First Trimester Bleeding Approaches to Failed First Trimester Pregnancy

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Disclosures

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

Acknowledgements

Carolyn Sufrin and Jody Steinauer

Objectives

1. Review terminology of early pregnancy loss
2. Review clinical, serum, and ultrasonographic diagnostic features of failed intrauterine pregnancy (IUP)
3. Compare management options for failed IUP
   - 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

**STAGE:**
- Threatened
- Closed
- Inevitable
- Open
- Incomplete
- Complete

**Os:**
- No tissue passed IUP on U/S
- No tissue passed IUP on U/S
- Tissue passed +/- IUP on U/S
- Tissue passed

**Tissue & U/S:**
- No IUP on U/S

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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Beta Curves, Redefined

**Letting go of the “double in 48 hours” rule**

- 287 women with pain or bleeding and +UPT
  - No IUP on U/S but eventually had normal IUP
  - Initial β-HCG < 5000
- Ave GA by LMP = 38 days (range, 0-107)
- At least 2 β-HCG’s within 7 days

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β-hCG increase in normal early pregnancy

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

Daya et al. AJOG 1987
**β HCG trends in normal IUP**

<table>
<thead>
<tr>
<th>Percent</th>
<th>Slope of HCG rise</th>
<th>Relative increase in HCG concentration from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>1 day later</td>
<td>100%</td>
</tr>
<tr>
<td>3.4</td>
<td>2 day later</td>
<td>200%</td>
</tr>
</tbody>
</table>

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

Slowest expected 48 hr increase for normal pregnancy = 53%

Barnhart 2004 Obstet Gynecol

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**Ultrasound & normal early pregnancy: Key findings**

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

- **Yolk Sac**
  - Early “circulatory system”
  - Grows ~ 1mm/day

- **Embryonic Pole**

Cardiac Activity

100 bpm → 140 bpm

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**Ultrasound milestones**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>When should you see it?</th>
</tr>
</thead>
<tbody>
<tr>
<td>r/o ectopic</td>
<td>Discriminatory Level β = 1500-2000 (4+ wks)</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td>MSD&gt;13-16mm (5+ wks)</td>
</tr>
<tr>
<td>Complete SAB</td>
<td>MSD ≥20mm (16-25mm)</td>
</tr>
<tr>
<td>Anembryonic gestation</td>
<td>Fetal pole ≥ 5mm (6+ wks)</td>
</tr>
<tr>
<td>Embryonic demise</td>
<td>Growth?</td>
</tr>
</tbody>
</table>

Mean sac diameter ≥ 20mm AND no fetal pole

Growth?
- Cut off 0.6mm/day → 90% spec
- Cut off 0.2mm/day → 99% spec
- 1.4mm/week

Abdallah et al 2011 (Aug) Ultrasound Obstet Gynecol

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**Ultrasound diagnosis of EPL: Anembryonic gestation**

- Mean sac diameter ≥ 20mm
- AND no fetal pole

Growth?
- Cut off 0.6mm/day → 90% spec
- Cut off 0.2mm/day → 99% spec
- 1.4mm/week

Abdallah et al 2011 (Aug) Ultrasound Obstet Gynecol
Ultrasound diagnosis of EPL: Embryonic demise

- Fetal pole >= 5-6mm AND no cardiac activity

Growth? Poor predictor!
- .6mm/d (4.2mm/wk) → 56% spec
- .2mm/d (1.4mm/wk) → 100% spec

Abdallah et al 2011 (Aug) Ultrasound Obstet Gynecol

Ultrasound: Poor prognostic signs

- Yolk sac >5 mm
- Low fluid (MSD-CRL < 6mm)
- 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

Sensitivity of Ultrasound: below the discriminatory zone

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

Bamhart et al Obstetrics and Gynecology 1999

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

<table>
<thead>
<tr>
<th>D&amp;C finding</th>
<th>U/S: empty n=77</th>
<th>U/S: not empty n=168</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pos villi n=177</td>
<td>35 (20%) [45%]</td>
<td>142 (80%) [85%]</td>
</tr>
<tr>
<td>Neg villi n=68 [28%]</td>
<td>17 (25%) [22%]</td>
<td>5 (7%) [3%]</td>
</tr>
<tr>
<td>EP</td>
<td>24 (37%) [32%]</td>
<td>21 (31%) [13%]</td>
</tr>
<tr>
<td>SAB</td>
<td>24 (37%) [32%]</td>
<td>21 (31%) [13%]</td>
</tr>
</tbody>
</table>

Dart et al Acad Emerg Med 1999

Summary: Diagnosis of EPF

- Be cautious of only one point of information (Lab and ultrasound errors occur)
- Clinical history varies, heavier and longer bleeding -> worse prognosis
- HCG rise in 48 hours: Minimum 53%
  Average 124%
- Ultrasound:
  - No growth of small sac (IUP not confirmed)
  - No cardiac motion of pole > 5-6mm
  - Anembryonic sac ≥ 20 mm MSD

EPF Management

Medical
Surgical

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–.87)

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

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

Expectant Management: Contraindications

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

Same contraindications for medical management

Nanda 2006 Cochrane Database Syst Rev, Trinder 2006 BAJ

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 for 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/tx 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

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**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
  - side effects with PO, buccal, SL
  - 400-600 mcg buccal or sublingual

- **Success** (avoid surgical intervention) 70-96%
  - Incomplete: higher success
  - More acceptable than surgical

1. Zhang et al, NEJM, 2005
2. Weeks et al, Obstet Gynecol 2005

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**Medical: Mifepristone along with miso?**

- Anti-progesterone, used in medical ab.
- Does not add much to EPF mgmt!
  - Mife 600 + Miso 400 PV vs. Miso alone
    - 74% vs. 71% success at 1 week
  - Mife 200 + Miso 800 PV
    - 84\%70\%80\%3 success at 3 days or 1 week

2. Wagaarachchi 2001 Human Reproduction
3. Schreiber 2006 Contraception
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

Example of Misoprostol Algorithm

```
Miso 800 mcg PV

Cramping w/ clot/tissue in 24-48 hrs

2 Days
Clinical f/u U/S if indicated

No clinical passage in 24-48 hrs

7 Days
Clinical f/u

Sac present or (Endometrium >30 mm)

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

No Sac & (endometrium <=30 mm)

DONE!

If still sac (or endo >30 mm) after 2 doses: Recommend suction
If wants expectant mgmt, f/u 2-4 wks
Suction if signs of infection or HD instability

Done!`

Example of Misoprostol Algorithm

```
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Suction if signs of infection or HD instability

Done!`

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%)

“A Comparison of medical management with misoprostol and surgical management for early pregnancy failure”

- Misoprostol success varied by diagnosis:
  - 81% anembryonic
  - 88% embryonic or fetal demise
  - 93% incomplete or inevitable
- Lower abdominal pain, vaginal bleeding, nulliparity and Rh negative status associated with successful medical management
“A Comparison of medical management with misoprostol and surgical management for early pregnancy failure”

- Misoprostol group had higher rates of nausea, vomiting, diarrhea, and abdominal pain
- Complications with misoprostol occur at a rate of less than 1/70
- Acceptability – 83% would recommend to their friends and 78% would use it again

Surgical management:

MUA

- Safe, fast, cost-effective for management of EPF and SAB
- MUA in ER compared to EVA in OR:

<table>
<thead>
<tr>
<th></th>
<th>EVA in OR</th>
<th>MUA in ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wait time (↓52%)</td>
<td>7.14 hrs</td>
<td>3.45 hrs</td>
</tr>
<tr>
<td>Procedure time</td>
<td>33 min</td>
<td>19 min</td>
</tr>
<tr>
<td>Total cost (↓41%)</td>
<td>$1404</td>
<td>$827</td>
</tr>
</tbody>
</table>

- MUA vs. EVA: no difference in complication rates (2.5% vs. 2.1%)²

Surgical Management: EVA to MUA

<table>
<thead>
<tr>
<th></th>
<th>EVA</th>
<th>MUA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vacuum</td>
<td>Electric pump</td>
<td>Manual aspirator</td>
</tr>
<tr>
<td>Noise</td>
<td>Variable</td>
<td>Quiet</td>
</tr>
<tr>
<td>Portable</td>
<td>Not easily</td>
<td>Yes</td>
</tr>
<tr>
<td>Cannula</td>
<td>4–16 mm</td>
<td>4–12 mm</td>
</tr>
<tr>
<td>Capacity</td>
<td>350–1,200 cc</td>
<td>60 cc</td>
</tr>
<tr>
<td>Suction</td>
<td>Constant</td>
<td>Decreases to 80% (50 mL) as aspirator fills</td>
</tr>
</tbody>
</table>


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

1. Blumenthal 1992 Int J Gynecol Obstet
2. Goldberg 2004 Obstet Gynecol
Moving MUA out of OR

90% uterine aspirations are done in OR

- Process described by U Michigan
  - Medical evidence review
  - Review of hospital policy for office procedures
  - Trained physicians, nurses, and MAs
    - Hands-on workshops
  - Institution of privileging program
  - Review experience of patients
  - Review cost – gyn reimbursement same, lower institutional cost - $1965 vs. $968

Harris, AJOG, 2007.

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

Overall success rates

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

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)

  Cowett 2004 Obstet Gynecol, p<.001

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

  Reeves 2008 Obstet Gynecol

  Various cut-off values for need for D&C gave PPV < 40%!

  Don’t base decision for intervention on thickness of endometrium!!!

  Clinical judgment, persistent sac...
Women’s Preferences

- Patients report higher quality-of-life and satisfaction when treated according to preference

- Surgery
  - Quick resolution
  - Want and value support from hospital staff

- Expectant
  - Desire a natural solution
  - Fear of operation
  - More preferred with higher level information & support
  - 71% with success would opt for same in future

- Misoprostol
  - Faster resolution
  - More natural solution without surgery


The Patient – provider Interaction

- Affects patient choice and satisfaction
- One half of women would change their decision based on our recommendation

Support women in identifying their values in and priorities for management.

Be prepared to offer all options, including misoprostol and office-based uterine aspiration.

Molnar 2000

Women’s Preferences

- There is no “one best way.”

- Expectant management is preferred over aspiration by 70% of women.

- When uterine aspiration is indicated or preferred, the majority of women will choose an office-based procedure over one in the OR.

Smith 2006; Wieringa-de Waard 2002; Dalton 2006

Patient Priorities

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

Adapted from Wallace et al 2010 Patient Educ Couns ©Robin Wallace, 2011
Provider Issues
- Training
- Safety Concerns
- Efficacy
- System Resources
- Time
- Assumptions of patients

EPF Management Practices in the U.S.

Key Points: Management
- Offer all 3 management options if stable
  – Know success rates when counseling patients
  – Patient preference plays a major role
  – Minimal difference in risk
- Need for surgical intervention should be based on clinical judgment
- Outpatient MUA is acceptable to women and cost-effective
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: Epidemiology

- Increasing incidence: 2% all US pregnancies
  - 2-10% after IVF-ET
- Decreasing hospitalizations: 45,000/yr
- Increased incidence with age
  - 15-24: 6.6/1,000; 35-44: 21.5/1,000
- Most EP in multigravida: 10-15% in nulligravida

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%

<table>
<thead>
<tr>
<th>Clinicians’ assessment + physical</th>
<th>Pregnancy outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Viable</td>
</tr>
<tr>
<td>Viable</td>
<td>366</td>
</tr>
<tr>
<td>Nonviable</td>
<td>2</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>2</td>
</tr>
<tr>
<td>Others</td>
<td>--</td>
</tr>
<tr>
<td>Total</td>
<td>370</td>
</tr>
</tbody>
</table>

Kappa = 0.57

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

Progesterone

• < 5 ng/ml: ectopic pregnancy or nonviable IUP
• > 25 ng/ml: 97% viable IUP
• 5-25 ng/ml: indeterminate
• ovulation agents increase progesterone for both intrauterine and ectopic pregnancy

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)

Surgery, MTX, and Expectant Mgmt 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 mIU/mL, <1500 single dose cost effective
• Laparoscopic surgery is the most cost-effective, systemic MTX good alternative in select patients

Mol et al Human Reproduction Update 2008
**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

**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.

**Other Causes of 1st trimester bleeding**

- Malignancy
- Infection
- Polyps
- Trauma

**Conclusions**

- Early intrauterine pregnancy failure – discussed diagnosis and management.
- Reviewed patient preferences with regard to treatment of EPF.
- Discussed diagnosis and management of ectopic pregnancy.
- Reviewed non-obstetric causes of 1st trimester bleeding.