ECTOPIC PREGNANCY PROTOCOL

PURPOSE
To establish a system at UAB by which symptomatic early pregnancies are managed using the best available evidence in order to provide outstanding care.

BACKGROUND
- Symptomatic early pregnancies (pain, bleeding) ultimately fall in to 1 of 3 categories:
  1) Viable intrauterine pregnancy
  2) Non-viable intrauterine pregnancy
  3) Ectopic, or extrauterine, pregnancy
- Ectopic pregnancies account for ~2% of all pregnancies, and 6% of pregnancy-related deaths
- >90% of ectopic pregnancies implant in the fallopian tube; other sites include ovary, cervix.
- Risk factors for ectopic pregnancy include tubal disease (STDs, tubal surgery, prior ectopic pregnancy), infertility, use of assisted reproductive technology, pelvic surgery, and smoking.
- Early detection and treatment of ectopic pregnancy is key to avoiding morbidity and mortality

TERMINOLOGY
- Pregnancy of unknown location: Pregnancy where the location is not definitively known either by visualization or by exclusion.
- Intrauterine pregnancy: Pregnancy visualized in the uterus, by presence of yolk sac and/or fetal pole. The “double decidual” sign should not be used as sole criteria for determining an IUP.
- Viable intrauterine pregnancy: Ultrasound confirms intrauterine fetal pole with cardiac activity.
- Non-viable intrauterine pregnancy: Confirmed intrauterine pregnancy with ultrasound or HCG findings that are not consistent with viability (e.g. fetal pole ≥5mm without cardiac activity).
- Ectopic pregnancy: Visualized ectopic pregnancy, with yolk sac or fetal pole outside the uterus.
- Presumed ectopic pregnancy: Pregnancy where location has not been identified but is suspicious for ectopic; e.g. serum hCG above discriminatory zone without evidence of intrauterine pregnancy, complex adnexal mass, presence of free fluid.
- Likely completed miscarriage: Pregnancy with recent heavy bleeding, history of passing tissue and/or an open cervical os, but no ultrasound confirmation of pregnancy location.

DIAGNOSIS OF ECTOPIC PREGNANCY
Various clinical parameters can be used to diagnose ectopic pregnancy:
- Serum human chorionic gonadotropin (hCG) levels: With 99% sensitivity, an increase in serum hCG of less than 53% in 48hrs in early pregnancy (when serum hCG is less than 2000) confirms an abnormal pregnancy. hCG levels above the discriminatory zone should be used with caution; serial ultrasound is more useful in this group.
- Pelvic ultrasonography: Can identify embryonic development (yolk sac, fetal pole) in the adnexa, or have findings suspicious for an ectopic such as pelvic free fluid or a complex adnexal mass. Of note, both an ectopic pregnancy and corpus luteum are vascular structures that can present as a “ring of fire” in the adnexa.
- Endometrial sampling: Presence of chorionic villi confirms an intrauterine pregnancy; absence of villi from sampling suggests an ectopic pregnancy, however villi can be missed due to sampling error or tissue processing. Tissue is typically processed as a frozen section. An hCG level can be drawn 24 hours post-sampling; an hCG plateau or rise supports diagnosis of an ectopic.
DIAGNOSIS OF ECTOPIC PREGNANCY (cont.):

- **Gestational age, if known and accurate**: A gestational sac is TYPICALLY seen by 24 days after conception (5+3 weeks), yolk sac by 5+5 weeks, and fetal pole by 6 weeks on TVU. These landmarks are only useful with certain dating, and may be of limited value in the E.D. setting.
- **Serum progesterone level**: serum progesterone <5ng/mL has a specificity of 100% for an abnormal pregnancy; >20 ng/mL typically indicates a normal intrauterine pregnancy. This information can be helpful in women followed with serial hCG levels, and may be less useful in the E.D. setting.

Serum hCG levels and transvaginal ultrasonography (TVU) should be used until a symptomatic early pregnancy can be determined to be a viable IUP, non-viable IUP or ectopic pregnancy (see Figure 1).

- **Ectopic pregnancy is confirmed** when there is evidence of embryonic development outside the uterus on ultrasound, confirmed by read of attending physician (Ob/Gyn or Radiology Attending).
- **Treatment for a presumed ectopic pregnancy** can be considered:
  1) When there is a persistent abnormal hCG rise or plateau with no evidence of IUP on TVU and/or no villi on diagnostic D&C
  2) When the serum HCG level is beyond the discriminatory zone (1500-2000 mIU/mL for TVU) and no IUP is visualized on TVU and/or no villi on diagnostic D&C; gestational age, if accurate and known, should also be considered given the higher hCG levels seen with multiple gestations.

LOGISTICS OF PATIENT FOLLOW-UP

- Weekdays: Gyn Continuity Clinic
- Weekend:
  - Blood draws (e.g. MTX follow-up labs): UAB Hospital Outreach Lab (6am-2:30pm, 2nd floor Spain-Wallace. Place IMPACT order & give patient paper requisition slip; sign-out to on-call Gyn team.
  - Urgent patient evaluations require an E. D. visit
- As is feasible, all hCG levels should be run in the UAB Hospital Lab to avoid assay variability.

SURGICAL MANAGEMENT OF ECTOPIC PREGNANCY

- Surgical removal of tubal ectopic pregnancy can usually be performed laparoscopically; in the case of rupture, a laparotomy may be needed to expedite the procedure and control bleeding.
- Options:
  1) Salpingectomy – removal of fallopian tube, recommended if fertility is not desired (i.e. post-tubal ligation), recurrent ipsilateral ectopic pregnancy, or uncontrolled bleeding
  2) Linear Salpingostomy – incision made in tubal wall, pregnancy tissue removed and tube flushed
     - hCG levels must be followed to <5 mIU/mL post-op in the case of a linear salpingostomy to ensure all trophoblastic tissue was removed
- Patency of tube following linear salpingostomy ~75-80%, comparable to results following medical management with methotrexate (MTX)

MEDICAL MANAGEMENT OF ECTOPIC PREGNANCY

- Early diagnosis of ectopic pregnancy allows for medical management in appropriate candidates.
- Methotrexate can be considered in those women with a Confirmed or Presumed Ectopic Pregnancy who are hemodynamically stable with an unruptured mass.
- Success with systemic MTX is >90% when initial hCG level is <5000 mIU/mL
MEDICAL MANAGEMENT OF ECTOPIC PREGNANCY (cont.)

- Contraindications to MTX therapy:

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Pregnancy of unknown location</td>
<td>6. Peptic Ulcer disease</td>
</tr>
<tr>
<td>2. Intrauterine pregnancy</td>
<td>7. Sensitivity to MTX</td>
</tr>
<tr>
<td>4. Immunodeficiency</td>
<td>9. Unwilling/unable to</td>
</tr>
<tr>
<td>5. Active pulmonary disease</td>
<td>return for f/u visits</td>
</tr>
<tr>
<td></td>
<td>4. hCG &gt; 5000 mIU/mL</td>
</tr>
</tbody>
</table>

- Pre-treatment evaluation:
  - Blood type, serum hCG (to be used as “Day 1” level)
  - “Safety labs” : CBC, AST/ALT, BUN/Cr, also repeated prior to additional MTX dosing

- Protocol:
  1) Single-dose regimen:
     - Day 1: MTX 50mg/m² intramuscular injection
     - Day 4 & Day 7: measure hCG level, a rise may be seen on Day 4 compared to baseline Day 1
     - If ≥15% drop from Day 4 to Day 7 continue to follow weekly until hCG <5 mIU/mL
     - If <15% drop from Day 4 to Day 7, repeat MTX 50mg/m² and repeat serum hCG Day 4 & 7
  2) Two-dose regimen:
     - Day 1: MTX 50mg/m² IM injection
     - Day 4: MTX 50mg/m² IM injection and serum hCG level
     - Day 7: serum hCG level; if ≥15% drop from Day 4 to Day 7 continue to follow weekly until hCG <5 mIU/mL
     - If <15% drop from Day 4 to Day 7, repeat MTX 50mg/m² and check hCG on Day 11; if ≥15% drop from Day 7 to Day 11 continue to follow weekly until hCG <5 mIU/mL
     - If <15% drop from Day 7 to Day 11, repeat MTX 50mg/m² and check hCG on Day 14; if ≥15% drop from Day 11 to Day 14 continue to follow weekly until hCG <5 mIU/mL
  3) Multi-dose regimen:
     - MTX 1mg/kg IM Days 1, 3, 5, 7. Alternate with folic acid 0.1mg/kg IM Days 2, 4, 6, 8.
     - Measure serum hCG on MTX dose days; continue dosing until hCG decreases 15% from previous measurement
     - Follow hCG levels until <5 mIU/mL

☞ To date, no study compares single-dose and two-dose regimens head-to-head.
☞ Two-dose should be considered if medical management is planned despite relative contraindications (e.g. hCG >5000 mIU/mL, + ectopic cardiac activity).
☞ Multi-dose should be reserved for extreme cases (e.g. cervical ectopic, hCG>10,000 in poor surgical candidate); other interventions such as an u/s-guided KCl injection should also be considered.

- Other treatment guidelines:
  - RhoGAM if Rh negative
  - Advise patient to discontinue folic acid supplementation during MTX treatment
  - Avoid pelvic exams and pelvic intercourse during treatment
  - Caution patients re: GI side-effects, to avoid alcohol and NSAIDs, and sun-sensitivity
  - Avoid new conception until serum hCG is undetectable
FINAL NOTES

- Randomized trials have demonstrated tube-sparing surgery and medical management with MTX to have comparable tubal patency, repeat ectopic pregnancies, and future fertility
- Baseline serum hCG level can be used to estimate success rate of MTX therapy:

<table>
<thead>
<tr>
<th>SERUM HCG CONCENTRATION (mIU/ml)</th>
<th>SUCCESS</th>
<th>FAILURE*</th>
<th>SUCCESS RATE (95% CI) percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1000</td>
<td>118</td>
<td>2</td>
<td>98 (96-100)</td>
</tr>
<tr>
<td>1000-1999</td>
<td>40</td>
<td>3</td>
<td>93 (85-100)</td>
</tr>
<tr>
<td>2000-4999</td>
<td>90</td>
<td>8</td>
<td>92 (86-97)</td>
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<tr>
<td>5000-9999</td>
<td>39</td>
<td>6</td>
<td>87 (79-98)</td>
</tr>
<tr>
<td>10,000-14,999</td>
<td>18</td>
<td>4</td>
<td>82 (65-98)</td>
</tr>
<tr>
<td>≥ 15,000</td>
<td>15</td>
<td>7</td>
<td>68 (49-88)</td>
</tr>
</tbody>
</table>


*Failure = HCG not falling or persistent cardiac activity after 3 doses of MTX, or rupture.

ECTOPIC LIST MANAGEMENT

- The GYN chief resident is primarily responsible for management of the ectopic list with at least weekly oversight by the GYN attending of the week.
- A list of all patients currently being evaluated and/or treated for an ectopic pregnancy will be kept by the Gynecology Service.
- The list will be managed as a shared IMPACT list, accessible to all UAB Gynecology providers.
- The Ectopic List should be signed-out by the Gyn team to the Gyn night float resident and weekend call team.
- Coverage for ED consults and OR cases between 5p and 6a by Gyn Night Call Attending.
- If the initial work up of a potential ectopic pregnancy is not completed during the day (GYN Attending of the week or Continuity clinic), the attending managing the work-up should check out to the GYN Night Call Attending.

REFERENCES


UAB Dept Ob/Gyn, rev December 2011
Figure 1. Management of Symptomatic Early Pregnancy

1. Obtain hCG and pelvic ultrasound.
2. Serum hCG > 1500 mIU/mL:
   - Confirmed IUP
   - Non-diagnostic
   - Ectopic pregnancy

   **IUP Options**
   - Repeat hCG every 48 hours
   - Repeat ultrasound in 1 week
   - Diagnostic surgical intervention (DnC) +/- LSC
   - See box bottom right

3. Serum hCG > 1500 mIU/mL:
   - Repeat serum hCG in 48 hours
   - hCG plateau
   - hCG drop <5%
   - hCG rise ≥53%

   **Spontaneous abortion**
   - Obtain transvaginal ultrasound once hCG ≤1500 mIU/mL
   - See left side of flowchart

   **Confirmed or Presumed Ectopic Pregnancy**
   - hCG: fled & non-diagnostic
     - Best management choice depends on clinical situation
     - Patients with pain or bleeding likely best served by diagnostic surgical intervention
     - Patients with delayed presentation and nausea need hCG 48hrs
     - Patients with no pain and minimal bleeding with likely IUP can have repeat ultrasounds in 1 week

   - Surgical management
   - Medical management (MTX)