

Original Articles

Safety and Efficacy of Methotrexate In Unruptured Ectopic Pregnancy

QUORRATA EYNUL FORHAD¹, MASUDA BEGUM², IRIN PARVEEN ALAM³, MD. SHAH ALAM⁴

Abstract:

Introduction: Medical management of an unruptured ectopic pregnancy with intramuscular methotrexate is a common and cost-effective alternative to surgery¹. This therapeutic transition from surgical emergency to medical management has been attributed to early diagnosis through the use of sensitive assays for β -hCG and the high definition vaginal ultrasound.

Objectives: The aim of the study was to observe the efficacy and safety of medical treatment either by a single or multiple dose of methotrexate to cure ectopic pregnancy.

Materials and methods: A retrospective study from January 2005 – June 2008 was carried out, collecting clinical imaging data and serum β -hCG, time taken for complete β -hCG resolution was recorded and negative β -hCG result was used as an endpoint of successful outcome. Out of 14 cases, where Methotrexate (50 mg I/M) was used, two required surgery for symptom of rupture. In the remaining 12 cases, there was no side effects, complete β -hCG resolution was achieved in 10 of the 12 medically treated cases (85% success rate) within 28 days. Rest of the 2 cases needed multiple doses of Methotrexate.

Results: Over all success rate was 85%. In 71% cases recovery was uneventful and complete within 7 days of treatment (Table 1). Two patients needed surgical treatment and in another one case there was abdominal pain which subsided after analgesic. Ten patients were cured by single dose only and 2 patients needed multiple dose. There was no side effects or complication of drug in any case.

Conclusion: Methotrexate is safe and effective for unruptured ectopic pregnancies that satisfy the strict criteria with no side effects and the advantage of avoiding invasive surgery. This small trial gave a good impression about medical treatment in selective cases.

Key words: Ectopic pregnancy; Methotrexate.

Introduction: Ectopic pregnancy is disaster in human reproduction. It is one of the most important causes of death during 1st trimester of pregnancy. Ectopic pregnancy is more threatening for women than normal vaginal delivery and induced abortion². Timely diagnosis and appropriate treatment can reduce the risk of maternal mortality and morbidity related to ectopic pregnancy³. If not diagnosed and treated expeditiously it may also take the life of the mother or at the very least, compromise her future ability to reproduce. Although it has been recognized for over

400 years, ectopic pregnancy continues to be an ever increasing affliction, affecting approximately 2% of all pregnancies⁴. The rising incidence of ectopic pregnancy in the past 25 years has been attributed to a number of factors like tubal surgery and tubal ligation, previous ectopic pregnancy, IUCD use, tubal pathology, morning after pill, assisted reproductive technique (ART), salpingitis, genital tract infection and the treatment has progressed from salpingectomy by laparotomy to conservative surgery by laparoscopy and more recently to medical therapy^{5,6}. With

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1. Associate Prof. Gynae and Obs. – Shahabuddin Medical College Hospital
 2. Associate Prof. Gynae and Obs. – Dhaka Medical College Hospital
 3. Assistant Prof. Gynae and Obs. - Faridpur Medical College Hospital
 4. Ex-Professor Gynae and Obs. – Dhaka Medical College Hospital.

improving diagnostic methods and suitable treatment, mortality rate from ectopic pregnancy has decreased dramatically⁷.

Modern diagnostic methods now permit early recognition of most ectopic pregnancies, attention has shifted from emergency surgery for the control of life threatening hemorrhage to medical treatments aims at avoiding surgery and preserving anatomy and fertility. At times, identification of an early unruptured tubal pregnancy may be difficult, but clinical suspicion, diagnostic methods and careful evaluation are the best way to reach a correct diagnosis⁸. Currently over 90% of ectopic pregnancies can be visualized on Transvaginal scan(TVS), this means that early ectopic pregnancies can be detected in asymptomatic women⁹. Early pregnancy units(EPU) with their access to high resolution TVS and the rapid immunoassay of serum β -hCG allow early diagnosis of pregnancy location. Surgery is not always the most appropriate form of treatment¹⁰. Medical management avoids the inherent morbidity of anaesthesia and surgery and reduce costs. Methotrexate, Potassium chloride, hyperosmolar glucose, Actinomysin D and Prostaglandins have been used successfully to treat ectopic pregnancy^{11,12}. Methotrexate (MTX) has been established as an effective first line medical therapeutic alternative to surgical treatment. Methotrexate, a folic acid antagonist, highly toxic to rapidly replicating trophoblastic cells has been the mainstay of the medical management of ectopic pregnancy¹³.

Methodology:

A retrospective study was conducted at private setting, the medical records of patients having ectopic pregnancies were collected from January 2005 to June 2008 for review. Cases were included only when the diagnosis was made either on serial β -hCG and on ultrasonographic features having an empty uterine cavity, adnexal mass less than 3cm with no fetal heart beat and no free fluid. Most of the women in the selection criteria were informed regarding the treatment. All the patients had initial investigations before the administration of Methotrexate. Selection criteria for medical therapy were positive pregnancy test, abdominal pain, per vaginal bleeding, haemodynamically stable condition, β -hCG < 3000 IU/L and sonographic(TVS) findings of adnexal mass <3cm with no cardiac pulsation. Criteria for medical therapy in this study included a stable clinical condition, no evidence of rupture on ultrasound, normal liver and renal function, patients' reliability for follow

up. These patients were treated with 50 mg of intramuscular methotrexate (single or multiple doses) depending on the fall of β -hCG levels. β -hCG levels were measured on day 4 and day 7 and weekly thereafter until they were less than 5 IU/L. Repeat complete blood count liver and renal function tests were carried out on day 4 and day 7. Success of treatment was defined as the resolution of the β -hCG level to less than 5 IU/L¹⁴. Treatment failure was defined as the need for surgical intervention for any reason.

Results:

A series of 40 ectopic pregnancies were managed in private setting over this period, among them 14 cases, fulfilled the criteria for methotrexate therapy. Of these 14 cases 2 underwent surgery for suspected rupture symptoms. All the 14 patients had positive pregnancy test but only 10 presented with abdominal pain and only 8 had pervaginal bleeding. (Figure 1). In this study all the patients (cited before) were haemodynamically stable but only 12 patients had β -hCG < 3000 IU/ml. (Figure 2). Fourteen of the patients had ultra sound to fulfill the selection criteria. Ten out of 14 patients had only single dose of methotrexate and only 2 patients needed more than one dose which were two and three doses respectively, and 2 patients needed laparotomy for suspected ruptured ectopic.

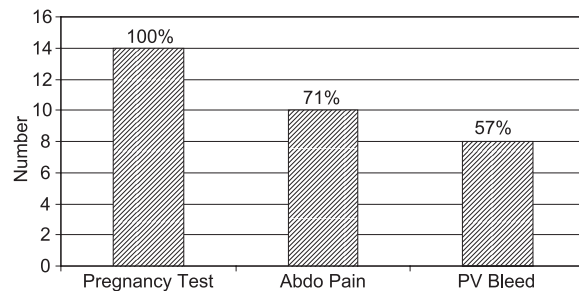


Fig.-1: Pregnancy test and clinical signs

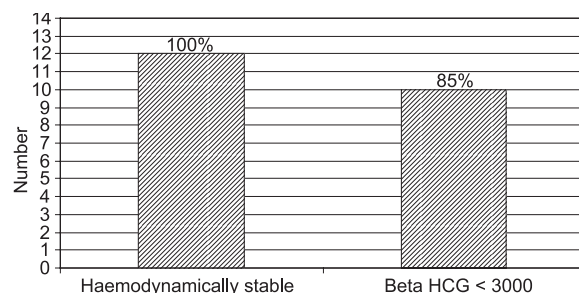


Fig.-2: Criteria of medical treatment

Most of the women in the selection criteria were informed regarding the treatment, however documentation and obtaining the consent were universal. All the patient had initial investigations before the administration of Methotrexate. Table-1 shows that 10 out of 14 patients had only single dose of methotrexate and only 2 patients needed more than one dose which were two and three doses respectively, and 2 patient needed laparotomy for suspected ruptured ectopic. But there was no side effects or complications of drug in any case.

Over all success rate was 85%. In 71% cases recovery was uneventful and completed within 7 days of treatment (Table 1). Two patients needed surgical treatment and in another one case there was abdominal pain which subsided after analgesic. There was no side effects or complication of drug in any case.

Table-I
Outcome of treatment

	No. of patient	Percentage
Complete and uneventful recovery	10	71
Tubal rupture	2	14.2
Tubal abortion	2	14.2
Single dose Methotrexate	10	71
Multi dose	2	14.2
Complication of drug	0	0
Overall success rate	12	85

Twelve of the 14 patients who had methotrexate their β -hCG returned to the normal within 28 days. One patient took 42 days for her β -hCG to return to normal. (Figure: 3)

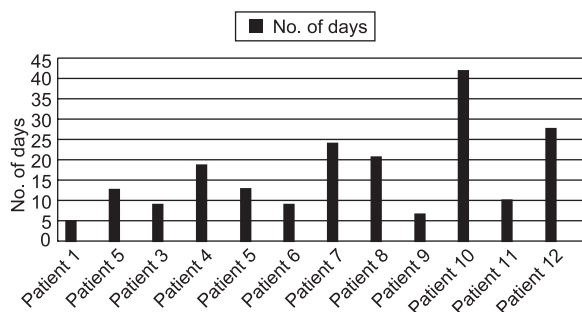


Fig.-3: Time taken for resolution of β -hCG to <5 I.U/L.

Discussion:

Ectopic pregnancy remains the great puzzle of Gynaecology; no other pelvic conditions give rise to

more diagnostic errors like this condition. The patient may or may not have symptoms pointing to pregnancy, with or without a period of amenorrhea patients may complain of pelvic pain and irregular vaginal bleeding. However report shows that only half of patients with ectopic pregnancy are correctly diagnosed based on clinical feature alone¹⁵.

Since the late 1980s, systemic Methotrexate has been employed to treat ectopic pregnancy with excellent result. The initial studies were done using Methotrexate and Leucoverin for the treatment of unruptured ectopic pregnancy in selected, stable patients. Patients were closely monitored during therapy with complete blood count, liver and renal function tests and β -hCG levels¹⁵.

This study supports the use methotrexate as a safe and highly effective alternative treatment of ectopic pregnancies with a success rate of 85%. This highly efficacious result was obtained with strict adherence of our selection criteria. Our experience with this method of treatment showed a negligible side effect profile and it allows for only a short hospital stay¹⁶.

Management of ectopic pregnancy has shifted from emergency life saving intervention to more conservative treatment modalities aimed at reducing mortality and morbidity, preserving fertility and reducing costs. Laparoscopic surgery is still the cornerstone of the treatment in the majority of women with tubal pregnancy.

If the diagnosis of ectopic pregnancy can be made earlier noninvasively, medical treatment with systemic intramuscular Methotrexate in a single or multiple dose regimen is an alternative treatment option, but only after properly informing patients about the risk and benefit of the available treatment option if the following criteria are satisfied^{17,18} as follows haemodynamically stable women, unruptured tubal pregnancy, no sign of active bleeding and low initial serum β -hCG concentration.

Three to seven days after receiving methotrexate, some patients may also experience pelvic pain which may be caused by tubal abortion and can be confused as tubal rupture. In presence of stable vital signs and serial normal haematocrits, these episodes are self-limited and do not warn surgical intervention. The first quantitative β -hCG should not be obtained sooner than 4 days post methotrexate treatment as an initial increase in the β -hCG level is frequently noted presumably due to trophoblast lysis. Side effects of medical treatment may include transient increase in liver enzymes, gastroenteritis, hair loss¹⁹.

The reasons for change towards Methotrexate treatment are minimal intervention/ no intervention,

less morbidity and lower cost implications. Diagnosing the condition earlier in its natural history has changed management options. The classic presentation with a “collapsed ectopic women” has become less common when good facilities for early diagnosis are available. Early ectopic pregnancy tend to be smaller and have lower baseline β -hCG level, thus more time is available for conservative management options with comparable outcome to that of surgical treatment. A randomized study in 2013 came to the result that the rates of intrauterine pregnancy 2 years after treatment of ectopic pregnancy are approximately 67% with medication, consideration should be given to increase rate of Methotrexate management²⁰.

Conclusion:

In conclusion this small trial gave a good impression about medical treatment in selective cases. The advent of modern diagnostic and therapeutic modalities has changed the clinical scenario of ectopic pregnancy from one of possible disaster to one of potential success. So we recommended increasing its use in the treatment of unruptured ectopic pregnancies.

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