Approaches to Failed Intrauterine Pregnancy

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• I have no relevant financial disclosures
• I will be discussing off-label use of misoprostol

Acknowledgements
• Robin Wallace & Karen Meckstroth

Objectives
1. Review terminology of early pregnancy loss
2. Review clinical, serum, and ultrasonographic diagnostic features
3. Compare management options
   – Discuss role of patient preferences
   – Expectant, medical, surgical (office vs. OR)

Early Pregnancy Loss (EPL):

Clinical diagnosis:
- Spontaneous abortion: Vaginal bleeding + IUP, <20 wks (threatened), inevitable, incomplete, complete

Ultrasound diagnosis:
- Anembryonic gestation: trophoblast development without development of an embryo
- Embryonic demise: 5mm embryo with no cardiac activity

- 15-20% of clinically recognized pregnancies
- 1 in 4 women experience EPL
### Stages of SAB:
**VB, + IUP, <20 wks**

<table>
<thead>
<tr>
<th>STAGE:</th>
<th>Os:</th>
<th>Tissue &amp; U/S:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threatened</td>
<td>Closed</td>
<td>No tissue passed</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IUP on U/S</td>
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<tr>
<td>Inevitable</td>
<td>Open</td>
<td>No tissue passed</td>
</tr>
<tr>
<td></td>
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<td>IUP on U/S</td>
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<tr>
<td>Incomplete</td>
<td>Open</td>
<td>Tissue passed</td>
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<td>+/- IUP on U/S</td>
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<tr>
<td>Complete</td>
<td>Closed</td>
<td>Tissue passed</td>
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<tr>
<td></td>
<td></td>
<td>No IUP on U/S</td>
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</table>

### Normal Implantation
- **Implantation:**
  - 5-7 days after fertilization
  - Takes ~72 hours
  - Invasion of trophoblast into decidua → production of HCG

### Diagnosis of EPL
1. **Clinical presentation**
   - Bleeding, pain, LMP

2. **β-HCG**
   - Isolated value, trend

3. **Ultrasound**
   - Sac, pole, pseudosac

### Beta Curves, redefined
- **Letting go of the 48 hour dogma...**
  - Rate of increase depends on gestational age
  - Early studies used 85% CI as lower limit
  - Newer data suggest different median and mean

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β HCG trends in normal IUP

Table 1. Predicted Increase in Log hCG Over Time

<table>
<thead>
<tr>
<th>Percentile</th>
<th>Slope of Log hCG</th>
<th>1 day</th>
<th>2 days</th>
<th>3 days</th>
<th>4 days</th>
<th>5 days</th>
<th>6 days</th>
<th>7 days</th>
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<tbody>
<tr>
<td>1</td>
<td>1.34</td>
<td>1.34</td>
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<td>5</td>
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<tr>
<td>50</td>
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<tr>
<td>75</td>
<td>1.01</td>
<td>1.01</td>
<td>1.01</td>
<td>1.01</td>
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<td>1.01</td>
<td>1.01</td>
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<tr>
<td>90</td>
<td>0.96</td>
<td>0.96</td>
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<td>0.96</td>
<td>0.96</td>
<td>0.96</td>
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<tr>
<td>95</td>
<td>0.91</td>
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<td>0.91</td>
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</tr>
</tbody>
</table>

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

Slowest expected 48 hr increase for normal pregnancy = 53%

Stehrer 1984 Obst Gynecol

β HCG Clearance

1st Trimester TAB, D&C
Median = 30 d (16-60)

1st Trimester SAB, D&C
Median = 19 d (9-35)

Ectopic, laparotomy
Median = 8.5 d (1-31)

Ultrasound & normal early pregnancy: Key findings

- Gestational sac
  - Double decidual sign
  - Grows ~ 1mm/day

- Yolk Sac
  - Early "circulatory system"
  - Grows ~ 1mm/day

- Embryonic Pole
  - Early embryonic activity
  - Grows ~ 1mm/day

- Cardiac Activity
  - 100bpm → 140 bpm

Ultrasound milestones

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>GSD</th>
<th>Discriminatory Level</th>
<th>When should you see it?</th>
</tr>
</thead>
<tbody>
<tr>
<td>r/o ectopic</td>
<td>1500-2000</td>
<td>β = 1500-2000</td>
<td>Gestational Sac</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete SAB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(wait for fetal pole)</td>
<td>MSD &gt; 13-16mm</td>
<td>Yolk sac</td>
<td></td>
</tr>
<tr>
<td>Anembryonic gestation</td>
<td>MSD ≥ 20mm (16-25mm)</td>
<td>Fetal pole</td>
<td></td>
</tr>
<tr>
<td>Embryonic demise</td>
<td>Fetal pole ≥ 5mm</td>
<td>Cardiac activity</td>
<td></td>
</tr>
</tbody>
</table>

5mm cut off = 8.3% false +
5.3mm cut off = 0 false +
(Abdallah et al 2011 Oct Ultrasound Obstet Gynecol)
Ultrasound diagnosis of EPL: Anembryonic gestation

Mean sac diameter $\geq 20$ mm AND no fetal pole

Growth?
- Cut off $0.6$ mm/day $\rightarrow$ 90% spec
- Cut off $0.2$ mm/day $\rightarrow$ 99% spec

1.4 mm/week

Abdallah et al 2011 (Aug) Ultrasound Obstet Gynecol

Ultrasound diagnosis of EPL: Embryonic demise

Fetal pole $\geq 5$-6 mm AND no cardiac activity

Growth? Poor predictor!
- $0.6$ mm/d (4.2 mm/wk) $\rightarrow$ 56% spec
- $0.2$ mm/d (1.4 mm/wk) $\rightarrow$ 100% spec

Abdallah et al 2011 (Aug) Ultrasound Obstet Gynecol

Ultrasound: Poor prognostic signs

- Yolk sac $> 5$ mm
- Low fluid (MSD-CRL $< 6$ mm)
- Slow embryonic heart rate (~85)
- Subchorionic hemorrhage
- Thin decidual reaction (<3 mm):
- Irregular contour sac
- Low position in Uterus

Not diagnostic, but may help with counseling

Summary: Diagnosis of EPF

- Be cautious of only one point of information (Lab and ultrasound errors occur)
- Clinical history varies
- HCG rise in 48 hours: Minimum 53% Average 124%
- Ultrasound:
  - No growth of small sac (IUP not confirmed)
  - No cardiac motion of pole $\geq 5$-6 mm
  - Anembryonic sac $\geq 20$ mm MSD
EPF Management

**Expectant**

**Medical**

**Surgical**

Depends on:
1. Hemodynamic stability
2. Stage in miscarriage process
3. Local resources
4. Patient preference

Expectant Management: Completion rates

<table>
<thead>
<tr>
<th></th>
<th>By day 7 (%)</th>
<th>By day 14 (%)</th>
<th>By day 46 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incomplete Ab (n=221)</td>
<td>53</td>
<td>71-84</td>
<td>91</td>
</tr>
<tr>
<td>Anembryonic gestation (n=92)</td>
<td>25</td>
<td>52</td>
<td>66</td>
</tr>
<tr>
<td>Embryonic demise (n=138)</td>
<td>30</td>
<td>35-59</td>
<td>76</td>
</tr>
<tr>
<td>Total (n=451)</td>
<td>40</td>
<td>61-70</td>
<td>81</td>
</tr>
</tbody>
</table>

**MIST Trial**
RCT of 1200 ♀ – expectant, medical, surgical
Expectant success = 66% at 2 weeks

Expectant Management: Risks?

**MIST Trial**

- **Infection:**
  - No difference b/t expectant, medical, surgical (3%, 2%, 3%, p=NS)
  - **Cochrane:** Lower than surgical (RR=0.29, 0.09–0.87)

- **Unscheduled D&C**
  - 44% (expectant) vs. 5% (miso)

- **Transfusion:**
  - expectant > surgical (2% vs. 0%)

- **Cochrane:** Lower than surgical (RR=0.29, 0.09–0.87)

Expectant Management: Contraindications

- Uncertain diagnosis
- Severe hemorrhage or pain
- Infection
- Suspected gestational trophiclastic disease
- Indicated karyotyping

Same contraindications for medical management
Expectant Management: Limitations?

- **Size**: Studies generally include gestations up to 9 week size
- **Time**: Safety established up to 6 weeks of observation
- **Maternal conditions**: inappropriate for bleeding at home
- **Social**: inability to obtain prompt emergency care, understand precautions

Expectant Management

**Advantages**
- Non-invasive
- Body naturally expels non-viable pregnancy
- Avoids anesthesia and surgery risks
- Allows for patient privacy and continuity of care

**Disadvantages**
- Unpredictable outcome and timescale
- Process can last days to weeks
- Can have prolonged bleeding and cramping
- Despite waiting, may still need uterine aspiration

Medical management: Misoprostol

- PGE1 analogue
- Inexpensive
- Rapidly absorbed PO, PV, PR, SL, buccal
- FDA approved for prevention/treatment of gastric ulcers
- Common obstetrical uses: labor induction, medical abortion, PPH, cervical ripening

Physiologic Effects of Misoprostol

- **Uterine**: Stimulates contractions
- **Cervical**: Softens and primes cervix
- **Gastrointestinal**: Prevents/treats ulcers, Nausea & vomiting, Diarrhea
- **Systemic**: Fever, chills
Medical management: misoprostol for EPL

- Small studies with wide range of doses, follow-up and definition of success
  - 800 mcg vaginally, repeated in 24h PRN\(^1,2\)
  - side effects with PO, buccal, SL
  - 400-600 mcg buccal or sublingual\(^3\)
- Success (avoid surgical intervention) 70-96%\(^4\)
  - Incomplete: higher success
- More acceptable than surgical\(^5,6\)

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Medical: Mifepristone along with misop?

- Anti-progesterone, used in medical ab.
- Does not add much to EPF mgmt!
  - Mife 600 + Miso 400 PV vs. Miso alone\(^1\)
    - 74% vs. 71% success at 1 week
  - Mife 200 + Miso 800 PV
    - 84%-90%\(^3\) success at 3 days or 1 week\(^2,3\)

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Medical Management

**Advantages**
- Highly cost-effective
- Non-invasive
- Safe
- Can be highly effective
- Avoids anesthesia and surgery risks
- Allows for patient privacy and continuity of care

**Disadvantages**
- Increased need for analgesics and pain control
- May cause heavier or longer bleeding
- May cause short-term gastrointestinal and other side effects
- May still need uterine aspiration

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Example of Misoprostol Algorithm

Miso 800 mcg PV

- Cramping w/ clot/tissue in 24-48 hrs
- 2nd Dose Miso
- Sac present or (Endometrium >30 mm)
- No Sac & (endometrium <=30 mm)

Follow up precautions:
- Bleeding should stop in 2-3 wks
- Menses should resume in 6-8 weeks

Adapted from Goldberg 2009 in Mgmt of unintended & abnl pregnancy
Misoprostol vs. Surgical: MEPF Study

- RCT of 652 ♀ w/ EPL or incomplete Ab
  - Miso vs. D&C
- D1: Miso 800 PV
  - D3: repeat miso if not complete
  - D8: D&C if still not complete
  - D15: follow-up (all)
- **Success** (no need for additional D&C)
  - Miso: 84% (CI, 81-87) vs. D&C: 97% (CI, 94-100)
  - Lowest for embryonic demise (81%)
- **Complications:** No difference
- **Satisfaction:** No difference (78% vs. 83%)

Surgical Management: MEPF Study

- **EVA to MUA**
  - **EVA** vs. **MUA**
    | Vacuum       | Electric pump | Manual aspirator |
    | Noise        | Variable      | Quiet            |
    | Portable     | Not easily    | Yes              |
    | Cannula      | 4–16 mm      | 4–12 mm          |
    | Capacity     | 350–1,200 cc | 60 cc            |
    | Suction      | Constant     | Decreases to 80% (50 mL) as aspirator fills |

Surgical Management: MUA

- Safe, fast, cost-effective for management of EPF and SAB
- MUA in ER compared to EVA in OR:
  - **EVA in OR** vs. **MUA in ER**
    |                  | EVA in OR | MUA in ER |
    | Wait time (↓52%) | 7.14 hrs  | 3.45 hrs  |
    | Procedure time   | 33 min    | 19 min    |
    | Total cost (↓41%)| $1404     | $827      |
- MUA vs. EVA: no difference in complication rates (2.5% vs. 2.1%)

Office-based Aspiration

**Advantages**
- Predictable
- Offers fastest resolution of miscarriage
- Reduced duration of bleeding
- Low risk (<5%) of needing further treatment
- Pain control with local plus oral or IV meds

**Disadvantages**
- Rare risks of invasive procedure
- Less pain control options in some settings

Compared to OR management:
- May allow improved patient access and continuity of care
- Improved privacy
- Less patient and staff time
- Resource and cost savings

**Notes:**
1. Blumenthal 1992 Int J Gynecol Obstet
2. Goldberg 2004 Obstet Gynecol
Overall success rates

<table>
<thead>
<tr>
<th>Method</th>
<th>Expectant (7 – 14 days)</th>
<th>Misoprostol 800 mcg PV (7 days)</th>
<th>Aspiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anembryonic gest. &amp; Embryonic demise</td>
<td>30 - 70%</td>
<td>70% - 90%</td>
<td>97% - 100%</td>
</tr>
<tr>
<td>Incomplete</td>
<td>84% - 96%</td>
<td>81%</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>88%</td>
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<td></td>
<td></td>
<td>93%-95%</td>
<td></td>
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</tbody>
</table>

Follow-up for miscarriage

Confirm pregnancy passed:
- Surgical: done at time of aspiration
- Expectant & Medical
  - Symptoms, ultrasound or pregnancy test
  - Phone call is an option

Other benefits of an office visit:
- Emotional support
- Preconception counseling or contraception
- Recurrence risk

Ultrasound after SAB, D&C?

- Mean endo thickness 7-10 d after medical ab:
  - Successful abortion: 4.01 mm (0.67-13.4)
  - Failed ab (surgery or miso): 6.15 mm (3.35-10.0)

- Mean endo thickness 14 d after EPL mgmt:
  - Misoprostol: 9.0 mm (0.1-20)
  - D&C: 6.9 mm (0.1-1.5)

Don’t base decision for intervention on thickness of endometrium!!!
Clinical judgment, persistent sac.

EPF Management

CLINICAL EQUIPOISE
All methods are effective, with equivalent safety and patient acceptability

Patients have strong and widely divergent preferences:
Higher quality-of-life scores and satisfaction when treated according to preference

NSFG 2004; Chen 2007; Wieringa-de Waard, 2002; Zhang 2006; Trinder 2006
EPF Management Practices in the U.S.

Expectant Misoprostol Office aspiration OR

Percent of EPF providers

- Ob/Gyn
- CNM
- FP

Adapted from Dalton AJOG 2010

Provider Issues

- Training
- Safety Concerns
- Efficacy
- System Resources
- Time
- Assumptions of patients

Patient Priorities

- Pain
- Time
- Complications
- Safety
- Bleeding
- Privacy
- Anesthesia
- Past experience
- Finality

Adapted from Wallace et al 2010 Patient Educ Couns ©Robin Wallace, 2011

- Personal Priorities
  - Treatment by your own provider
  - Recommendation of treatment from friend or family member
  - Provider recommendation of treatment
  - Experience symptoms of bleeding and cramping in private
    - Family responsibilities/needs
- Emotional Priorities
  - Most natural process
  - Avoid seeing the pregnancy tissue
- Time and Cost Priorities
  - Shortest time before miscarriage is complete
  - Shortest time in the clinic or hospital
  - Fastest return to fertility or normalcy
  - Fewest number of clinic visits
  - Lowest cost of treatment to you

Adapted from Wallace et al 2010 Patient Educ Couns ©Robin Wallace, 2011

- Physical Priorities
  - Least amount of pain possible
  - Fewest days of bleeding after treatment
  - Lowest risk of complications
  - Lowest risk of need for other steps
  - Avoid invasive procedure
  - Avoid medications with side effects
  - Avoid seeing blood
  - Avoid going to sleep in case of a surgical procedure
  - Want to be asleep in case of a surgical procedure

Adapted from Wallace et al 2010 Patient Educ Couns ©Robin Wallace, 2011

Previous Miscarriage or Abortion

(if applicable)

- Different treatment from previous
- Similar treatment to previous
Key Points: EPL Management

CLINICAL EQUIPOISE
All methods are effective, with equivalent safety and patient acceptability

- Know success rates when counseling patients
- Elicit patient preferences
- If surgical mgmt, office MUA is acceptable and cost-effective

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