Ectopic Pregnancy

Amy (Meg) Autry, MD
Professor
Department of Obstetrics, Gynecology, & Reproductive Sciences
University of California, San Francisco

Ectopic Pregnancy Objectives

- Review epidemiology
- Describe best approach for diagnosis
- Review the evidence for various treatment options including efficacy and future fertility

Ectopic Pregnancy: Epidemiology

- Increasing incidence: 2% pregnancies
- Increasing prevalence
- Increasing incidence of risk factors

Ectopic Pregnancy: Morbidity and Mortality

- Decreasing death-to-case ratio
- Leading cause 1st-trimester maternal deaths in US
- Most common cause maternal death AA
- Risk of death 10x > childbirth, 50x > legal abortion
- Treatment delay from misdiagnosis contributes to half of deaths
**EP: Symptoms**

- Abdominal pain: 90-100%
- Amenorrhea: 75-95%
- Vaginal spotting/bleeding: 50-80%
- Dizzy/fainting: 20-35%
- Urge to defecate: 5-15%
- Pregnancy symptoms: 10-25%
- Passage of tissue: 5-10%

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**EPF: Sign/Symptoms/DDX**

- Clinical assessment unreliable
- Vaginal bleeding/spotting
  - DDX: EP, subchorionic hemorrhage
  - urethral, condy, trauma, friable cx, polyp
  - Molar pregnancy, hemorrhoids
- Abdominal pain/cramping/pressure
  - DDX: EP, appy, uti, stone, ruptured ov cyst, torsion, salpingitis, infarcted myoma

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**Table 1: Clinicians' assessment vs. Pregnancy outcome**

<table>
<thead>
<tr>
<th>Clinicians' assessment</th>
<th>Viable</th>
<th>Nonviable</th>
<th>Ectopic</th>
<th>Molar</th>
<th>Others</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viable</td>
<td>365</td>
<td>236</td>
<td>13</td>
<td>3</td>
<td>7</td>
<td>624</td>
</tr>
<tr>
<td>Nonviable</td>
<td>4</td>
<td>132</td>
<td>6</td>
<td>1</td>
<td>--</td>
<td>143</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>1</td>
<td>--</td>
<td>3</td>
<td>--</td>
<td>--</td>
<td>4</td>
</tr>
<tr>
<td>Others</td>
<td>--</td>
<td>1</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>370</td>
<td>369</td>
<td>22</td>
<td>4</td>
<td>7</td>
<td>772</td>
</tr>
</tbody>
</table>

Kappa = 0.33

Yip et. Al. Gynecol Obstet Invest 2003;56:38-42

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**Table 2: Clinicians’ assessment + physical vs. Pregnancy outcome**

<table>
<thead>
<tr>
<th>Clinicians’ assessment + physical</th>
<th>Viable</th>
<th>Nonviable</th>
<th>Ectopic</th>
<th>Molar</th>
<th>Others</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viable</td>
<td>366</td>
<td>147</td>
<td>5</td>
<td>3</td>
<td>4</td>
<td>525</td>
</tr>
<tr>
<td>Nonviable</td>
<td>2</td>
<td>219</td>
<td>7</td>
<td>1</td>
<td>--</td>
<td>229</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>2</td>
<td>2</td>
<td>10</td>
<td>--</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Others</td>
<td>--</td>
<td>1</td>
<td>--</td>
<td>--</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>370</td>
<td>369</td>
<td>22</td>
<td>4</td>
<td>7</td>
<td>772</td>
</tr>
</tbody>
</table>

Kappa = 0.57

Yip et. Al. Gynecol Obstet Invest 2003;56:38-42
Ultrasound Milestones

- Gestational sac (GS): 2-3mm, c/w 4+ wks
  - mean sac diam increases by 1 mm/d if normal
  - **GA (d) = mean sac diam + 30 (+3 d)**
  - Double Decidual Sac sign: by 10 mm
- Yolk sac: visible by 6-8mm GS, 5+ wks
- Fetal Cardiac activity: 5mm pole, 6+ wks
- CRL increases by 1 mm/d if normal
  - **GA (d) = CRL + 42 (+3 d)**

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Figure 6-6. Transverse endovaginal sonogram of an early gestation sac (before visualization of a yolk sac). Mean sac diameter is being measured. This image depicts the transverse diameter (diameter) measured from the chorionic tissue-fluid interfaces.

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β-hCG increase in normal early pregnancy

<table>
<thead>
<tr>
<th>Gestational Age</th>
<th>% ↑ in 48 hr</th>
<th>Lower 2SD</th>
<th>Doubling time</th>
<th>Lower 2SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤41d</td>
<td>103%</td>
<td>73%</td>
<td>1.94 d</td>
<td>2.55 d</td>
</tr>
<tr>
<td>41-57d</td>
<td>33%</td>
<td>20%</td>
<td>4.75 d</td>
<td>7.53 d</td>
</tr>
<tr>
<td>57-65d</td>
<td>5%</td>
<td>4.3%</td>
<td>26.4 d</td>
<td>82.5 d</td>
</tr>
</tbody>
</table>

Daya et al. AJOG 1987
**β-hCG: single value & trends**
- EP rarely present with β-hCG >50,000
- EP and β-hCG at presentation
  - 50% <3,000
  - 33% <2,500
  - 19% <1,500
- Study screening women “at risk” for EP
  - 64% with EP had normal doubling
  - 80% EP and 35% EPF rising values initially
  - <50% increase 48 hr invariably nonviable

**β-hCG & Ultrasound**
- Combined: 97-100% sens; 95-99% spec
- Discriminatory Zone: quantitative β-hCG above which normal IUP visualized by U/S consistently
  - locally defined: realistically set
    - quality of equipment
    - experience of sonographer
  - range 1200-3500 mIU/ml transvaginal

**Endometrial stripe**
- Spandorfer et al: 117 pts, DZ 1,500
  - IUP: 13.4±.7mm [no nl IUP <6mm, 100% sens]
  - SAB: 9.3± .9mm
  - EP: 6.0± .4mm [no EP if >13mm, 100% spec]
  - 97% <= 8mm abnormal (EP, sab)
- Mehta et al: 128 pts, DZ 2,000
  - EP: 9.0±4.8 mm (range 2-20)
  - SAB: 8.4±4.6 mm (range 2-18)
  - IUP: 11.4±5.3 mm (range 2-22)
- Mol et al: stripe of no value

**Progesterone**
- <5ng/ml: ectopic pregnancy or nonviable IUP
- >25ng/ml: 97% viable IUP
- 5-25 ng/ml: indeterminate
- ovulation agents increase progesterone level for both intrauterine and ectopic pregnancy
### Strategies for Diagnosis

<table>
<thead>
<tr>
<th>STRATEGY</th>
<th>Missed EP/10,000</th>
<th>Interrupted IUP/10,000</th>
<th>Days to diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>US-&gt;hCG</td>
<td>0</td>
<td>70</td>
<td>1.46</td>
</tr>
<tr>
<td>hCG-&gt;US</td>
<td>0</td>
<td>122</td>
<td>1.66</td>
</tr>
<tr>
<td>P-&gt;US-&gt;hCG</td>
<td>24</td>
<td>25</td>
<td>1.25</td>
</tr>
<tr>
<td>P-&gt;hCG-&gt;US</td>
<td>24</td>
<td>39</td>
<td>1.26</td>
</tr>
<tr>
<td>US-&gt;US</td>
<td>0</td>
<td>121</td>
<td>1.21</td>
</tr>
<tr>
<td>Clinical Exam</td>
<td>940</td>
<td>0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Gracia et al Obstetrics and Gynecology 2001

### Strategies for Diagnosis

- In hemodynamically stable women presenting with abdominal pain or bleeding in the first trimester, transvaginal ultrasound followed by hCG, if ultrasound nondiagnostic, is best strategy

### Clinical Presentation

- **Age**
  - Younger than 18 +1
  - Older than 38 +3
- **Prior ectopic pregnancies**
  - One +2
  - 2 or more +3
- **Bleeding** +4
- **Prior miscarriage** -1
- **hCG > 2,000 mIU/mL** -1

*Risk of non-viable gestation = -1 or -2 low risk, 0-4 intermediate, 5 or more high risk*

Barnhart et al Obstetrics and Gynecology 2008

### Sensitivity of Ultrasound : below the discriminatory zone

- **Intrauterine Pregnancy** – 33.3%
- **Spontaneous Miscarriage** – 28.2%
- **Ectopic Pregnancy** – 25%

Barnhart et al Obstetrics and Gynecology 1999
Dart et al

**Ultrasound**

- 1/3 of patients with ectopic pregnancy and hCG <1,000 identified with ultrasound *(Annals of Emergency Med 1999)*
- Echogenic material in uterus, likelihood of normal IUP low *(Academic Emergency Med 1999)*
- Isolated cul de sac fluid at moderate risk for ectopic, risk increases with increased volume or echogenicity *(American Journal of Emergency Medicine 2002)*

**Indeterminate Ultrasound**

- Empty uterus the most worrisome – 5 times greater risk of ectopic pregnancy *(Annals of Emergency Medicine 2002)*
- Endometrial stripe thickness predictive when hCG level <1,000 mIU/mL *(Academic Emergency Med 1999)*
- hCG rate of change and empty uterus:
  - increase <66%, OR 24.8
  - decrease <50%, OR 3.7
  - increase >66%, OR 2.6 *(Annals of Emergency Medicine 1999)*

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**R/O EP, Indeterminate U/S: Utility D&C**

<table>
<thead>
<tr>
<th>D&amp;C finding</th>
<th>U/S: empty</th>
<th>U/S: not empty</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=245</td>
<td>n=77</td>
<td>n=168</td>
</tr>
<tr>
<td>Pos villi</td>
<td>35 (20%)</td>
<td>142 (80%)</td>
</tr>
<tr>
<td>n=177</td>
<td>[45%]</td>
<td>[85%]</td>
</tr>
<tr>
<td>Neg villi</td>
<td>17 (25%)</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>n=68</td>
<td>[22%]</td>
<td>[3%]</td>
</tr>
</tbody>
</table>

**Presumed Diagnosis of Ectopic Pregnancy**

- Villi found in 70% of D&E specimens with indeterminate US *(Dart Academic Emergency Medicine 1999)*
- Inaccurate diagnosis in 40% of cases *(Barnhart et al Obstetrics and Gynecology 2002)*
- “Empiric Treatment does not reduce complications or save money” *(Ailawadi Fertility and Sterility 2005)*
- Pipelle is not an adequate substitute because the sensitivity and predictive values are unacceptable *(Barnhart et al Am J Obstet Gynecol 2003)*
Methotrexate

- Folic acid analog
- Prevents reduction of folate to its active form, tetrahydrofolate
- Impairs DNA synthesis, repair, and cellular replication
- 1982 – first report of MTX use in treatment of ectopic pregnancy
- Initially all protocols involved citrovorum rescue factor

MTX Protocol

Single Dose Regimen

- Dose: 50 mg/sq meter BSA IM, actual body wt
- Measure β-hCG Days 1,4 and 7 (Day 1 = injection day)
  - if >15% decline day 4 to 7, follow β-hCG q wk
    - mean resolution 35 d (up to 109)
    - longest interval to rupture 42 d
  - if <15% day 4-7, repeat MTX
    - 20% need second dose
- Measure baseline LFT, Cr, H/H, Plt

Contraindications to Medical Therapy

ACOG Practice Bulletin #94, June 2008

ABSOLUTE
- Breastfeeding
- Immunodeficiency
- Alcoholism or other chronic liver disease
- Blood dyscrasias
- Sensitivity to MTX
- Active pulmonary disease
- Peptic Ulcer Disease
- Hepatic, renal, or hematologic dysfunction

RELATIVE
- Gestational sac larger than 3.5 cm
- Embryonic cardiac motion

Fixed multidose regimen

- MTX 1mg/kg IM (days 1,3,5,7) alternate daily with folinic acid 0.1mg/kg IM (days 2,4,6,8)
- Measure hCG levels on MTX dose days and continue until hCG has decreased by 15% from its previous measurement
- Once 15% decrease, follow hCG weekly until reaching nonpregnant level
- Consider repeating if hCG levels plateau or increase
**MTX counseling/side effects**

- Complications rare: bone marrow suppression, hepatotoxicity, pulmonary fibrosis, alopecia
- Side effects: nausea, diarrhea, oral irritation, transient transaminase elevation
- 60% have increase pain: d 3-7, 4-12 hrs

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**Predictors of Success of MTX for EP’s (Single Dose)**

<table>
<thead>
<tr>
<th>Serum β-hCG</th>
<th>Success Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1,000</td>
<td>98% (118/120)</td>
</tr>
<tr>
<td>1,000-1,999</td>
<td>93% (40/43)</td>
</tr>
<tr>
<td>2,000-4,999</td>
<td>92% (90/98)</td>
</tr>
<tr>
<td>5,000-9,999</td>
<td>87% (39/45)</td>
</tr>
<tr>
<td>10,000-14,999</td>
<td>82% (18/22)</td>
</tr>
<tr>
<td>&gt;15,000</td>
<td>68% (15/22)</td>
</tr>
</tbody>
</table>

Lipscomb et al NEJM 1999

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**Single Dose vs. Multi-dose Meta-analysis, Barnhart et al Obstet and Gynecol 2003**

- Single Dose more often used
- Single dose significantly higher failure rate (OR 4.74; 1.04,2.82)
- Single dose fewer side effects
- Women with side effects more likely to have successful treatment

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**Single Dose vs. Multi-Dose**

- Cochrane 2007 – no difference
- Lipscomb, AJOG 2005 – no difference (90% vs. 95%)
- ACOG Practice Bulletin #94, Level B - “With an hcg level > 5,000 mIU/mL, multiple doses of methotrexate may be appropriate
- Barnhart, Fertil and Steril 2007 – “2-dose protocol may optimize the balance between convenience and efficacy”
**MTX Protocol**

*Two-dose fixed regimen (Barnhart, 2007)*

- 50mg/sq meter IM on Day 1
- Repeat 50 mg/sq meter IM on day 4
- Measure hCG levels on days 4 and 7, expect a 15% decrease between days 4 and 7
- If decrease is greater than 15%, measure hCG levels weekly until nonpregnant level
- If less than a 15% decrease, readminister MTX 50 mg/sq meter on days 7 and 11

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**Surgical Treatment of Ectopic Pregnancy**

*Cochrane Database Review 2007*

- Laparoscopic surgery is a cost-effective treatment (laparotomy more effective)
- Salpingostomy vs. Salpingectomy is a matter of debate

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**Salpingostomy vs. Salpingectomy**

- Salpingostomy associated with persistent trophoblastic disease
- Several reviews of cohort studies (Yao ‘96, Mol ‘96, Clausen ‘96), no benefit of conservative surgery on intrauterine pregnancy rate with risk of increased ectopic
- Mol ‘98 – benefit of salpingostomy with contralateral tubal pathology
- Several RCTs ongoing

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**Prophylactic MTX with salpingostomy**

- Persistent trophoblastic tissue complicates 5-20% of cases treated with tubal conservation
- Fewer cases of tubal rupture (.4% vs 3.7%), fewer procedures (1.9% vs. 4.7%) and lower cost (NNT 10), Gracia et al 2001
- Very early gestations, < 2 cm, high starting hCG levels are at increased risk of persistence
**Expectant Management**

Cochrane Database 2007

- An evaluation of expectant management of ectopic pregnancy cannot be adequately made yet

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**Surgery, MTX, and Expectant Mgmnt**

Systematic Review and Meta-analysis

- Laparoscopic salpingostomy less successful than open approach, but less costly
- Single dose of MTX given prophylactically significantly reduces persistent trophoblast
- Fixed multiple dose MTX more successful than laparoscopic salpingostomy (NS)
- Fixed multiple dose cost effective only at hCG < 3000 mlU/mL, <1500 single dose cost effective
- Laparoscopic surgery is the most cost-effective, systemic MTX good alternative in select patients

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**Reproductive outcome**

- Risk of recurrent ectopic pregnancy after MTX similar to salpingostomy (10%)
- Tubal patency (62%-89%) and intrauterine pregnancy rates (36%-64%) comparable between MTX and salpingostomy, trend to higher recurrent ectopic in salpingostomy
- Probably higher intrauterine pregnancy rate after salpingostomy vs. salpingectomy but at least double the risk of recurrent ectopic

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**Ectopic Pregnancy Conclusions**

- Start with ultrasound for diagnosis
- MUA/D&C for abnormal pregnancy unknown location
- Consider fixed multi-dose MTX for higher hCG
- Consider simultaneous MTX with salpingostomy

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*Mol et al Human Reproduction Update 2008*
“Three Ultrasound Markers Predict Successful Pregnancy”

- Postconception dates 33-36, infertility patients
- Cardiac activity = 90% success (no activity = 88% miscarriage rate)
- Gestational sac >12mm diameter = 92% success (<8mm = 96% sab)
- Yolk sac between 2 and 6mm diameter = 90% success
- All 3 markers present = 94% accurate

Third place oral prize, ACOG 2009
Bae et al, University of Toledo