The following is a suggested guideline, and does not replace ongoing clinical assessment and professional judgment.

PURPOSE AND INTENT

To guide the effective and safe use of Methotrexate as a pharmaceutical agent for the medical management of an ectopic pregnancy and pregnancy of unknown location.

For the purpose of this document, ectopic pregnancy and pregnancy of unknown location will be referred to as ectopic pregnancy.

1. BACKGROUND

Ectopic pregnancy is a significant cause of morbidity and mortality in the first trimester of pregnancy. Currently, a high index of suspicion, serial hormone assays, and transvaginal ultrasonography facilitate the diagnosis and treatment of ectopic pregnancy before rupture occurs. Early nonsurgical diagnosis and timely treatment have resulted in a dramatic decline in mortality due to ectopic pregnancy. (15). Evidence indicates Methotrexate is an effective and safe pharmaceutical agent for the medical management of an ectopic pregnancy. Methotrexate is a folic acid antagonist preventing DNA replication. It inhibits the rapidly dividing trophoblast cells of an ectopic pregnancy. (2)

2. DEFINITIONS

Definite Ectopic Pregnancy: extrauterine gestational sac with yolk sac and/or embryo (with or without cardiac activity)

Probable Ectopic Pregnancy: inhomogeneous adnexal mass or extrauterine saclike structure

Pregnancy of Unknown Location: no signs of either ectopic pregnancy or intrauterine pregnancy

Persistent Pregnancy of Unknown Location: the serum hCG levels fail to decline, there is no evidence of trophoblastic disease and the location of pregnancy cannot be identified using transvaginal ultrasound or laparoscopy

Probable intrauterine pregnancy: intrauterine echogenic sac-like structure

Definite intrauterine pregnancy: intrauterine gestational sac with yolk sac and/or embryo (with or without cardiac activity)


3. GUIDELINES

3.1 Indications:

3.1.1 A good candidate for methotrexate has the following characteristics:

- hemodynamic stability
- no active bleeding
- low serum β-hCG, ideally less than 1500 international Units/Litre but can be up to 5000 international Units/Litre
- no fetal cardiac activity seen on ultrasound scan
- certainty that there is no intrauterine pregnancy
- willingness to attend for follow-up
- no known sensitivity to methotrexate
- no significant pain
- normal liver and renal function test
CLINICAL PRACTICE GUIDELINE

Practice Guideline:
Medical and Expectant Management of Ectopic Pregnancy and Pregnancy of Unknown Location

Approval Date:
March 2019

Pages:
2 of 12

Supercedes:
N/A

- an unruptured ectopic pregnancy with a mass smaller than 35 mm with no visible heartbeat
- Non-tubal ectopic: cervical, cornual, ovarian, and abdominal
- Persistent ectopic pregnancy following salpingostomy
- Failed expectant management of ectopic pregnancy or pregnancy of unknown location
- Pregnancy of unknown location on ultrasound where patient requests termination

3.2 Contraindications to Methotrexate Therapy

<table>
<thead>
<tr>
<th>Absolute contraindications</th>
<th>Relative contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>o Intrauterine pregnancy in a wanted pregnancy</td>
<td>o Embryonic cardiac activity detected by transvaginal ultrasonography</td>
</tr>
<tr>
<td>o History of Immunodeficiency Syndrome or Disorders</td>
<td>o High initial β-hCG concentration (&gt;5,000 IU/mL)</td>
</tr>
<tr>
<td>o Moderate to severe anemia, leukopenia, or thrombocytopenia</td>
<td>o Ectopic pregnancy greater than 40 mm in size as imaged by transvaginal ultrasonography</td>
</tr>
<tr>
<td>o Sensitivity to Methotrexate</td>
<td>o Refusal to accept blood transfusion</td>
</tr>
<tr>
<td>o Active pulmonary disease</td>
<td>o Inability to participate in follow-up</td>
</tr>
<tr>
<td>o Active peptic ulcer disease</td>
<td></td>
</tr>
<tr>
<td>o Clinically important hepatic dysfunction</td>
<td></td>
</tr>
<tr>
<td>o Clinically important renal dysfunction</td>
<td></td>
</tr>
<tr>
<td>o Breastfeeding</td>
<td></td>
</tr>
<tr>
<td>o Ruptured ectopic pregnancy</td>
<td></td>
</tr>
<tr>
<td>o Hemodynamically unstable patient</td>
<td></td>
</tr>
</tbody>
</table>


3.3 Treatment and drug side effects associated with Methotrexate

3.3.1 Treatment side effects:
- Increase in abdominal girth
- Increase in β-hCG during initial therapy
- Vaginal bleeding or spotting
- Abdominal pain

3.3.2 Drug side effects
- Gastric distress, nausea, and vomiting
- Stomatitis
- Dizziness
- Severe neutropenia (rare)
- Reversible alopecia (rare)
- Pneumonitis (rare)


Rupture is possible even several weeks after Methotrexate treatment.
Expect some abdominal pain for two to four days after Methotrexate treatment.
If severe pain is experienced:
- clinically reassess
- complete serial hemoglobins
- repeat ultrasound
- consider surgery
3.4 Pre-Treatment Lab Results
3.4.1 CBC
3.4.2 Liver enzymes (AST, ALT, GGT, LDH, Alkaline phosphate), and creatinine
3.4.3 Quantitative β-hCG (day 1)
3.4.4 RH status
   • Unknown – determine
   • RH negative – treat Rho (D) Immune Globulin (WinRho SDF™)
   Best Blood Manitoba GUIDELINES FOR PERINATAL TESTING and ADMINISTRATION OF WINRHO® SDF (Rh IMMUNE GLOBULIN)

3.5 Methotrexate administration
3.5.1 Methotrexate is a cytotoxic medication. Follow WRHA policy 110.160.010 Safe Handling of Hazardous Medication (Cytotoxic and Non-Cytotoxic) during preparation, administration, and disposal of this medication.
3.5.2 50 mg/m² IV or IM. Administration of this drug is height and weight dependent. Please refer to dose banding table. Dosing is rounded to the nearest 5 mg. Dose banding calculation is incorporated into EPR (SBH) and on reverse of order sheet (HSC) (See Appendix A).
3.5.3 Discontinue any medications containing folic acid (folate) including prenatal vitamins.
3.5.4 Refer to site specific Methotrexate Drug Monograph in the Parenteral Drug Manual for information regarding this medication.
3.5.5 Methotrexate is only available from either the Health Sciences Centre or St Boniface Hospital Pharmacies; all other WRHA sites will need to transfer patients to HSC or SBH.

3.6 Treatment Protocol - Ectopic Pregnancy
SINGLE DOSE PROTOCOL
Day 1  β-hCG, Methotrexate as above
Day 4  Repeat β-hCG
Day 7  Repeat β-hCG. Reassess treatment plan. If there is a 15% decline, continue weekly surveillance. Consider repeating Methotrexate if less than a 15% decline from day 4 to day 7. If repeat Methotrexate treatment is implemented, repeat bloodwork and follow the chart on form ‘DISCHARGE INFORMATION: After Methotrexate Treatment for Ectopic Pregnancy’. (NS00832-HSC, 7102-4300-4-SBH)
   Note: There is no benefit in giving a third dose.
Day 14  Repeat β-hCG, CBC
Weekly quantitative β-hCG until less than 10 International Units/Litre

TWO-DOSE PROTOCOL
CONSIDER USE IF INITIAL BHCG >3600
Day 1  β-hCG, Methotrexate as above
Day 4  2ND DOSE OF Methotrexate, β-hCG
Day 7  repeat β-hCG, follow protocol as above for SINGLE DOSE
Day 14  repeat β-hCG, CBC

NOTE: Resolution time is 14 to 90 days.
Rupture is possible even several weeks after Methotrexate treatment
Expect some abdominal pain for two to four days after Methotrexate treatment
If severe pain is experienced, then clinically reassess and do:
   • Serial hemoglobins
   • Repeat ultrasound and consider surgery
Success of single dose Methotrexate for ectopic pregnancy according to β-hCG concentration

<table>
<thead>
<tr>
<th>β-hCG concentration (IU/L)</th>
<th>Number of women successfully treated (percent)</th>
<th>Number of women failing treatment (percent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000</td>
<td>133 (99)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>1000 to 1999</td>
<td>51 (94)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>2000 to 4999</td>
<td>106 (96)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>5000 to 9999</td>
<td>42 (86)</td>
<td>7 (14)</td>
</tr>
<tr>
<td>10,000 to 150,000</td>
<td>18 (82)</td>
<td>4 (18)</td>
</tr>
</tbody>
</table>


3.7 Patient education and follow-up information

Utilize the WRHA, Women’s Health Program DISCHARGE INFORMATION: After Methotrexate Treatment for Ectopic Pregnancy HSC NS00832, SBH 7102-4300-4
Pregnancy of Unknown Location

Asymptomatic

- Positive Urine Pregnancy Test
  - TVU – No IUP/EP/RPOC
  - PUL
  - Clinical Assessment plus βhCG

Symptomatic

- Surgical Management
  - Laparoscopy/Laparotomy

Expectant Management

- ΒhCG levels at 0 and 48 hours
  - Falling greater than 15% drop
    - Query spontaneously resolving PUL
      - Repeat βhCG in 1 week to confirms falling PUL
      - Consider weekly βhCG monitoring until less than 10 IU/L
      - Further TVU not necessary
    - Ectopic pregnancy visualized
      - Management as clinically indicated
  - Rising (Doubling) greater than 53% rise
    - Query ectopic pregnancy
      - Serial βhCG
        - Until greater than 1000 IU/L OR
        - 3 measurements showing suboptimal increase or decrease/Plateauing/Fluctuating pattern
        - Decreasing repeat TVU
    - Query intrauterine pregnancy
      - Serial βhCG – until greater than 1000 IU/L
      - Repeat TVS
  - Suboptimal Increase or decrease
    - Query spontaneously resolving PUL

Negative TVU

- Suspect persistent PUL
  - then consider
    - Medical management

Early intrauterine pregnancy visualized

- No further βhCG Assays
  - Repeat TVU at 1-2 weeks for viability

PUL – pregnancy of unknown location
IUP – intrauterine pregnancy
EP – Ectopic pregnancy
RPOC – retained products of conception
TVU – transvaginal ultrasound
IU/L – international units per litre

* consider rescanning at 24-48 hours if PUL and initial βhCG is greater than 1000 international units/litre

Nomenclature for pregnancy of unknown location Fertil Steril Vol. 95, No. 3, March 1, 2011
4. REFERENCES:


6. PRIMARY AUTHOR (S)

Dr. H. Pymar, Dr. d. Robinson, Dr. C. Schneider, L. Sabeski
### PREPRINTED ORDERS

**Women’s Health Program Methotrexate for Treatment of Ectopic Pregnancy**

<table>
<thead>
<tr>
<th>DATE</th>
<th>TIME</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Height** ________ cm  **Weight** ________ kg

- Methotrexate _____ mg IM x 1 dose (dose 50 mg/m² rounded to the nearest 5 mg as defined in the table on the reverse page)

If the patient height and weight cannot be found in the table on the reverse page, physician may manually calculate the Body Surface Area (BSA)

BSA = ________

---

**Physician’s Signature**:  
**Printed Name**:  
**Transcribed**:  
**Reviewer**:  
**Faxed Date**:  
**Time**:  
**Initials**:
<table>
<thead>
<tr>
<th>Height (cm)</th>
<th>Min</th>
<th>Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>126</td>
<td>38-44</td>
<td>45-51</td>
</tr>
<tr>
<td>128</td>
<td>37-43</td>
<td>44-50</td>
</tr>
<tr>
<td>130</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>132</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>134</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>136</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>138</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>140</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>142</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>144</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>146</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>148</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>150</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>152</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>154</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>156</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>158</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>160</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>162</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>164</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>166</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>168</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>170</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>172</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>174</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>176</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>178</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>180</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>182</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>184</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>186</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>188</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>190</td>
<td>37-42</td>
<td>43-50</td>
</tr>
<tr>
<td>192</td>
<td>37-42</td>
<td>43-50</td>
</tr>
</tbody>
</table>

Methotrexate DOSE of 50 mg/m² rounded to nearest 5 mg

Find patient’s height in rows at left, then read across and find weight (kg) in correct column below. Dose is read above.
# Practice Guideline:

## Medical and Expectant Management of Ectopic Pregnancy and Pregnancy of Unknown Location

<table>
<thead>
<tr>
<th>Approval Date:</th>
<th>Pages:</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2019</td>
<td>9 of 12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Supercedes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/A</td>
</tr>
</tbody>
</table>

## Appendix B

### Women’s Health Program

Date: ________________  Number of pages faxed: ______

Fax to: Dr______________  Fax Number: ________________

Fax from:

- Women’s Health Ambulatory Care  
  Health Sciences Centre  
  WR035 – 735 Notre Dame Avenue  
  FAX number: 204-787-2876

- Antepartum Gynecology Inpatient Unit  
  Health Sciences Centre  
  WR55 – 735 Notre Dame Avenue  
  FAX number: 204-787-2875

- Antepartum Gynecology Inpatient Unit  
  6AW – St Boniface Hospital  
  FAX number: 204-237-2294

Dear Dr ______________________________:

You have received this fax because you have been identified as the responsible physician ordering methotrexate for the patient identified on the attached form. Please arrange for follow-up including scheduling and reviewing β-hCG tests, on your patient.

Please see the attached form: Women’s Health Program DISCHARGE INFORMATION: After Methotrexate Treatment for Ectopic Pregnancy.
# Women's Health Program

## DISCHARGE INFORMATION: After Methotrexate Treatment for Ectopic Pregnancy

You are being treated for an ectopic pregnancy. This means that the fertilized egg is growing outside of your uterus (womb). The treatment you have received is a drug called Methotrexate. This drug stops the growth of the placenta (afterbirth) and ends the pregnancy. Your body will then absorb the pregnancy in about 2 to 12 weeks. Methotrexate is a cytotoxic medication which can be harmful to others if exposed. Methotrexate can remain in your body for several hours after you receive it. Small amounts of this medication may be present in your urine, stool, and vomit.

To protect your family, please do the following for 48 hours after you receive Methotrexate:
- Close the toilet lid before flushing the toilet, flush the toilet twice
- Wash your hands or any exposed surfaces with soap and water
- If urine, stool, or vomit gets on your skin, wash the area with soap and water.

A **blood test** called Quantitative B-hCG is done for several weeks after receiving Methotrexate. The level of this blood test should slowly drop. This tells your Doctor that the drug is working. If the B-hCG level does not drop you may need further treatment.

**You must contact the office of Dr.** as soon as you get home, to arrange for these blood tests.

The chart below can be used to keep a record of when and where you have these important tests done:

<table>
<thead>
<tr>
<th>Day</th>
<th>Date</th>
<th>Location</th>
<th>Quantitative B-hCG Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If possible, go to the same lab each time for your blood tests. Take this information sheet with you when you see your doctor and if you return to the hospital.

To help you recover at home, please follow these guidelines:

**Pain**
- You may have mild pain in your abdomen for 2 to 4 days.
- If you start to feel faint or have severe pain in your abdomen, go to the Emergency Department at Health Sciences Centre or St. Boniface Hospital.

**Bleeding**
- This may mean that your ectopic pregnancy has ruptured.
- You may have vaginal bleeding much like a heavy menstrual period.
- Use only sanitary pads. Change your pads often.
- Do not use tampons or douche.

**Hygiene**
- You may shower or sponge bath at any time. Do not tub bath, swim, or use a hot tub until your bleeding stops.

**Emotional Health**
- Losing a pregnancy may cause many emotions. Each woman will have her own way of dealing with this loss.
- Because an ectopic pregnancy occurs so early, you may have not even realized that you were pregnant. Many women feel confused and sad.
- Your partner may also feel similar emotions and need support as well. Members of our health care team will give you reading material about pregnancy loss. Please ask your nurse or doctor if you or your partner want further assistance to help deal with your feelings.

**Diet**
- Eat your normal diet. Please do not drink alcohol until your doctor says it is okay to do so.

**Activity**
- Do not have sex until your doctor says it is okay to do so.

**Drugs**
- Do not take pills with folate acid/folate, including prenatal vitamins. Also, do not take any pain pills with aspirin (ASA). Talk with your doctor or pharmacist about any other medications that you take.

**Contraception**
- Talk with your doctor about future pregnancies and about family planning.

If you have any questions or concerns, contact your doctor. If you are unable to contact your doctor or someone on-call for her/him: Call Health Links - Info Santé at 204-778-0200 or toll-free 1-888-315-9257.
Appendix D

Women's Health Program

DISCHARGE INFORMATION:
After Methotrexate Treatment for Ectopic Pregnancy
Programme de la santé des femmes
INFORMATION POUR LA MISE EN CONGÉ DE LA PATIENTE :
Après un traitement par méthotrexate pour une grossesse ectopique

You are being treated for an ectopic pregnancy. This means that the fertilized egg is growing outside of your uterus (womb). The treatment you have received is a drug called methylprednisolone. This drug stops the growth of the placenta (afterbirth) and ends the pregnancy. Your body will then absorb the pregnancy in about 2 to 12 weeks. You have been treated with methotrexate to end the pregnancy. In this type of pregnancy, the fetus develops outside the uterus. You have received a medication called methotrexate. This medication will cause the placenta to degenerate and be absorbed by your body. After 2 to 12 weeks, your body will absorb the pregnancy.

Methotrexate is a cytotoxic medication which can be harmful to others if exposed. Methotrexate can remain in your body for several hours after you receive it. Small amounts of this medication may be present in your urine, stool, and vomit.

To protect your family, please do the following for 48 hours after you receive Methotrexate:
- Close the toilet lid before flushing the toilet, flush the toilet twice.
  - Baisser le couvercle de la cuvette avant d’appuyer la chasse d’eau, actionner la chasse d’eau à deux reprises.
- Wash your hands or any exposed surfaces with soap and water.
  - Se laver les mains ou toute autre surface exposée, à l’eau et au savon.
- If urine, stool, or vomit gets on your skin, wash the area with soap and water.
  - Si de l’urine, des selles ou des vomissements se retrouvent sur la peau, laver la région touchée à l’eau et au savon.

A blood test called Quantitative B-hCG is done for several weeks after receiving Methotrexate. The level of this blood test should slowly drop. This tells your Doctor that the drug is working. If the B-hCG level does not drop you may need further treatment.

Une analyse de sang appelée dosage quantitatitif de B-hCG sera faite pendant plusieurs semaines après la prise du méthotrexate. Le taux mesuré par cette analyse sanguine devrait diminuer graduellement. Cette diminution indique à votre médecin que le médicament fonctionne. Si le taux de B-hCG ne diminue pas, vous pourriez avoir besoin d’un autre traitement.

You must contact the office of Dr. [Name] as soon as you get home, to arrange for these blood tests.

Vous devez communiquer avec le bureau de Dr. [Name] dès que vous revenez à la maison, pour organiser ces analyses sanguines.

The chart below can be used to keep a record of when and where you have these important tests done:

Vous pouvez utiliser le tableau ci-dessous pour faire le suivi de ces tests importants:

<table>
<thead>
<tr>
<th>Day</th>
<th>Date</th>
<th>Location</th>
<th>Quantitative B-hCG Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If possible, go to the same lab each time for your blood tests. Take this information sheet with you when you see your doctor and if you return to the hospital.

Si possible, allez au même laboratoire pour chacune des analyses sanguines. Apportez cette feuille d’information lorsque vous verrez votre médecin et si vous retournez à l’hôpital.
Medical and Expectant Management of Ectopic Pregnancy and Pregnancy of Unknown Location

Approval Date: March 2019

Supercedes: N/A