SCHOOL OF MEDICINE
DEPARTMENT OF OBSTETRICS & GYNECOLOGY

STANDARD OPERATING PROCEDURE- POLICY

METHOTREXATE FOR ECTOPIC PREGNANCY

POLICY STATEMENT

This protocol is for medical management of ectopic pregnancy with methotrexate. Methotrexate (MTX) is a dihydrofolate reductase inhibitor that acts to inhibit DNA replication.

PROCEDURE:

- Obtain Complex Family Planning consultation for all suspected non-tubal ectopic pregnancies through RH PALS 24-7.

- All patients who receive MTX must first be seen and evaluated by an OB-GYN attending physician. It is expected that if a patient is sent to OB Triage for MTX, there will be a discussion between the referring attending and covering L&D attending about the final patient plan. For questions, please contact Complex Family Planning through RH PALS 24-7.

DIAGNOSIS:

The following should be considered when making the diagnosis of ectopic pregnancy and considering methotrexate (MTX) management:

- A formal diagnostic imaging (DI) or Women's Imaging (WI) ultrasound is required prior to administering MTX.
- A **manual or electric vacuum aspiration should be <u>strongly</u> considered to confirm diagnosis of ectopic pregnancy prior to treatment with MTX**, particularly in cases where diagnosis is not clear (i.e., no clear ectopic pregnancy visualized on diagnostic ultrasound, hCG below discriminatory zone but plateauing or falling more slowly than expected, or early gestational sac in the uterus with abnormal hCGs etc.). *Patients may be referred to CRH for next-day add-on for a diagnostic uterine aspiration, or MVA may be performed in OBT under special circumstances after discussion with RH PALS Complex Family Planning attending about feasibility of add-on at CRH.*

CANDIDATE CONSIDERATIONS

1. Prior to administration of MTX:
    a. Verify no absolute contraindications to MTX management (see below).
    b. Provide the patient with a **full explanation of both medical and surgical management as well as expectant management in select cases of ectopic pregnancy with risks and benefits of each approach**.
    c. Include the following in patient counseling:
        i. the risk of ectopic pregnancy rupture, the need to avoid folic acid and nonsteroidal anti-inflammatory medications which may decrease MTX efficacy and clearance of MTX, respectively

ii. the risks if the patient becomes pregnant again prior to 3 months after MTX.
iii. the potential for fetal death or teratogenic effects if MTX is administered in the setting of a normal or ongoing pregnancy.

d. Enter all patients treated with MTX into the "beta book:" they must be signed out via EMR messaging to the resident and attending managing the "beta book" along with multiple phone numbers for contacting the patient.

2. Absolute contraindications to MTX:
   a. Intrauterine pregnancy
   b. Suspicion for ruptured ectopic pregnancy
   c. Hemodynamic instability
   d. Breastfeeding
   e. Clinically important hepatic or renal dysfunction
   f. Evidence of immunodeficiency
   g. Moderate to severe anemia, leukopenia, or thrombocytopenia
   h. Hemodynamic instability
   i. Patient not able to follow up for lab testing and subsequent care
   j. Active pulmonary disease; asthma is not a contraindication
   k. Active peptic ulcer disease
   l. Sensitivity to methotrexate

3. Relative contraindications to MTX:
   a. Ectopic pregnancy >4 cm in greatest dimension as imaged by transvaginal ultrasound.
   b. Embryonic cardiac motion
   c. Refusal to accept blood transfusion

4. High risk patients are those for whom medical management has a higher likelihood of failure:
   a. Initial hCG >5,000 mIU/ml
   b. Ectopic pregnancy with gestational cardiac activity
   c. Interstitial pregnancy

METHOD:
Resident physicians will consult with the responsible OB-GYN (L&D) attending physician to approve the plan to administer methotrexate. Most patients come through OB Triage: the L&D attending is the responsible physician in those cases, but consultation with the Reproductive Health PALS Complex Family Planning attending/fellows is always available.

1. **Baseline lab workup:** Hgb/Hct, T&S, AST/Cr. Administer Rh(D) immune globulin if indicated.

2. **Single dose regimen:**

- Methotrexate 50 mg/m^2 IM on Day 1
- Patients should be counseled that approximately 20% of patients require a second dose for inadequate decline in hCG.

- **Administration and follow up**:
- Day 1: MTX 50mg/m^2 IM
- Day 4 & Day 7: serum quantitative hCG
    i. If ≥15% decline between Day 4 and Day 7, then follow hCG weekly until below 50 or 10 as per below.
    ii. If <15% decline between Day 4 and 7, offer repeat MTX or surgery. Consult with the Complex Family Planning service.
    iii. If 2nd dose of MTX given, repeat hCG levels on Day 4 and Day 7 from 2nd dose of MTX, again assessing for 15% drop. If no appropriate drop, consider uterine aspiration if not previously performed and offer repeat MTX or surgery. Consult with the Complex Family Planning service.
    iv. If weekly hCG levels plateau, offer repeat MTX or surgery. Consult with the Complex Family Planning service.
- Follow hCG weekly until*:
    i. <50 mIU/ml if initial level was >500 mIU/ml (arbitrary cut-off)
    ii. <10 mIU/ml if initial level was <500 mIU/ml
    iii. *Although traditionally ectopic pregnancies treated medically with MTX are followed to undetectable hCG levels, the above protocol reflects a safe practice in the context of patient-centered care.
- Provide patient education "Methotrexate for Ectopic Pregnancy"

3. **Two dose regimen:** Should be **considered** in "High risk patients" (see above)
    - Methotrexate 50mg/m^2 IM on Day 1
    - Repeat 50mg/m^2 IM on Day 4

    - **Administration and follow up**:
    - Day 1: MTX 50mg/m^2 IM
    - Day 4: MTX 50mg/m^2 IM and serum quantitative hCG
    - Day 7: serum quantitative hCG
        i. If ≥15% decline between Day 4 and Day 7, then follow hCG weekly until below 50 or 10 as per below.
        ii. If <15% decline between Day 4 and 7, offer repeat MTX or surgery. Consult with the Complex Family Planning service.
        iii. If 3rd dose of MTX given on Day 7, repeat hCG levels on Day 7 and Day 11, again assessing for 15% drop. If <15% drop between Day 7 and 11, consider uterine aspiration if not previously performed and offer repeat MTX or surgery. Consult with the Complex Family Planning service.

iv. If 4th dose of MTX given on Day 11, repeat hCG levels on Day 11 and Day 14, again assessing for 15% drop. If <15% drop between Day 11 and 14, consider surgery. Consult with the Complex Family Planning service.
v. If weekly hCG levels plateau, offer repeat MTX or surgery. Consult with the Complex Family Planning service.

- Follow hCG weekly until*:
  i. <50 mIU/ml if initial level was >500 mIU/ml (arbitrary cut-off)
  ii. <10 mIU/ml if initial level was <500 mIU/ml

*Although traditionally ectopic pregnancies treated medically with MTX are followed to undetectable hCG levels, the above protocol reflects a safe practice in the context of patient-centered care.

- Provide patient education "Methotrexate for Ectopic Pregnancy"

4. **Multi-dose regimen:** May be **considered** in "High risk patients" (see above)
   - Up to 4 cycles of MTX 1mg/kg IM alternating every 24 hours with leucovorin 0.1 mg/kg

   - **Multi-dose regimen administration and follow up**:
   - Day 1, 3, 5, 7 administer MTX (1mg/kg IM) **and** check serum quantitative hCG
   - Day 2, 4, 6, 8 administer leucovorin (0.1mg/kg IM, round up to nearest 5mg dose)
     i. If hCG declines >15% from previous value, subsequent MTX administration halted and surveillance begins
     ii. If hCG does not decrease after four doses, consider surgical management.
   - Follow hCG weekly until*:
     i. <50 mIU/ml if initial level was >500 mIU/ml (arbitrary cut-off)
     ii. <10 mIU/ml if initial level was <500 mIU/ml
     iii. *Although traditionally ectopic pregnancies treated medically with MTX are followed to undetectable hCG levels, the above protocol is proposed with the goal of providing more patient-centered care.
   - Provide patient education "Methotrexate for Ectopic Pregnancy"

5. Post-salpingostomy MTX:
   - Consider at attending's discretion to reduce likelihood of persistent trophoblast
   - Dose 1mg/kg IM
   - Follow up: serum hCG one week after surgery. If declining, follow weekly until <5.
   - Consider re-dosing MTX or surgery if no decline

6. Side effects:
   - Nausea, vomiting, diarrhea, hot flashes, gastrointestinal mucositis, interstitial pneumonitis, mild liver and renal dysfunction and bone marrow suppression.
   - Approximately 33% of women report an increase in abdominal pain during treatment.

i. In person evaluation is necessary if pain is unrelieved by acetaminophen.
ii. Most pain resolves without surgical intervention. Consider inpatient observation if pain is worrisome but patient is otherwise stable.
iii. **Free fluid in an otherwise stable patient on ultrasound for in person evaluation of abdominal pain after MTX is not necessarily an indication for surgery**. Monitor for signs of active bleeding.
iv. Similarly, **it is normal for the mass to increase in size** even if the MTX is treating the ectopic pregnancy, thus this also is not necessarily an indication for surgery.

7. Follow up:
   - Sign out all patients to the Family Planning resident and attending and enter into "Beta Book" patient list as above
   - All patient communication should be documented in PowerChart, under the OBGYN Beta Book note type.
   - Schedule patients for follow up at the Center for Reproductive Health. An adhoc referral should be placed in PowerChart. In person evaluation is NOT necessary once decline in hCG has been established. Follow up can then be performed virtually with patient presenting only for lab draws.
   - Contact any patients who miss appointments, or who have been lost to follow up to reschedule their appointments.
   - Send a certified letter to patients who remain lost to follow up after multiple contact attempts (copy into or document in PowerChart).
   - Provide contraception counseling to all patients who are not actively seeking subsequent pregnancy.

CONSULTATION

Twenty-four hour consultation is available by calling the Division of Complex Family Planning service at the University of New Mexico Hospital through Reproductive Health PALS.

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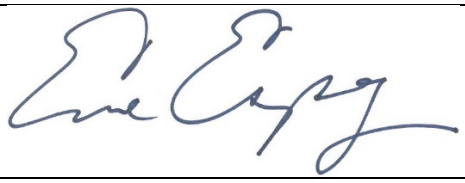
APPROVALS:

SOP Owner:	Division of Complex Family Planning	Date: 4/13/21
Chair Approval:		Date: 6/7/21
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