hCG level to < 20 mIU/mL. Treatment failures were defined as the need to undergo surgical intervention for any reason after methotrexate administration. Ethical approval for the present study was obtained from the Human Investigations Committee of Faculty of Medicine Chiang Mai University. Statistical analysis was performed with SPSS software (version 12.0). The mean  $\pm$  SD, Median, number and percent were used to describe the variables. The Student *t* test was used for continuous variables; the Fisher exact or Chi-square test was used for categoric variables. A p-value of < 0.05 was considered statistical significant.

### Results

One hundred and six women met the criteria and were eligible for analysis. The mean ( $\pm$  SD) age was 27.0 ( $\pm$  6.1) years and the mean ( $\pm$  SD) gestational

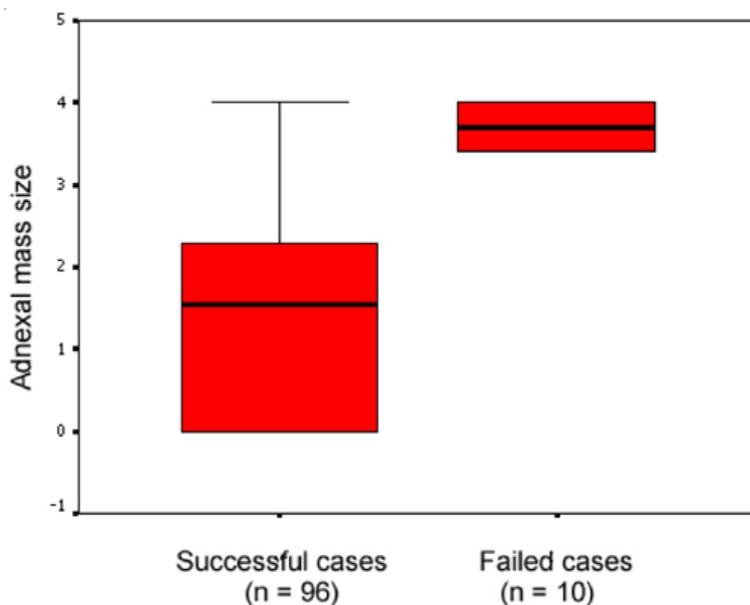


Fig. 1 The size of adnexal masses in the successful group significantly ( $p < 0.01$ ) smaller than that in the failed group

**Table 1.** Characteristics of 106 women with ectopic pregnancies treated with methotrexate

Clinical characteristics	No (%)
Treatment outcomes	
Success	96 (90.6)
Failure	10 (9.4)
Days to resolution (median)	21
Second-dose methotrexate	4 (3.8)
Mean pretreatment $\beta$ -hCG (mIU/mL)	
All cases	873
Cases with success	610
Cases with failure	9 (8.5)
Adnexal mass on ultrasound scan	65 (61.3)
Mean diameter of adnexal mass	
All cases	2.41 cms
Cases with success	2.23 cms
Cases with failure	3.79 cms
Free fluid on ultrasound scan	54 (50.9)
Pseudosac in the uterine cavity	9 (8.5)

age was 7.31 ( $\pm$  1.9) weeks. Most of them were nulliparous (64.2%). Nine patients had a history of previous ectopic pregnancy. Of 106 patients, 96 patients (90.6%) were treated successfully with methotrexate (Table 1). Only four patients needed the second doses of methotrexate but all of them finally resulted in successful treatment. The median time until the resolution of the ectopic pregnancy was 21 days. When a second dose of methotrexate was required, the ectopic pregnancy took 33 days to resolve. Among all patients, ultrasound findings showed an empty uterus in all cases, though four cases had pseudosac, no adnexal mass in about one-third (41/106 women, 38.7%), and mass compatible with ectopic pregnancy in about two-third (65/106 women, 61.3%). The mean pretreatment  $\beta$ -hCG level was 873 mIU/mL (range 48-4600 mIU/ml.). The mean pretreatment  $\beta$ -hCG level in the successfully treated patients was significantly lower than in those with treatment failure (778 vs 1871 mIU/mL,  $p < 0.001$ , Student's *t* test). In addition, a positive correlation was found between the adnexal mass size and the success rate. All of the ten patients with failed medical treatment had the adnexal masses of larger than 3.5 cms in diameter ( $3.8 \pm 0.4$  cms on average), whereas the mean diameter of adnexal masses in the successful group with adnexal masses seen through ultrasound was  $2.3 \pm 0.8$  cms. Furthermore, all of the patients with no visible adnexal mass were successful with medical treatment. No serious side effect of methotrexate was seen in any case, including the cases requiring second doses.

## Discussion

The present study represents the success rate of medical treatment of ectopic pregnancy in real practice or actual-use setting, unlike several previous studies in which the treatment strictly followed the protocol as an ideal condition of research setting. The result in the present report seems to be better than that noted in other actual-use setting reports in which the success rate was rather low<sup>(7,10)</sup>.

The success rate in the present study is rather high in the actual-use setting this might be due to the fact that the cases recruited into the present study had more favorable criteria for medical treatment including no fetal heartbeat, low mean  $\beta$ -hCG level of only 873 mIU/ml and small adnexal mass on average of only 2.4 cms in diameter in cases of visible adnexal mass. Additionally, several cases, as many as one-third, had no adnexal mass seen on ultrasound examination, in which the diagnosis was based on the poor doubling time of  $\beta$ -hCG combined with no villi on pathological diagnosis of curettage.

Because medical treatment with methotrexate is rather new in the authors' settings, several physicians were reluctant to offer this option to the patients and had a tendency to perform surgery in cases with rather high  $\beta$ -hCG and large adnexal mass. For example, patients with  $\beta$ -hCG  $> 4000$  mIU/ml but  $< 10,000$  mIU/ml, or adnexal mass size of more than 3.5 cms but less than 4.0 cms were very unlikely to be offered the medical treatment. Obviously, the cases included in the present study had lower  $\beta$ -hCG and had smaller adnexal mass size than other previous reports. In other words, the presented patients might have had less advanced ectopic pregnancies than patients in other previous actual-use settings<sup>(7,10)</sup>. This seems to be the main reason to explain the best result in actual-use setting, unlike the lower success rate in some reports<sup>(7,10)</sup>.

The presented experience indicated that medical treatment for ectopic pregnancy is highly effective in selective cases and it should be an option for the patients with favorable factors. However, although the present result is rather impressive, it must be emphasized that the medical treatment of ectopic pregnancy should be performed with high precaution and the ectopic pregnancy is still at risk for rupture.

Although the authors excluded the adnexal mass of more than 4 cm diameter as suggested by several authors, the authors observed that the mass size still had an influence on the success rate. Notably, all of ectopic pregnancies without detectable adnexal

mass responded to methotrexate, whereas the size of 3.5-4.0 cms had the highest failure rate.

For the failure of treatment, some serious clinical signs of ectopic pregnancy undoubtedly influenced some attending clinicians to more promptly intervene surgically, too soon for decision of failure. Indeed, the authors found that several patients who underwent operation after receiving methotrexate had unruptured ectopic pregnancy at the time of operation. However, most patients for whom methotrexate therapy failed to resolve the ectopic pregnancy underwent an operation because of increasing pain and/or inappropriately declining  $\beta$ -hCG levels after a single treatment dose.

Several limitations of the present study should be noted. It is possible that some women with failed intrauterine pregnancies received methotrexate and were included in this data set, even if the authors did not start medical treatment until the evidence of persistent hCG. The result of the present study may represent the effectiveness of medical treatment in only less advanced ectopic pregnancy as mentioned above. Finally, the authors' treatment was done in the tertiary center with optimal compliance with follow-up visits. This may not be always possible for all actual-use settings.

Despite the presented relatively high success rate, there is still opportunity for improvement. Efforts should be made at the presented study institution to ensure adequate patient follow-up evaluation and adherence to the single-dose methotrexate protocol.

In conclusion, like other reports, the findings suggested that medical treatment of ectopic pregnancy could be selectively offered, though the present study represents the patients with relatively favorable factors of treatment, medical treatment is highly effective even in the actual-use setting.

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## ประสบการณ์การรักษาครรภ์นอกมดลูกด้วยยา methotrexate จำนวน 106 ราย

กาญจนา ศรีวิชัย, จ่านง อุตวิชัย, อีระ ทองสง

**วัตถุประสงค์:** เพื่อประเมินถึงประสิทธิภาพของการรักษาครรภ์นอกมดลูกด้วยการฉีดยา methotrexate ครั้งเดียว เขากล้าม ที่โรงพยาบาลมหาราชนครเชียงใหม่

**วัสดุและวิธีการ:** เป็นการศึกษาย้อนหลัง ด้วยการทบทวนระเบียบประวัติผู้ป่วยที่เคยวินิจฉัยครรภ์นอกมดลูก และได้รับการรักษา ด้วยยา methotrexate ระหว่างปี พ.ศ. 2539 ถึง พ.ศ. 2548 การวินิจฉัยและรักษาถือตามแบบมาตรฐาน ที่รายงานไว้โดย Stovall และคณะ โดยถือว่าประสบความสำเร็จในการรักษาถ้าผู้ป่วยไม่ต้องได้รับการผ่าตัด หลังได้รับยา

**ผลการศึกษา:** จากจำนวนผู้ป่วยที่เข้าเกณฑ์การศึกษา 106 ราย พบว่าประสบความสำเร็จในการรักษา 96 ราย หรือ ร้อยละ 90.6 ในจำนวนนี้ 4 ราย ได้รับยา 2 ครั้ง ระดับของ  $\beta$ -hCG ก่อนการรักษามีความสัมพันธ์กับการตอบสนองต่อการรักษา โดยพบว่าในกลุ่มที่ล้มเหลวในการรักษามีระดับสูงกว่าอย่างมีนัยสำคัญ (ค่า  $P < 0.01$ ) ค่าเฉลี่ยของระดับ  $\beta$ -hCG ก่อนการรักษา 873 มิลลิยูนิต/มล. ระยะเวลา (มัธยฐาน) สำหรับการลดจนหายไปของ  $\beta$ -hCG ประมาณ 21 วัน นอกจากนี้ยังพบว่าในกลุ่มที่ล้มเหลวต่อการรักษามีขนาดของก้อนที่ปีกมดลูก (โดยอัลตราซาวด์) ขนาดเส้นผ่าศูนย์กลางใหญ่กว่า 3.5 ซม. ทุกราย ซึ่งมีขนาดใหญ่กว่ารายที่ประสบความสำเร็จอย่างมีนัยสำคัญ

**สรุป:** ในกระบวนรายงานนี้พบว่าการรักษาครรภ์นอกมดลูกด้วย methotrexate ในรายที่เลือกแล้วอย่างเหมาะสม จะประสบความสำเร็จสูงถึงกว่าร้อยละ 90 ในรายที่มีระดับ  $\beta$ -hCG สูงและขนาดก้อนที่ปีกมดลูกโตมีแนวโน้มจะประสบความสำเร็จล้มเหลวในการรักษาสูงขึ้น

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