Medical Management of Ectopic Pregnancy using Methotrexate
S Vitthala, M Cheema, P Kumar Misra

Citation

Abstract
Background: Medical treatment of the ectopic pregnancy with methotrexate has been considered an alternative to surgical intervention.

Aims & Objectives:
1) To review adherence to guidelines for the medical management of ectopic pregnancy
2) To determine: a) diagnostic investigations. b) Suitability for Methotrexate treatment
3) To ascertain: a) follow-up investigations b) outcome

Methods:
A retrospective study from January 2002 - May 2006 was carried out, collecting clinical imaging data and serum beta-human chorionic gonadotrophin (βhCG). Time taken for complete βhCG resolution was recorded, and a negative βhCG result was used as an endpoint of successful outcome.

Results:
Of the 17 cases, where Methotrexate (50mg I.M) was used, three required surgery for symptoms of rupture. In the remaining 14 cases, there were no side-effects, complete βhCG resolution was achieved in 13 of the 14 medically treated cases (91% success rate), with in 28 days.

Conclusion:
Methotrexate used as treatment is safe and effective for unruptured ectopic pregnancies that satisfy the strict criteria with no side-effects and the advantage of avoiding invasive surgery. Subsequent tubal patency and reproductive functions were comparable to the surgery.

INTRODUCTION
An ectopic pregnancy refers to the pregnancy occurring outside the uterine cavity usually in the fallopian tube. Ectopic pregnancy is still a major problem in the United Kingdom; it affects 11 in 1000 pregnancies.

Historically ectopic pregnancies were diagnosed at the time of laparoscopy or surgery, often in women who were unaware that they were pregnant. Now the commercially available home pregnancy tests can detect βhCG levels at less than 25 IU/L, a pregnancy can easily be diagnosed even before a menstrual period has been missed, as a consequence women present at early gestational age.

Currently over 90% of ectopic pregnancies can be visualized on Transvaginal scan (TVS), this means that early ectopic pregnancies can often be detected in asymptomatic women.

Early pregnancy units (EPUs) with their access to high-resolution TVS & the rapid immunoassay of serum βhCG allow early diagnosis of pregnancy location. Surgery is not always the most appropriate form of treatment as third of the ectopic pregnancies will miscarry.

MATERIALS & METHOD
The retrospective audit was conducted at the Furness
Medical Management of Ectopic Pregnancy using Methotrexate

General Hospital, a district general hospital in Barrow in Furness. The medical records of those with ectopic pregnancies were retrieved from January 2002 to May 2006 for review and to ensure that all patients were identified, the admission list to the gynaecology ward was checked. Cases were included only when the diagnosis was made either on serial ? hCG or on ultrasonographic features: (i) an empty uterine cavity, ii) adnexal mass <3cm with no foetal heart iii) no free fluid.

Our criteria for medical therapy include a stable clinical condition, no evidence of rupture on ultrasound, normal liver and renal function, and patient reliability for follow-up. These patients were treated with 50 mg of intra muscular methotrexate (single or multiple doses) depending on the fall of hCG levels. hCG levels were then measured on days 4 and 7 and weekly thereafter until they were less than 5 IU/L. Repeat full blood count and liver and renal function tests were carried out on day 4 & day 7. Treatment success was defined as the resolution of the hCG level to less than 5 IU/L. Treatment failure was defined as the need for surgical intervention for any reason.

**SELECTION CRITERIA**

1. Pregnancy test Positive
2. Abdominal pain
3. Bleeding PV
4. Heamodynamically stable
5. hCG <3000 IU/l
6. USS (TVS) – adnexal mass <3cm with no foetal heart
7. Case to be discussed or reviewed by the consultant
8. Methotrexate Information Leaflet given to the patient

Patient fully understands & will be compliant with regular follow-up until hCG returns to normal.

**RESULTS**

A series of 52 ectopic pregnancies was managed at our institution over this period; 17 cases of 52 ectopic pregnancies fulfilled the criteria for methotrexate, this constitutes 32.6% of all ectopic pregnancies. Of these 17 cases, three underwent surgery for suspected rupture symptoms.

1) ECTOPIC OCCURRENCE AT FGH

The number of ectopic pregnancies in our hospital increased from 2002 to 2006 and a third of them were treated with methotrexate avoiding the surgical intervention.

**Figure 1**

**2) CLINICAL SIGNS; N=17**

All the 17 patients had positive pregnancy test but only 11 presented with abdominal pain & only 10 had per vaginal bleeding.

**Figure 2**

**3) SUITABILITY FOR METHOTREXATE THERAPY**

All the patients were hemodynamically stable for the administration of Methotrexate but only 15 patients had hCG level less than 3000 IU/ml.
4) ULTRASOUND SCANNING
16 of the 17 patients had ultrasound scanning before the treatment to fulfil the selection criteria; however the missing one might not had been documented.

5) INFORMATION & CONSENT
Most of the women in the selection criteria were informed regarding the treatment however documentation and obtaining the consent were not universal.

6) INITIAL INVESTIGATIONS
All the patients had initial investigations before the administration of the Methotrexate.

7) METHOTREXATE ADMINISTRATION
15 out of the 17 patients had only single dose of methotrexate and only 2 patients needed more than one dose which were two & three doses respectively.
8) FOLLOW-UP BLOOD TESTS
Most of them had follow up bloods as per criteria after Methotrexate administration.

9) SURGICAL INTERVENTION
3(17%) patients underwent Laparotomy for suspected ruptured ectopic, namely

Laparotomy (1), Laparotomy & salpingotomy (1) and
Ruptured ectopic day 6 (1) (wrong selection of the case with βhCG >3000 I.U/ml, due to the patients wish)

Laparotomy was performed due to increased pain rather than any clinical features of ruptured ectopic pregnancy (no tachycardia or hypovolaemia, non-ruptured ectopic with minimal free fluid and stable haemoglobin). Pain is an associated feature of Methotrexate treatment & could be feature of tubal miscarriage.

10) OUTCOME: METHOTREXATE ALONE
Three patients had intrauterine pregnancy after the treatment, three patients referred to the assisted conception unit, two patients were sterilised and in six patients pregnancy were not documented.

11) TIME TAKEN FOR THE βHCG TO RETURN TO THE NORMAL (< 5 I.U/L)
13 of the 14 patients who had methotrexate their βhCG returned to the normal with in 28 days. One patient took 42 days for her βhCG to return to normal.

DISCUSSION
This study supports the use of methotrexate as a safe and highly effective alternative treatment of ectopic pregnancies with a success rate of 82%. 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 stay.

We had started our EPU in 2002 and from then EP were diagnosed at early gestation age. Management of EP has shifted from emergency life-saving intervention to more conservative treatment modalities aimed at reducing mortality & morbidity, preserving fertility, & reducing costs. Laparoscopic surgery is still the cornerstone of treatment in the majority of women with tubal pregnancies.

If the diagnosis of ectopic pregnancy can be made earlier non-invasively, 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 risks & benefits of the available treatment options if the following criteria are satisfied as follows:

- haemodynamically stable women
- unruptured tubal pregnancy
- no signs of active bleeding
- low initial serum hCG concentrations

The reasons for change towards methotrexate treatment are minimal intervention/non 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/woman' has become less common when good facilities for early diagnosis are available. Early ectopic pregnancies tend to be smaller & have lower baseline hCG levels, thus more time is available for conservative management options with comparable outcomes to that of surgical treatment. Comparisons have been made between the use of methotrexate & surgery.

A study in the Netherlands has shown that systemic methotrexate therapy could reduce costs if administered to patients with low initial serum hCG levels without confirmatory laparoscopy. In New Zealand it has been shown that single-dose methotrexate resulted in a 52% reduction in direct costs & a 40% reduction in indirect costs compared to laparoscopic surgery. Women with hCG levels > 1500 IU/L had higher indirect costs owing to an increased likelihood of surgical intervention & the need for prolonged follow-up.

**RECOMMENDATIONS**

1. As 1/3 of all ectopics avoided surgery & 25% achieved a subsequent normal intra-uterine pregnancy, consideration should be given to increased role of methotrexate management – if eligibility criteria is strictly followed with minimal side-effects
2. It is important to ensure completion of all documentation, including consent and protocol explanation
3. Consideration of an agreed standardised Ectopic Pregnancy Proforma is needed to ensure appropriate patient selection and adequate documentation
4. Re-audit is recommended

**CONCLUSIONS**

We conclude that the intramuscular methotrexate is safe and cost effective alternative to the surgical intervention in the unruptured ectopic pregnancies that were diagnosed at early gestation in early pregnancy units and adhere to the strict criteria with no side-effects and the advantage of avoiding invasive surgery. Subsequent tubal patency and reproductive functions were comparable to the surgery, so we recommend increasing its use in the treatment of unruptured ectopic pregnancies.

**References**

Author Information

Srisailesh Vitthala, M.D., M R C O G., D F F P
Specialist Registrar, Department of Obstetrics & Gynaecology, Furness General Hospital

M. K. Cheema
Specialist Registrar, Department of Obstetrics & Gynaecology, Furness General Hospital

Prabas Kumar Misra, FRCOG
Consultant, Department of Obstetrics & Gynaecology, Furness General Hospital