

# Methotrexate treatment for ectopic pregnancy at the KK Women's and Children's Hospital, Singapore

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## ABSTRACT

**Introduction:** Ectopic pregnancy is an acute emergency in the first trimester where surgery is the mainstay of treatment. With the advent of improved diagnostic techniques like high-resolution transvaginal ultrasonography and expedient serum human chorionic gonadotrophin (HCG) assay, ectopic pregnancy is now diagnosed early. At this stage, the conceptus is often small, causing minimal or no symptoms. Medical management may then present an appealing alternative to surgery. Methotrexate has been widely used to treat ectopic pregnancy. A methotrexate ectopic treatment protocol was introduced by the Minimally Invasive Surgery Centre at KK Women's and Children's Hospital, Singapore. We present the results of this treatment.

**Methods:** A prospective review of 110 cases of medical management of ectopic pregnancy since the implementation of the treatment protocol was undertaken. Demographical data, clinical presentation, treatment progress and outcome were captured using a computer database. All patients were managed as outpatients, and a telephone call-out service was provided to ensure that treatment side effects were monitored and potential treatment failures were identified early.

**Results:** From August 2003 to October 2006, 93 (84.5 percent) patients with ectopic pregnancy were successfully treated with intramuscular methotrexate. 16 patients eventually required surgery and only one patient defaulted on follow-up. There was no major side effect detected in this cohort. The minor side effects reported included mucositis (19.1 percent) and abdominal pain (28.2 percent).

**Conclusion:** Methotrexate treatment of ectopic

pregnancy is safe. Our treatment protocol enabled us to achieve a reasonable treatment success rate of 84.5 percent.

**Keywords:** ectopic pregnancy, methotrexate

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## INTRODUCTION

Ectopic pregnancy is an important diagnosis to exclude when a woman presents with bleeding in early pregnancy. This is because ectopic pregnancy remains a leading cause of maternal mortality in the first trimester. In the recent Confidential Enquiry into Maternal and Child Health for 2003–2005, there were ten maternal deaths due to ectopic pregnancy.<sup>(1)</sup> The incidence of ectopic pregnancy appears to be rising from 0.5% 30 years ago to the current day of 1%–2%.<sup>(2)</sup> In pregnancies from assisted reproductive techniques, the incidence can be as high as 3%–5%.<sup>(3)</sup> Surgical treatment of ectopic pregnancy forms the mainstay of management, and laparoscopic surgery is currently the gold standard.<sup>(4)</sup>

As sensitive urine pregnancy test kits are now easily accessible, many women are booking earlier in their pregnancies. With the availability of high-resolution transvaginal ultrasonography (US) and expedient serum human chorionic gonadotrophin (HCG) assay at most early pregnancy assessment units, ectopic pregnancy can now be diagnosed early. Often the conceptus is small, less than 12 weeks in gestation and presenting with minimal or no symptoms. Medical management of such cases of ectopic pregnancy thus becomes a viable alternative to surgery. Systemic methotrexate has been widely used as a successful treatment modality for selected ectopic pregnancy. The objective of our study was to review the results of our treatment protocol. We present our prospective results of methotrexate treatment of ectopic pregnancy at the KK Women's and Children's Hospital, Singapore.

## METHODS

A methotrexate ectopic treatment protocol was introduced in August 2003 by the Minimally Invasive Surgery Centre at KK Women's and Children's Hospital. The main aim of

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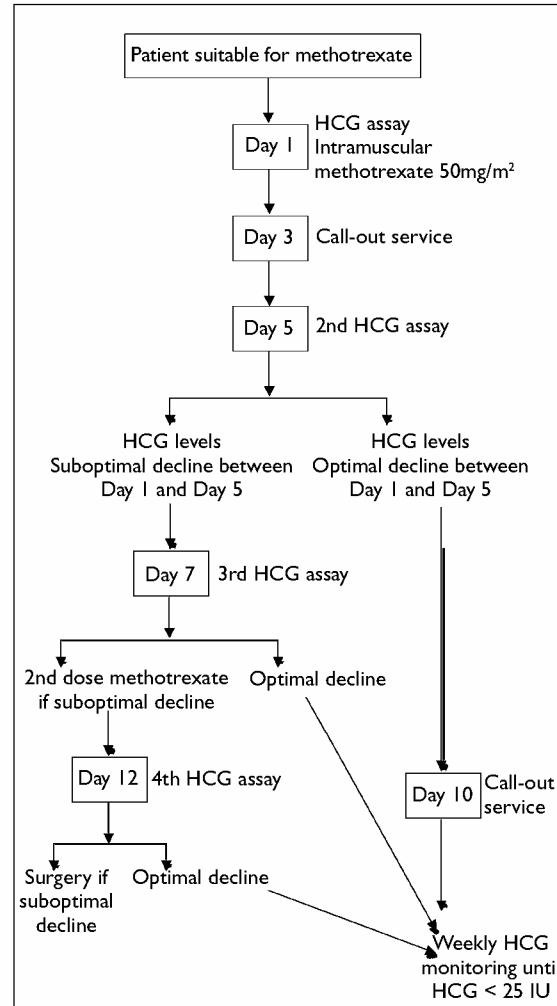
this protocol was to provide a viable alternative to surgery for cases where ectopic pregnancy was diagnosed very early (before 12 weeks' gestation), or in cases where the diagnosis was equivocal despite a period of HCG testing and US monitoring. Hence, the treatment protocol had two sets of inclusion criteria; one for patients with high suspicion of ectopic pregnancy and another for patients with probable ectopic pregnancy possibly at an unknown location.

The inclusion criteria for patients with high suspicion of ectopic pregnancy were: haemodynamically-stable with non-acute abdomen;  $\beta$ -HCG levels < 5,000 IU; tubal or adnexal mass < 2 cm; and absent foetal cardiac activity. The inclusion criteria for patients with probable ectopic pregnancy were: haemodynamically-stable with non-acute abdomen; absent US features of uterine, tubal or adnexal mass; and  $\beta$ -HCG levels < 10,000 IU with suboptimal rise for viable pregnancy, suboptimal fall for failed pregnancy, or plateau serial readings.

Patients who satisfied the inclusion criteria were given the option of medical treatment as an alternative to conventional surgical management. The patients were counselled regarding the treatment protocol, schedule of follow-up, possible side effects of methotrexate and potential treatment failure needing urgent surgical recourse. After informed consent was taken, the patient's clinical details were entered into a computer database and a schedule of follow-up was created (Fig. 1). Day 1 marked the day intramuscular methotrexate at a dose of 50 mg/m<sup>2</sup> was administered, and the patient was followed-up as an outpatient on Day 5 where a second serum HCG was measured. A telephone call-out service was carried out on Day 3 and Day 7 to enquire about any methotrexate side effects. The call-out service also formed a "safety net" to diagnose treatment failures early. All patients were scheduled to follow-up until HCG declined to < 25 IU, which is the sensitivity of HCG in our urine pregnancy test kits. A second dose of intramuscular methotrexate (50 mg/m<sup>2</sup>) was given for suboptimal decrease in HCG levels of < 15% between Day 1, Day 5 and Day 7. Surgical intervention was considered in patients with increasing levels of HCG, increasing abdominal pain or emerging signs and symptoms of ruptured ectopic pregnancy.

## RESULTS

From August 2003 to October 2006, prospective data on 110 patients treated with intramuscular methotrexate for ectopic pregnancy was reviewed. The mean age was 30 (range 17–44) years, with gravidity between one and seven. 57 (51.8%) patients were primigravidae. The presenting symptoms were vaginal bleeding (88 or 80.0%), period



**Fig. 1** Flow chart shows methotrexate for ectopic pregnancy workflow.

Optimal decline: HCG levels decline > 15%

Suboptimal decline: HCG levels decline < 15%

of amenorrhoea (22 or 20.0%), and mild and transient lower abdominal pain (61 or 55.5%); the remaining 13 (11.8%) cases were asymptomatic. The majority of patients presenting with vaginal bleeding were mostly mild and less than a normal menstrual flow. Slightly more than half of the cohort complained of mild and transient pelvic pain that did not amount to an acute abdomen. In all these patients, cervical excitation was negative. There were 13 patients where ectopic pregnancy was diagnosed when they booked for an apparent normal pregnancy.

29 (26.4%) patients had apparent normal US findings but abnormal HCG trend and were considered as probable ectopic pregnancy. 81 (73.6%) patients had US findings showing an empty uterus with adnexal masses of 2–5 cm in size and were considered as high suspicion of ectopic pregnancy. The mean HCG level of the 110 patients at Day 1 was 1,414.7 (range 18.3–10,073.0) IU. Of the 81 patients with adnexal mass, 29 measured larger than 2 cm in size (22 were 2–3 cm, 7 were 3–5 cm). In this group, two also

had HCG higher than 5,000 IU, while the remainder had HCG in the range of 65–4,636 IU. Although these patients did not satisfy the criteria of the methotrexate ectopic treatment protocol, treatment was administered because they were adamant about avoiding surgery as the first line of management. Additional counselling was provided to clarify that the success rates may be lower than expected in these cases. Seven of these 29 patients eventually required surgery resulting in a failure rate of 24.1% when the protocol was not adhered to.

Of the 110 patients, 87 (79.1%) were successfully treated with a dose of methotrexate within a mean of 33 (range 12–113) days. Six required a second dose of methotrexate and were successfully treated after a mean of 55 (range 28–98) days. 16 patients eventually required surgery due to a combination of reasons. Nine patients complained of pain mostly between Days 4 and 8 after methotrexate injection, with only one patient having a ruptured cornual ectopic pregnancy at laparoscopy. Two patients needed surgery for bleeding, increasing HCG values and enlarging adnexal mass. The remaining five patients were asymptomatic with two having enlarging adnexal mass and the remaining three were not keen for a second dose of methotrexate when HCG did not decline as expected. There was only one patient who was lost to follow-up after methotrexate was given. This was a foreign patient who wanted medical treatment before returning home. Her US did not reveal any adnexal mass and her HCG levels were 9,891 IU at Day 1 and 8,691 IU at Day 7.

Following methotrexate injection, 53 (48.2%) patients continued to have mild vaginal bleeding that was not more than at initial presentation. 86 (78.2%) patients experienced some side effects. The most common side effects appeared to be nausea and low-grade fever (< 37.8°C) that resolved spontaneously in less than five days. The 21 (19.1%) patients who complained of mucositis had mainly mouth ulcers and sore throat, with 12 (10.9%) patients experiencing gastric pain and diarrhoea. Although 31 (28.2%) patients had some abdominal pain, only ten (9.1%) patients eventually required surgery because of increasing pain. At surgery, apart from one patient with ruptured cornual ectopic pregnancy, there were no ruptured tubal ectopic pregnancies. In summary, our methotrexate ectopic treatment protocol successfully treated 93 (84.5%) patients, with 16 (14.5%) patients requiring surgery despite medical management.

## DISCUSSION

Methotrexate therapy for ectopic pregnancy of all routes and doses combined has a success rate of between 74% and 84%.<sup>(5-8)</sup> The success rate appears to be higher when

applied to carefully selected cases. Kooi and Koch noted a success rate of 94% when the initial HCG level was less than 10,000 IU, as compared to 68% when the initial HCG was above 10,000 IU.<sup>(7)</sup> Lipscomb et al also concurred with respective rates of 94% and 75%.<sup>(9)</sup> Stika et al found that patients with an initial HCG of above 5,000 IU had a greater probability of requiring either multiple doses of methotrexate or surgery for their ectopic pregnancy.<sup>(10)</sup> Based on these findings, we formulated our protocol to accept patients with a maximal initial HCG of 5,000 IU when there was a high suspicion of ectopic pregnancy and a maximal initial HCG of 10,000 IU when there was no definite US features of ectopic pregnancy. Because Stoval and Ling<sup>(11)</sup> and Lipscomb et al<sup>(9)</sup> found that the presence of cardiac activity within the ectopic pregnancy reduced the success rates from 95% to 70%, we excluded ectopic pregnancies with a positive cardiac activity.

With regard to the gestational size of ectopic pregnancy, Shalev et al found a success rate of 76% when the conceptus was smaller than 2 cm, and 52% when it was larger than 2 cm.<sup>(12)</sup> Although we limited the gestational size to 2 cm, it was not uncommon for patients to request for medical treatment. This was especially so when the presentation was early with minimal or no symptoms and the HCG values low. There were 29 patients who received methotrexate despite having a gestational size exceeding 2 cm. One patient had a 5-cm caesarian section scar ectopic pregnancy (initial HCG 673 IU), while two patients had initial HCG above 5,000 IU (ectopic pregnancy 2.8 cm). Of these three, only one required laparoscopic salpingectomy for tubal ectopic pregnancy because of increasing HCG levels.

Our success rate after single-dose methotrexate was 79.1% (87/110), and after two doses of methotrexate, 84.5% (93/110). Seven of 29 cases that did not adhere to the protocol required surgery after a dose of methotrexate, giving an out-of-protocol success rate of 75.9% (22/29). If we considered only the cases which met the protocol criteria, the success rate after a single-dose methotrexate would be 80.2% (65/81), and after two doses of methotrexate, 87.7% (71/81). We believe that the main contributory factor to our high success rate was the low mean initial HCG level of 1,414 IU. Before the implementation of this protocol, 70 mg of methotrexate was given, irrespective of the size of the patient. This resulted in variable treatment success rates. With the implementation of the protocol, methotrexate was administered at a dose of 50 mg/m<sup>2</sup> body surface area, as this dose has been shown to achieve an ectopic pregnancy resorption rate of 92% with a subsequent intrauterine pregnancy rate of 58% and a recurrent ectopic pregnancy rate of 9%.<sup>(13-15)</sup>

The side effects of methotrexate are related to the dose and mode of administration. The incidence varied from 2% with local injection to 21% in those treated systematically. With single-dose methotrexate, most authors have reported no significant adverse effects.<sup>(11)</sup> The incidence of side effects in our cohort was higher than that of most studies. This is most likely due to the prospective nature of data collection with telephone call-out services on Day 3 and Day 7. It was reassuring to note that most of the side effects were mild and almost fully resolved by the time the second telephone call-out service was made. Although 31 patients complained of pain following methotrexate administration, only ten of them required surgery when the pain worsened.

The aetiology of pain following methotrexate medication is still unexplained, although some believe it to be linked to tubal abortion or directly related to the drug itself.<sup>(16)</sup> It is often hard to differentiate if a rupture of tubal ectopic pregnancy has occurred, as the presence of peritoneal fluid on US may not be confirmatory of a rupture. It is always good practice to consider a diagnostic laparoscopy when the pain worsens despite decreasing HCG levels, because ruptured ectopic pregnancy has occurred in such instances before.<sup>(10)</sup> Of the 16 patients who failed methotrexate treatment, none had a ruptured tubal ectopic pregnancy although the majority complained of abdominal pain and bleeding. There was only one case of ruptured cornual ectopic pregnancy that occurred five days after methotrexate injection. Her initial HCG was 4,634 IU, and it had declined to 1,922 IU when the rupture occurred.

Intramuscular methotrexate, apart from saving the patient from requiring surgery, has the advantage of preserving the future fertility of the patient. Stovall and Ling showed that after a single-dose methotrexate, 82.3% of patients had patent ipsilateral tubes on hysterosalpingogram with 69.3% of patients achieving a future intrauterine pregnancy.<sup>(11)</sup> Yao and Tulandi also found similar rates of future intrauterine pregnancy (54%) with an 8% risk of recurrent ectopic pregnancy.<sup>(5)</sup> These results are similar to that of laparoscopic salpingostomy. The ability to preserve reproductive function is even more relevant in our patients since most presented with very early and small ectopic pregnancies. Surgery for these patients may not be the best option as there is a possibility of losing a fallopian tube given that salpingectomy is the current Grade B recommendation from the treatment guidelines of the Royal College of Obstetricians and Gynaecologists.<sup>(17)</sup>

In conclusion, the review of our methotrexate ectopic

treatment protocol showed that our criteria delivered a success rate of 84.5% safely, with no severe treatment morbidity. The telephone call-out service provided additional reassurance that such management can be carried out as outpatient. A comprehensive monitoring of the side effects of treatment as well as early detection of an unsuccessful treatment was possible with a low default rate.

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