

Guideline for the Medical Management of Ectopic Pregnancy with Methotrexate

A clinical guideline recommended

For use in:	Gynaecology, Early Pregnancy Assessment Unit
By:	Doctors, Registered Nurses
For:	The medical management of ectopic pregnancy
Division responsible for document:	Women and Children
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Name of document author:	Anna Haestier
Job title of document author:	Consultant in Obstetrics and Gynaecology
Name of document author's Line Manager:	Richard Smith
Job title of document author's Line Manager:	Clinical Director – Obstetrics and Gynaecology
Supported by:	Gautam Raje
Assessed and approved by the:	Gynaecology Guidelines Committee (GGC) If approved by committee or Governance Lead Chair's Action; tick here <input type="checkbox"/>
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Compliance links: <i>(is there any NICE related to guidance)</i>	NICE clinical guideline 154. Diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage. December 2012.
If Yes – does the strategy/policy deviate from the recommendations of NICE? If so, why?	No

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Quick reference guideline/s

Careful patient selection is the key to successful and safe management of ectopic pregnancy with methotrexate treatment (see below). It should be offered as a first-line treatment to women with unruptured ectopic pregnancy with serum β HCG < 1500 IU/L and offered as an option for treatment of unruptured ectopic pregnancy with serum β HCG < 5000 IU/L.

Version and Document Control:

Version Number	Date of Update	Change Description	Author
4	20/04/2018	Reviewed and amended.	Anna Haestier
5	17/07/2020	Document reviewed and updated. Links to Cytotoxic Policy: Cytotoxic Waste added.	Anna Haestier

This is a Controlled Document

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Objective of Guideline

The aim is to ensure appropriate selection of patients for methotrexate treatment and to give guidance on how to effect the treatment and organise appropriate follow up.

Rationale for the recommendations

- Management of ectopic pregnancy can be conservative, medical or surgical. Women who meet the criteria below can be successfully treated medically using the single- dose methotrexate 50mg per m² (IM).
- Methotrexate is safe and effective in the medical treatment of unruptured ectopic pregnancy. Overall, success rates of single-dose methotrexate range from 65-95%. The success rate of methotrexate was found to be 90% in the largest study to date.
- There are a number of predictors of success:
 - 1) Initial serum β HCG (Human chorionic gonatrophin) level – success rates are higher with lower β HCG levels. Success rates of 81-98% have been reported if serum β HCG levels are less than 1000 iu/l compared to only 38% if β HCG levels are greater than 5000 iu/l.
 - 2) Ultrasound appearance of the ectopic pregnancy – success rates are higher when no gestational sac is visualised. Presence of yolk sac, fetal pole and / or fetal cardiac activity are significant predictors of failure.
 - 3) Pretreatment changes in serum β HCG levels – the smaller the increase in β HCG level prior to administration of methotrexate, the higher the chance of successful medical treatment. An increase of up to 11 – 20% over 48 hours prior to the administration of methotrexate has been associated with higher rates of success.

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4) Decrease in β HCG level from day 1 to day 4 after methotrexate – success rates of 88-100% have been reported if serum HCG level decreases from day 1 to day 4 post administration of methotrexate compared to only 42-62% if the serum HCG level increases.

- If the treatment is successful, the tube is conserved with good chance of patency (80%). Subsequent fertility appears to be as good as conservative therapy (>70%) and the risk of recurrent ectopic is the same (10%). In about 10%, surgery will be required as the ectopic ruptures during treatment or hCG levels do not drop as expected.
- The disadvantages of methotrexate therapy are the risk of adverse effects and the need for compliance in follow-up to ensure resolution of pregnancy. The most common side effects of methotrexate include excessive flatulence and bloating (due to intestinal gas formation), stomatitis and a transient mild elevation in liver enzymes.

Serious adverse effects include bone marrow suppression, pulmonary fibrosis, nonspecific pneumonitis, liver cirrhosis, renal failure and gastric ulceration. In this regimen toxicity is unlikely and most of these effects resolve spontaneously within 4 weeks of treatment.

Inclusion criteria

Clinical characteristics:

1. Certainty that there is no intrauterine pregnancy.
2. Woman clinically stable with no evidence of intraperitoneal bleeding.
3. Minimal pain.
4. β hCG < 1500IU but can be considered with values < 5000IU.
5. No fetal heart activity on scan.
6. Ectopic mass < 35 mm.

Patient characteristics:

1. Would prefer medical option.
2. Willing to attend EPAU follow-up.
3. Willing to avoid sexual intercourse during treatment.
4. Prepared NOT to get pregnant for 3 months following treatment.

Contraindications to medical management with methotrexate

1. Thrombocytopenia (platelet count < 100,000) or blood dyscrasia (WBC < 2000).
2. Hepatic or renal dysfunction.
3. Immunocompromise or concurrent corticosteroid therapy.
4. Sensitivity to methotrexate.
5. Breastfeeding.
6. Peptic ulcer disease.

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7. Active pulmonary disease.
8. Haemodynamic instability.

Patient management

1. Decision for methotrexate treatment needs to be at senior registrar level or above.

Before making this decision, it is essential that the diagnosis of ectopic pregnancy is correct. If the ectopic pregnancy is visualised on ultrasound as a heterogenous mass, then it is prudent to repeat the β hCG after 48 hours. If the β hCG is dropping, expectant management may be appropriate. Should the level be rising at a rate that is consistent with a viable intrauterine pregnancy then a repeat scan should be arranged to check the diagnosis prior to the administration of methotrexate. For this reason, methotrexate should not be given at the first visit unless it is clear there is an ectopic pregnancy and a viable intrauterine pregnancy has been excluded.

2. Counsel woman and obtain signed consent.
3. Ensure that the woman is given the 'Methotrexate treatment for ectopic pregnancy' leaflet (M38).
4. Pre-treatment bloods:
 - FBC, Group & save serum.
 - Serum β HCG, U&Es, LFTs.
 - If anaemic reconsider whether treatment is appropriate (i.e. should surgical management be reconsidered).
 - White cell count, platelets, U&Es and LFTs should be normal before treatment.
5. Prescribe Methotrexate 50 (fifty) milligrams per m^2 . Pharmacy will calculate the surface area if the woman's height and weight are given on the prescription chart and will calculate the exact dose based on surface area. Pharmacy will issue a syringe with exact dose during week days. However over the weekend (Saturday and Sunday) pharmacy will provide a pre-filled syringe (90 mg in 3.6 mL i.e. 25 mg/mL) and the doctor on call will have to give the closest possible dose. If the patient is stable treatment may be deferred until the next working day.
6. Methotrexate is given intramuscularly in buttock or lateral thigh. The empty syringe or needle should be placed in a separate Sharp Safe, labelled "Cytotoxic waste for special incineration". Please see Cytotoxic policy: Cytotoxic Waste ([Trust Docs: 7913](#)).
7. Do not offer anti-D prophylaxis to rhesus negative women who receive solely medical management.
8. Give instructions about the symptoms of ectopic rupture. Note: transient abdominal discomfort occurs in more than 50% of women 3-7 days after the initiation of treatment due to separation pain. It is mild and normally lasts 4-12 hours and is never associated with an acute abdomen or haemodynamic instability. Significant free fluid on ultrasound scan would suggest ectopic pregnancy rupture and requires emergency surgery.
9. Sexual intercourse should be avoided. Aspirin or other NSAIDs should not be taken. A discharge letter should be sent to the GP.

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10. Follow-up in EPAU:

- Serum β HCG on Day 4 following methotrexate.
- Serum β HCG, FBC and LFTs on Day 7.
- Ultrasound scan on day 7 **only** if suboptimal fall in β HCG (<15%) between day 4-7 or the patient is symptomatic with increasing pain.

Note: A rise in β HCG is expected on day 4 of the treatment but thereafter the β HCG should fall by >15% between day 4-7. If this drop does not occur, a repeat transvaginal ultrasound scan should be considered to exclude ectopic fetal cardiac activity and/or haemoperitoneum. Once this has taken place to exclude these indications for surgical management, a second dose of methotrexate may be considered (needed in 3-27% of patients). Consultant involvement in decision making is needed.

- If the β HCG fall between day 4-7 is >15%, then repeat β HCG weekly until <15 IU.

Note resolution is slow - median 5 weeks with maximum up to 8 weeks.

11. Review if symptomatic. Check FBC and ultrasound to detect free fluid.
12. Women must avoid pregnancy after methotrexate for 3 months. Effective contraception should be recommended (e.g. combined oral contraceptive pill). If women wish to discuss additional methods, refer to the iCASH Clinic.
13. Women should be made aware of the increased risk of ectopic pregnancy in future pregnancies (10%) and that an early scan at 6-7 weeks gestation is recommended to ensure that the pregnancy is intrauterine.

Clinical Audit Standards derived from guideline

Success rate of methotrexate treatment (gold standard 90%).

References / source documents

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6. NICE clinical guideline 154. Diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage. December 2012.
7. Cytotoxic policy: Cytotoxic Waste - [Trust Docs: 7913](#)