METHOTREXATE FOR ECTOPIC PREGNANCY OR PREGNANCY OF UNKNOWN LOCATION (PUL)

This LOP is developed to guide clinical practice at the Royal Hospital for Women. Individual patient circumstances may mean that practice diverges from this LOP.

1. AIM

- To outline the medical management of ectopic pregnancy or PUL

2. PATIENT

- Woman with confirmed ectopic pregnancy/PUL suitable for medical management with single dose methotrexate.

3. STAFF

- Medical, midwifery and nursing staff

4. EQUIPMENT

- Pre-filled syringe
- Cytotoxic disposal bin
- Cytotoxic spill kit

5. CLINICAL PRACTICE

- Ensure woman meets all selection criteria for methotrexate treatment:
  - lives or staying in proximity to Royal Hospital for Women (RHW)
  - compliant with regular follow up
  - unruptured ectopic < 40 mm in diameter at transvaginal sonography
  - haemodynamically stable
  - normal liver function tests
  - empty uterus
  - beta human chorionic gonadotrophin (βhCG) < 5,000 units/L
  - no pelvic pain or tenderness
  - agrees to avoid pregnancy for three months after treatment
  - is suitable for single dose treatment methotrexate.
- Ensure an accredited clinician coordinates the treatment. Accredited clinicians at RHW are:
  - Prof Jason Abbott
  - Dr Michael Costello
  - Dr Glen McNally
- Obtain written consent from woman.
- Give woman written information (Appendix 1 or 2)
- Arrange treatment via the gynaecology-oncology Clinical Nurse Consultant (CNC) who can be contacted via:
  - page #44068
  - telephone extension 26229
  - mobile 0417944297
- Admit woman for a day stay admission if medically indicated, but otherwise manage as an outpatient.
- Obtain baseline:
  - βhCG
  - full blood count (FBC)
  - urea, electrolytes, and creatinine (UECs)
  - liver function tests (LFTs)

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- Commence treatment if the above blood values are within normal range and βhCG is < 5,000 units/L
- Measure woman's weight and height and calculate Body Surface Area (BSA) using the formula below:

$$\sqrt{\left(\frac{\text{height (cm)} \times \text{weight (kg)}}{3600}\right)}$$

i.e. Commence the calculation inside the brackets and then calculate the square root to reach the BSA

e.g. A woman with height 165cm and weight 60kg = 165 x 60 = 9900 ÷ 3600 = 2.75
square root of 2.75 = 1.65, which gives a BSA of 1.65m^2
Note: BSA is capped at 2m^2

- Calculate the dose of methotrexate (50mg/m^2) and prescribe on the National Inpatient Medication Chart (NIMC) as a single intramuscular (IM) injection. As BSA is capped at 2m^2 the maximum dose is 100mg.
- Consult with the gynaecology-oncology CNC, then take NIMC to pharmacy. Pharmacy will clinically review order and dispense pre-filled syringes of methotrexate 100mg. If access is required after hours, the after-hours nurse manager (AHNM) will be required to contact the on-call pharmacist to be called in to clinically review the order and dispense. If administration is to occur in another area e.g. radiology department, all staff involved in the administration and handling must be compliant with safe handling of cytotoxic medication guidelines and know how to manage a cytotoxic spill.
- Administer methotrexate as an IM injection in the buttock or lateral thigh.
- Ensure chemotherapy administered by staff trained in the handling, administration, and disposal of cytotoxic drugs. Refer to:
  - Workcover NSW Cytotoxic Drugs and Related Waste Guide 2008
  - Cancer Institute NSW (eviQ)® Safe handling and waste management of hazardous drugs 2014
- Place the empty syringe or needle in a purple cytotoxic sharp container as stated in cytotoxic handling guidelines.
- Provide woman with the methotrexate information leaflet along with contact numbers should they be required.
- Organise follow up for woman at Early Pregnancy Assessment Service (EPAS) clinic on:
  - Day 4 after treatment for repeat quantitative βhCG
  - Day 7 after treatment for quantitative βhCG, FBC, UECs, LFTs
- Continue quantitative βhCG estimations weekly until the level falls to biological zero.
- Advise the woman to:
  - refrain from intercourse until ectopic pregnancy has resolved
  - commence oral contraceptives or barrier contraception at the conclusion of treatment and to continue contraception for three months.
  - report any abnormal symptoms to the accredited clinician
  - avoid taking herbal or vitamin supplements containing folate, including folinic acid
  - avoid sun exposure to limit risk of methotrexate dermatitis
- Refer woman for gynaecological follow up approximately four weeks after cessation of the course of treatment assuming βhCG levels continue to fall. Earlier consultation should be arranged if βhCG levels plateau or rise.

METHOTREXATE FOR ECTOPIC PREGNANCY OR PREGNANCY OF UNKNOWN LOCATION (PUL) cont'd

- Repeat βhCG on day 10 if βhCG does not fall by > 15% between days 4 and 7
- Consider retreatment with methotrexate or surgical management if βhCG fall is ≤ 20% of baseline. The multi-dose treatment will not be further considered in this protocol and liaison between clinical medical and nursing teams is required if multi-dose treatment is considered following the failure of single dose treatment.

Live, Interstitial and Caesarean Scar Ectopic Pregnancy

- Medical team will arrange administration of methotrexate:
  - in RHW imaging under ultrasound guidance, or
  - laparoscopically
- Administer methotrexate as a direct local injection into the ectopic pregnancy sac transvaginally. The dose calculation for caesarean scar ectopic pregnancy is the same as above 50mg/m^2, however, part dose is administered into the sac and any remaining dose will be administered intramuscularly.
- Ensure cytotoxic handling precautions are adhered to in all areas of the hospital using personal protective equipment (PPE), spill kits and enclosed containers whilst transporting cytotoxic agents. Staff administering cytotoxic medications should have received appropriate training regarding safe handling and waste management.

6. DOCUMENTATION

- Medical records – written and electronic
- Medication Chart

7. EDUCATIONAL NOTES

- Methotrexate is a folic acid antagonist (anti-metabolite) which prevents the growth of rapidly dividing cells including trophoblasts and fetal cells by interfering with DNA synthesis. The dose of methotrexate used to treat ectopic pregnancy is relatively low, safe, and well tolerated.
- **Side effects:**
  - Adverse reactions to methotrexate are usually mild and self-limited
  - Approximately 30 % of patients in the single dose protocol will have side effects.
  - The most common are stomatitis and conjunctivitis.
  - Rare side effects include:
    - gastritis
    - enteritis
    - dermatitis
    - pneumonitis
    - alopecia
    - elevated liver enzymes
    - bone marrow suppression.
  - These side effects resolve as methotrexate exposure wanes.
- IM methotrexate administration is the predominant and preferred route for treatment of tubal pregnancy although it can also be given by direct local injection into the ectopic pregnancy sac transvaginally ultrasound guided or laparoscopically. This must be administered by appropriately trained medical staff and is not covered in this LOP.
- Since the rate of caesarean delivery has become more prominent, implantation of the gestational sac in the hysterotomy scar (caesarean scar) is also increased, resulting in interstitial and caesarean scar ectopic pregnancy. RHW manages these cases in RHW ultrasound under ultrasound guidance, or laparoscopically.

METHOTREXATE FOR ECTOPIC PREGNANCY OR PREGNANCY OF UNKNOWN LOCATION (PUL) cont'd

- Live ectopic pregnancies are optimally managed with both local and systemic methotrexate and these cases should be discussed with the gynaecologist on call. Single dose systemic methotrexate for live ectopic pregnancy has an increased failure rate of approximately 30% and is not recommended.

8. RELATED POLICIES / PROCEDURES / CLINICAL PRACTICE LOP

- Methotrexate - oral dosing and administration

9. RISK RATING

- High

10. NATIONAL STANDARD

- Medication safety

11. REFERENCES

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2. Cancer Institute NSW (eviQ)® Safe handling and waste management of hazardous drugs. 2014.
3. Bhattacharya S, McLernon DJ, Lee AJ, Bhattacharya S. Reproductive outcomes following ectopic pregnancy: register-based retrospective cohort study. PLoS Medicine. 2012;9(6): e1001243-e.
4. Royal College of Obstetricians and Gynaecologists. Ectopic pregnancy and miscarriage: Diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage. NICE Clinical Guidelines. 2012:1-287.
5. Stika C. Methotrexate: The Pharmacology Behind Medical Treatment for Ectopic Pregnancy. Clinical Obstetrics & Gynecology. 2012;55(2):433-9.
6. Timor-Tritsch E, Monteagudo A, Santos R, et al. American Journal of Obstetrics and Gynaecology 2012; 207:44. e1-13

REVISION & APPROVAL HISTORY
Reviewed and endorsed Maternity Services LOPs Nov/Dec 2020
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Reviewed and endorsed Therapeutic & Drug Utilisation Committee 13/12/16
Approved Quality & Patient Care Committee 7/7/16
Reviewed and endorsed Therapeutic & Drug Utilisation Committee 21/6/16
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Approved Quality & Patient Safety Committee December 2012
Reviewed and endorsed Therapeutic & Drug Utilisation Committee December 2012
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Approved RHW Council 27/11/00

FOR REVIEW: FEBRUARY 2022

…. /Appendices

Appendix 1

MANAGEMENT OF ECTOPIC PREGNANCY WITH METHOTREXATE

Royal Hospital for Women **DEC 2020**

ECTOPIC PREGNANCY occurs when the fertilised egg implants outside the uterus (womb), usually in the fallopian tube. In some cases, it can lead to rupture of the fallopian tube causing pain and bleeding and is occasionally life threatening. Treatment may involve surgery, or the use of a drug called methotrexate as an option for management.

METHOTREXATE is a cytotoxic (chemotherapy) drug that works by stopping the growth of rapidly dividing cells, that may be found in developing placental and embryonic tissue. As with all drugs, there are some potential side effects but, in most cases, they are minor.

Methotrexate can only be used in certain cases and your doctor will explain this to you. There is no clear scientific research to suggest that the use of methotrexate offers an improved outcome to your fertility compared to surgery, however, there is a good chance that you will avoid surgery. There are other considerations and/or disadvantages to taking methotrexate as well:

- it can take weeks to complete the treatment
- you will require regular monitoring of blood hormone levels
- you will be required to have several follow up visits and blood tests
- the drug itself is not without side effects
- you may require a second injection or may require surgery if the treatment is not successful
- you are also advised to wait at least 3 months before trying to become pregnant again.

TREATMENT WITH METHOTREXATE

Once your doctor has discussed this option with you, you will need to sign a consent form for the treatment. The dose of methotrexate will be individually calculated using your height and weight. You also are required to have a blood test prior to treatment. This will check your kidney, liver, and blood systems. There may be a delay of a few hours prior to your receiving the treatment.

Methotrexate is administered as a single injection into the buttocks. This will be given by a trained member of staff in the oncology unit. Providing there are no problems, you should be able to go home shortly after receiving the injection.

For 7 days after your treatment, you should flush the toilet twice after using it, with the toilet lid shut, as a portion of the drug is excreted in urine

FOLLOW UP

You will be monitored in the Early Pregnancy Assessment Clinic (EPAS) with blood tests and review on days 4 and 7 post treatment. The blood tests are to monitor your pregnancy hormone levels (this is called a βhCG test), kidneys, liver, and blood system. If all is going well, monitoring of the βhCG will continue weekly until it reaches zero.

SIDE EFFECTS OF TREATMENT

- Abdominal cramping usually occurs within 2-3 days of having your treatment. This should be relieved with paracetamol. As this is also a sign of a ruptured ectopic, you will need to report this to the hospital if the pain worsens or does not settle with paracetamol, or you feel faint or dizzy. You may want to avoid foods that cause bloating or wind such as beans, cabbage, and broccoli as they may make the pain worse
- Vaginal bleeding or spotting (again if this is excessive you need to report this)
- Nausea, vomiting or indigestion
- Skin sensitivity to sunlight. You will need to wear sunscreen, preferably factor 30, when out in the sun

RARE SIDE EFFECTS

- Mouth and throat ulcers. If you develop a sore mouth, use a non-alcohol-based mouthwash for relief. Sodium bicarbonate 1 teaspoon dissolved in a glass of water is an ideal mouth rinse.
- Bone marrow suppression (lowering of your blood count) can make you more susceptible to infections and feel tired
- Hair thinning
- Inflammation of the lung can cause pain when you breathe in and out

If you experience any of these symptoms you should contact the hospital on 93826111

THINGS TO AVOID

- Folinic acid - this is found in many multivitamins especially those designed for pregnancy
- Avoid hot baths, hot showers, and saunas whilst you are bleeding heavily as you may feel faint
- Use pads rather than tampons to reduce the risk of infection
- Use paracetamol rather than non-steroidal anti-inflammatory drugs (ibuprofen containing medication such as Nurofen®, Brufen®) as they can affect the level of methotrexate in your body.
- Smoking
- Alcohol
- Sexual intercourse (until you have had your follow up visit)
- If breastfeeding, it is advised that you express and discard for four days following injection (Further information available via the Infant Risk Centre website www.infantrisk.com)

CONTACT NUMBERS

EARLY PREGNANCY ASSESSMENT SERVICE **93826701**
Monday - Friday 7.30am till 11.30am
Nikki Collins **9382 6111** (page 46520)

JENNIE DUGGAN ONCOLOGY CNC
Monday - Friday 8.30am till 5.00pm **9382 6229 / 0417 944 297**
Office hours **9382 6111** (page 44068)

ROYAL HOSPITAL FOR WOMEN SWITCHBOARD **9382 6111**
(Ask to speak to the Registrar on call)

Date/Time	Appointment	hCG Level

Appendix 2

PREGNANCY OF UNKNOWN LOCATION (PUL)

Royal Hospital for Women **DEC 2020**

We are sorry you are experiencing a Pregnancy of Unknown Location or PUL. We hope the following information may be of help to you.

A PUL is defined as a pregnancy not seen on transvaginal ultrasound scan even though the pregnancy test is positive. There are several reasons for PUL:

- Your pregnancy is too early to be seen on ultrasound
- You may have already miscarried, and the womb is empty
- You may have an ectopic pregnancy which is too small to see on ultrasound, or cannot be seen due to poor views or fibroids

We will perform further blood tests, pregnancy hormone (hCG) and sometimes progesterone to try to reach diagnosis.

- If your pregnancy hormone is rising appropriately, a repeat ultrasound will be performed to diagnose ongoing pregnancy
- If your pregnancy hormone is falling, this is likely a miscarriage and you will need repeat hormone tests until negative
- If your pregnancy hormone levels decrease slowly, plateau, or increase slowly you may need treatment with methotrexate

METHOTREXATE is a cytotoxic (chemotherapy) drug that works by stopping the growth of rapidly dividing cells that may be found in developing placental and embryonic tissue. As with all drugs, there can be some side effects but in most cases they are minor. This drug can only be used in certain cases and your doctor will explain this to you. There is no clear scientific research to suggest that the use of this drug offers an improved outcome to your fertility compared to surgery, however, there is a good chance that you will avoid surgery. There are other considerations and/or disadvantages to taking methotrexate as well:

- it can take weeks to complete the treatment
- you will require regular monitoring of blood hormone levels
- you will be required to have several follow up visits and blood tests
- the drug itself is not without side effects
- you may require a second injection or may require surgery if the treatment is not successful
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  Skin sensitive to sunlight (you will need to wear sunscreen factor 30 or higher when out in the sun)

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- Use paracetamol rather than non-steroidal anti-inflammatory drugs (such as nurofen, brufen) as they can affect the level of methotrexate in your body
- Smoking
- Alcohol
- Sex (until you have had your follow up visit)
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