Diagnosis and Management of Pregnancy of Unknown Location
Ectopic, Early Pregnancy Loss, or Normal Pregnancy?

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Objectives
1. Define pregnancy of unknown location.
2. Describe a thoughtful approach to pregnancy of unknown location.
3. Review the workup of bleeding in the first trimester.

Patient Case: H&P
• Maya is a 26 yo G1P0 presenting to the emergency room for bleeding in early pregnancy.
• Maya’s sure LMP was 9 weeks ago.
• She had a positive UPT 2 weeks ago.
• This is a desired pregnancy.
• Her bleeding is like a “light period” for the past 3 days.
• She has no history of STIs or other risk factors for ectopic pregnancy.
• On exam her cervical os is closed.
• She is Rh-positive.

What can we tell Maya right now?

Disclosures
October 14, 2015
I have no disclosures.
Symptomatic Early Pregnancy Evaluation

Symptomatic Early Pregnancy: Presentation

- Urgent or emergency care visit
  - Vaginal bleeding
  - Abdominal or pelvic pain or cramping
  - Passage of pregnancy tissue from the vagina
  - Loss of pregnancy-related symptoms
  - Hemodynamic instability
- Incidental clinical finding
  - Bimanual exam inconsistent with LMP
  - Ultrasound suggestive of abnormal pregnancy

Symptomatic Early Pregnancy

- Ectopic pregnancy must be ruled out, but we must be careful to not diagnose a desired IUP as abnormal.
- There are new guidelines for hCG discriminatory zone, as well as EPL ultrasound diagnostic cut-offs.
- Choice of management is a preference-sensitive decision.

Bleeding in Early Pregnancy

- Keep the patient informed.
  - Reassure - not all vaginal bleeding & cramping signifies an abnormality, but avoid guarantees that "everything will be all right."
  - Assure you are available throughout the process.
- What does the bleeding mean?
  - Up to 20% chance of ectopic pregnancy
  - 50% ongoing pregnancy rate with closed cervical os
  - 85% ongoing pregnancy rate with viable IUP on sono
  - 30% of normal pregnancies have vaginal bleeding
Evaluation

- History
  - Risk factors for ectopic pregnancy
- Physical exam
  - Vital signs
  - Abdominal and pelvic exam
- Ultrasound
  - Transvaginal often necessary
- Lab
  - Rh factor
  - Hemoglobin or Hematocrit
  - β-hCG when indicated

Is the pregnancy desired?

Ectopic Pregnancy

- 1-2% of all pregnancies
- Up to 20% of symptomatic pregnancies
- ½ of ectopic patients have no risk factors
- Mortality has dramatically declined: 0.5/100,000
  - 6% of pregnancy-related deaths
  - 21 deaths per year in US
- Early diagnosis important
- Concern about management errors

Ectopic Pregnancy GOAL: Early Diagnosis

- Decreased chance of rupture (rupture can occur at any level of beta HCG and whether rising, falling or plateauing)
- Rupture associated with decreased fertility, increased morbidity and mortality
- More treatment options (eg methotrexate, conservative surgical treatment) if diagnosed earlier
- Methotrexate more effective if diagnosed earlier

Early Pregnancy Loss (EPL)

- 15-20% of clinically recognized pregnancies
- 1 in 4 women will experience EPL in their lifetime
- Includes all non-viable pregnancies in first trimester = miscarriage
### Patient Case: Physical Examination

- Maya has stable VS.
- She has a small amount of blood in her vagina, a closed os, a slightly enlarged, nontender uterus, and normal adnexa.
- Her pregnancy test is confirmed to be positive.
- The ultrasound does not show an IUP or an adnexal mass.

What can we tell Maya now?

### Pregnancy of Unknown Location

- When the pregnancy test is positive, but no signs of intrauterine or extraterine pregnancy on u/s
  - We try to follow these women until a diagnosis is made
  - We have to weigh risk of ectopic pregnancy (EP)
  - Sometimes there is never a final diagnosis as both EPL and EP may resolve spontaneously
- More commonly encountered in symptomatic early pregnancy, but can also be encountered in asymptomatic women, especially when u/s early
PUL Outcomes – Clinical Management

PUL Outcomes - Summary

PUL: Simplified

1. Where is the pregnancy? → U/S (same day)
2. If the pregnancy undesired? → uterine aspiration
3. If desired and we can’t tell where it is: Is it normal or abnormal? → quantitative (serial) Beta-HCG
   - If Bhcg above threshold and no IUP = Abnormal
   - Serial beta HCGs:
     • If Bhcg drops > 50% in 48 hours = Abnormal
     • If Bhcg rises > 50% in 48 hours = Most likely normal (can be EP) → Continue to follow and repeat u/s
     • If between = Most likely abnormal (still can be normal) – Continue to follow and repeat u/s
4. Once pregnancy determined to be abnormal or if undesired or if patient desires definitive dx → uterine aspiration to determine if IUP, EP tx if not

β-hCG Utility in Symptomatic Early Pregnancy Diagnosis

- β-hCG median serum concentration:
  - 4 weeks: 100 mIU/ml (5-450)
  - 10 weeks: 60,000 (5,000 – 150,000)

Discriminatory Level

- Serum β-hCG at which a normal intrauterine pregnancy should be visualized on ultrasound
  - If >2000 nl IUP unlikely but possible → new values
- Once beyond discriminatory level, limited role for “following betas”

IUP = Intrauterine pregnancy
Discriminatory & Threshold level

• 366 ♀ with VB/pain → nl IUP

99% Predicted Probability of Detection

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<thead>
<tr>
<th></th>
<th>Discriminatory</th>
<th>Threshold</th>
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<tbody>
<tr>
<td>Gestational sac</td>
<td>3510</td>
<td>390</td>
</tr>
<tr>
<td>Yolk sac</td>
<td>17,716</td>
<td>1094</td>
</tr>
<tr>
<td>Fetal pole</td>
<td>47,685</td>
<td>1394</td>
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</table>

• Highest seen in the study with no sac: 2,300

Old values: 1500 = 80% & 2000 = 91% prob. of seeing GS in viable IUP

Society of Radiologists in Ultrasound: No Gestational Sac

• HCG 2000 - 3000
  – Non-viable IUP most likely, 2X ectopic
  – Ectopic is 19 x more likely than viable IUP
  – For each viable pregnancy:
    • 19 ectopic pregnancies
    • 38 nonviable pregnancies
    – 2% chance of viable pregnancy
• HCG > 3000
  – Ectopic 70 x and nonviable IUP 140x more likely than viable pregnancy
  – 0.5% chance of viable IUP

In women with desired pregnancy consider beta hcg cut-off of >= 3000.

Balance of Diagnostic Tests

• Maximize sensitivity at the cost of diagnosing some IUPs as Ectopic Pregnancies
  – Error – interrupting desired IUP
• Maximize specificity at the cost of diagnosing some EPs as IUPs
  – Error – delay diagnosis resulting in rupture
• Engage the patient in decision-making
• Cut-off of 3,000 v. repeat beta hcg +/- u/s

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IUP=Intrauterine pregnancy
**β HCG trends in normal IUP**

<table>
<thead>
<tr>
<th>Slope of HCG rise</th>
<th>Relative increase in HCG concentration from baseline</th>
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<tbody>
<tr>
<td>1 day</td>
<td>50%</td>
</tr>
<tr>
<td>2 day</td>
<td>124%</td>
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</tbody>
</table>

Median rise:
1 day = 50%
2 day = 124%

Slowest expected 48-hour increase for normal pregnancy = 53% (20% of ectopics increase)

**β HCG trends: Other Key Points**

- Two hCG values may not be enough
- If close to the thresholds – check another

**PUL: Simplified**

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**If Diagnose as Abnormal...**

- Presumed ectopic pregnancy – uterine aspiration before MTX
  - High hCG nothing in the uterus (50% SAB)
  - Very low hCG with abnormal rise or definite fall (25% SAB)
Role of Ultrasound in Ectopic Diagnosis

- Only 2% of u/s are diagnostic for EP
  - “Diagnostic” = Gestational Sac with yolk sac or fetal pole visualized outside uterus
- Normal adnexal exam does not exclude ectopic
- Suggestive of ectopic
  - Empty uterus + hCG above discriminatory zone
  - Complex mass + fluid in cul-de-sac (94% are EP)
  - Should still follow them if desired pregnancy

Main role of U/S is to rule in IUP

Ultrasound Findings to R/o EP

- Remember that an EP has not been ruled out until there is an intrauterine pregnancy
  - Gestational sac with a yolk sac and/or embryo

First-trimester Bleeding Algorithm
EPL Diagnosis, Counseling, and Management

EPL Diagnosis

Clinical diagnosis:
- Spontaneous abortion
  - Vaginal bleeding + IUP, <20 wks threatened, inevitable, incomplete, complete
- Embryonic demise
  - Embryo with no cardiac activity
- Anembryonic gestation
  - Gestational sac without embryonic pole

Ultrasound diagnosis:
- Mean sac diameter >=21mm
  - 20 mm = 0.5% false positive
  - AND no fetal pole


GROWTH:
- 0 mm/d = 0 False+

MSD, + YS, no embryo

MSD (mm) | Specificity | False + | Growth per day (wk) | Specificity | False +
----------|------------|--------|---------------------|------------|--------
8mm       | 35.7%      | 64.3%  | 0.2mm (1.4mm)       | 98.6%      | 1.4%
16mm      | 97.4%      | 2.6%   | 0.6mm (4.2mm)       | 87.3%      | 12.7%
20mm      | 99.6%      | 0.4%   | 1.0mm (7mm)         | 43.7%      | 56.3%
21mm      | 100%       | 0      | 1.2mm (8.4mm)       | 25.2%      | 74.8%

MSD, no YS, no embryo

MSD (mm) | Specificity | False + | Growth per day (wk) | Specificity | False +
----------|------------|--------|---------------------|------------|--------
8mm       | 64%        | 36%    | 0.2mm (1.4mm)       | 99%        | 1%
16mm      | 95.6%      | 4.4%   | 0.6mm (4.2mm)       | 90%        | 10%
20mm      | 99.5%      | 0.5%   | 1.0mm (7mm)         | 45%        | 55%
21mm      | 100%       | 0      | 1.2mm (8.4mm)       | 24%        | 76%

Abdallah et al 2011 (Aug) Ultrasound Obstet Gynecol
Ultrasound Diagnosis of EPL: Embryonic Demise

Fetal pole ≥ 5.3 AND no cardiac activity

Abdallah et al. 2011 (Aug) Ultrasound Obstet Gynecol

CRL (mm) Specificity False + Growth per day (wk) Specificity False +

- 3mm 75% 25% 0.2mm (1.4mm) 100% 0%
- 4mm 91.7% 8.3% 0.6mm (4.2mm) 56.3% 63.7%
- 5mm 91.7% 8.3% 1.0mm (7mm) 0* 0%
- 5.3mm 100% 0 1.2mm (8.4mm) 0% 0%

*16 FP, 0 TN. 37 TP, 1 TN

Ultrasound Milestones

**Normal IUP findings** | **When should you see it?** | **Abnormality if landmark is absent**
---|---|---
**Gestational Sac** | Discriminatory Level \( \beta = 3,000 \) | Completed EPL. Multiple gestation. Ectopic pregnancy.
**Yolk sac** | MSD > 13-16mm | Suspicious for EPL.
**Fetal pole** | MSD ≥ 25mm | Anembryonic gestation.
**Cardiac activity** | CRL ≥ 7mm | Embryonic demise.
**Interval growth (MSD or CRL)** | 1 mm/day (over 3-7 days) | Confirmed EPL.
Early Pregnancy Loss Management

- Three (4) options for the clinically stable patient
  1. Uterine aspiration
     1. Aspiration w/ general/deep sedation (operating room)
     2. Aspiration w/ local/moderate sedation (office-based)
  2. Medication (misoprostol +/- mifepristone)
  3. Expectant

- All methods are effective, with equivalent safety and patient acceptability = clinical equipoise

EPL Treatment Options

**Expectant:** Success: 60% at 2 wks.
- Advantages: Privacy, some can avoid surgical treatment, ?decreased infection
- Disadvantages: up to 6 wks to complete, more bleeding & more visits, less patient satisfaction

**Misoprostol (800 PV): Success: 80% at 1 wk.**
- Advantages: Privacy, availability, most can avoid surgical tx, ?decreased infection, similar satisfaction as surgical
- Disadvantages: multiple visits, 30% require 2nd dose, more pain, N/V & bleeding than surgical

**Uterine Aspiration:** Success: ~100%
- Advantages: 2-4 hrs, high success rate, less blding & pain
- Disadvantages: less available, rare surgical complications, ?increased infection

EPL Mgt: A Preference-sensitive Decision

- Best choice for management reflects the woman's values and preferences
- Comprehensive management options can be offered in a typical primary care or outpatient setting
Ectopic Pregnancy Management

**Surgery**
- If hemodynamically unstable, patient desires surgery, contraindications to or failed MTX treatment
- Laparotomy or laparoscopy
- Salpingectomy or salpingotomy
  - Salpingectomy if tube compromised
  - Similar outcomes if not compromised and other tube healthy
  - If other tube absent or unhealthy – salpingostomy preferred
- 10% failure rate if salpingostomy, require b-hcg followup

**Expectant management**
- If beta HCG <200 88% resolve spontaneously
- Declining beta HCG - third value less than first
- Asymptomatic, informed consent
Medical Treatment of EP

Methotrexate
- Antimetabolite that interrupts DNA synthesis in actively dividing tissues
- Successful in 80-95%
- Beta HCG levels >5000 higher failure rate with single-dose tx (14% v. 4% if less than 5000)
- Single-, two-, multi-dose regimens
- Start with single-dose if b-hcg <5000
- Multi-dose for cervical or interstitial ectopics

Success of Single Dose MTX for EP

<table>
<thead>
<tr>
<th>Serum β-hCG</th>
<th>Success Rate</th>
</tr>
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<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>

Single Dose vs. Multiple Dose

<table>
<thead>
<tr>
<th></th>
<th>Single Dose</th>
<th>Multiple Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>88% (940/1067)</td>
<td>93% (241/260)</td>
</tr>
<tr>
<td>Range</td>
<td>86% - 90%</td>
<td>86% - 96%</td>
</tr>
</tbody>
</table>

40% of 862 subjects met inclusion criteria.

Ectopic Treatment: MTX vs Surgery

- Methotrexate is not for everyone
- No difference in future IUP or ectopic rates
- Single-dose less effective than salpingostomy (OR=0.38)
- 5% have rupture despite MTX
- Requires significant follow-up
Medical Treatment of EP

**Single**: Administer MTX 1 mg/kg IM (on days 1, 3, 5, 7), alternate daily with folic acid 0.1 mg/kg IM (on days 2, 4, 6, 8).

**Two-do**: Fixed multidose regimen:

1. **Measure hCG levels on MTX dose days and continue until hCG has decreased by 15% from its previous measurement.**
2. **If the dose is not decreasing weekly**:
   - **Repeat** administration of MTX until the hCG levels are not decreasing weekly until reaching the nonpregnant level.
   - **If the dose plateau or increases**, consider repeating MTX using the regimen described.

**Case:** Consider surgical intervention.

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**Conclusions**

- Bleeding in early pregnancy is common.
- Take possibility of ectopic pregnancy seriously!
- Pregnancy of unknown location takes patience to sort out.
  - New beta-HCG cutoffs
  - New ultrasound measurement cutoffs
  - If abnormal – do uterine aspiration before giving MTX
- Patient preference is important.