Medical Management Of Early Pregnancy Loss: Everyone Can Do It

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Women's Health Update

Objectives
- Discuss Definitions of Early Pregnancy loss (EPL)
- Review Etiology of EPL
- Review Diagnosis of EPL
- Describe evidence-based medical management of EPL

Disclosure
- I train providers in Nexplanon insertion and removal
- I do not receive any honoraria for this

Nomenclature
- Early Pregnancy Loss/Failure (EPL/EPF)
- Spontaneous Abortion (SAb)
- Miscarriage

These are all used interchangeably!
Early Pregnancy Loss is becoming the preferred term
Terminology

• MISSED ABORTION: a non-viable pregnancy that has been retained in the uterus without spontaneous passage for at least 4 weeks since the demise.

• EARLY PREGNANCY LOSS: any abnormal intrauterine first trimester pregnancy

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EPL Definitions

<table>
<thead>
<tr>
<th>TERM</th>
<th>EXPLANATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Abortion</td>
<td>All pregnancy tissue has passed from uterus</td>
</tr>
<tr>
<td>Incomplete Abortion</td>
<td>Some pregnancy tissue remains in uterus</td>
</tr>
<tr>
<td>Inevitable Abortion</td>
<td>Cervix is open so pregnancy is going to pass</td>
</tr>
<tr>
<td>Threatened Abortion</td>
<td>Bleeding during pregnancy with closed cervix and pregnancy appears viable</td>
</tr>
<tr>
<td>Anembryonic Gestation</td>
<td>Gestational sac with mean sac diameter ≥16 mm transvaginally without embryo</td>
</tr>
<tr>
<td>Embryonic Demise</td>
<td>Embryo present, &gt;5mm long and no gestational cardiac activity</td>
</tr>
<tr>
<td>Fetal Demise</td>
<td>Fetus present with no gestational cardiac activity</td>
</tr>
</tbody>
</table>

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Background

• Early Pregnancy Loss is the most common complication of early pregnancy
  • 8–20% clinically recognized pregnancies
  • 13–26% all pregnancies
  • ~ 800,000 EPL each year in the US
  • 80% of EPL occur in 1st trimester

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Imperfect obstetrics: most don’t continue

Samantha

- 26 yo G2P1 presents to your office for a new ob visit. An ultrasound shows a CRL of 7mm but no cardiac activity.
- She wants to know why this happened.

The most likely reason for her EPL is:
1. Chromosomal abnormality
2. Maternal smoking
3. Paternal marijuana use
4. Maternal alcohol use
5. Too much maternal exercise

Etiology

- 33% anembryonic
- 50% due to chromosomal abnormalities
  - Autosomal trisomies 52%
  - Monosomy X 19%
  - Polyploidy 22%
  - Other 7%
- Host factors
  - Structural abnormalities
  - Maternal infection/endocrinopathy/coagulopathy
- Unexplained

Risk Factors for EPL

- Age
- Prior SAb
- Smoking
- Alcohol
- Caffeine (controversial)
- Maternal BMI <18.5 or >25
- Celiac disease (untreated)
- Cocaine
- NSAIDs
- High gravidity
- Fever
- Low folate levels
Normal Implantation & Development

- Implantation:
  - 5-7 days after fertilization
  - Takes ~72 hours
  - Invasion of trophoblast into decidua
- Embryonic disc:
  - 1 wk post-implantation
  - If no embryonic disc, trophoblast still grows, but no embryo (anembryonic pregnancy)
- Embryonic disc embryonic/fetal pole

Milestone of embryology as assessed by TVUS

Timing of first appearance of gestational landmarks on transvaginal ultrasound examination

<table>
<thead>
<tr>
<th>Landmark</th>
<th>First appearance on transvaginal ultrasound examination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational sac</td>
<td>4.5 to 5 weeks</td>
</tr>
<tr>
<td>Yolk sac</td>
<td>5 weeks</td>
</tr>
<tr>
<td>Cardiac activity</td>
<td>5.3 to 6 weeks</td>
</tr>
<tr>
<td>Measurable crown-rump length</td>
<td>6 weeks</td>
</tr>
</tbody>
</table>

U/S Dating in Normal Pregnancy

\[
\text{Mean Sac Diameter (mm) + 30} \quad \text{OR} \quad \text{Crown-Rump Length (mm) + 42}
\]

Clinical Presentation of EPL

- Bleeding
- Pain/cramping
- Falling or abnormally rising ßhCG
- Decreased symptoms of pregnancy
- No symptoms at all
Transvaginal Ultrasound Findings of EPL

- Anembryonic Pregnancy
  - No fetal pole with mean sac diam ≥ 25 mm
  - Absence of embryo with heartbeat ≥ 2 wks after scan that showed a gestational sac without a yolk sac
  - Absence of embryo with heartbeat ≥ 11 days after a scan that showed a gestational sac with a yolk sac

- Embryonic Demise
  - No cardiac activity with CRL ≥ 5 mm
  - ≥ 7 mm for 100% specificity


Samantha
26 yo G2P1, CRL of 7mm but no cardiac activity
Samantha and her partner request information on all the treatment options. You confirm the rest of her history.
PMH: wisdom teeth removed
Ob Hx: term SVD without complication
All: NKDA

Management Options

**Do Nothing:** Expectant management

**Do Something:** Medical management

**Do Surgery:** Management with D&C

Sotiriadis A, Obstet Gynecol 2005
Nanda K, Cochrane Database Syst Rev 2006

Patient Satisfaction

Management of Early Pregnancy Loss

- Meta-analysis: studies report high satisfaction with medical management
- **Caution:** Few studies looked at satisfaction

- Satisfaction depended on choice:
  - If women randomized 55-74% satisfied
  - If women chose 84-88% satisfied
  - Both were independent of method

Sotiriadis 2005
Samantha
26 yo G2P1, CRL of 7mm but no cardiac activity

Samantha is uninterested in waiting for spontaneous passage, and chooses medical management of her early pregnancy loss.

<table>
<thead>
<tr>
<th>Do Something</th>
<th>Medical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Management</td>
<td>Requirement for Therapy</td>
</tr>
<tr>
<td>• Misoprostol</td>
<td>• ≤13 weeks gestation</td>
</tr>
<tr>
<td>• Misoprostol + Mifepristone</td>
<td>• Stable vital signs</td>
</tr>
<tr>
<td>• Misoprostol + Methotrexate</td>
<td>• No evidence of infection</td>
</tr>
<tr>
<td></td>
<td>• No allergies to medications used</td>
</tr>
<tr>
<td></td>
<td>• Adequate counseling and patient acceptance of side effects</td>
</tr>
</tbody>
</table>

No medical regimen for management of EPL is FDA approved

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Table 6. Adverse Events and Acceptability of Medical and Surgical Treatment of Early Pregnancy Loss.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Misoprostol</th>
<th>Misoprostol + Mifepristone</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage requiring hospitalization with or without blood transfusion — % (no., total no.)</td>
<td>1 (1/148)</td>
<td>1 (1/148)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hospitalization for endometritis — % (no., total no.)</td>
<td>≤1 (2/148)</td>
<td>0 (0/148)</td>
<td>1.0</td>
</tr>
<tr>
<td>Fever (temperature &gt;38°C [100.4°F]) — % (no., total no.)</td>
<td>3 (3/147)</td>
<td>4 (4/147)</td>
<td>0.41</td>
</tr>
<tr>
<td>Emergency visit in hospital within 24 hours after treatment — % (no., total no.)</td>
<td>3 (3/148)</td>
<td>2 (2/148)</td>
<td>0.39</td>
</tr>
<tr>
<td>Unscheduled hospital visits — % (no., total no. of patients)</td>
<td>28 (28/144)</td>
<td>17 (17/148)</td>
<td>0.08</td>
</tr>
<tr>
<td>Change in hemoglobin between day 1 and day 11 (g/dl)</td>
<td>-0.6 (0.16,-1.0)</td>
<td>-0.16 (0.16,-0.80)</td>
<td>0.081</td>
</tr>
<tr>
<td>Decrease in hemoglobin ≥2 g/dl — % (no., total no.)</td>
<td>9 (9/102)</td>
<td>4 (4/101)</td>
<td>0.03</td>
</tr>
<tr>
<td>Increase in hemoglobin ≥2 g/dl — % (no., total no.)</td>
<td>5 (5/102)</td>
<td>3 (3/101)</td>
<td>0.04</td>
</tr>
<tr>
<td>Nausea — % (no., total no.)</td>
<td>53 (53/102)</td>
<td>20 (20/101)</td>
<td>0.001</td>
</tr>
<tr>
<td>Vomiting — % (no., total no.)</td>
<td>20 (20/102)</td>
<td>7 (7/101)</td>
<td>0.021</td>
</tr>
<tr>
<td>Diarrhea — % (no., total no.)</td>
<td>24 (24/102)</td>
<td>10 (10/101)</td>
<td>0.001</td>
</tr>
<tr>
<td>Abdominal pain — % (no., total no.)</td>
<td>99 (99/102)</td>
<td>95 (95/101)</td>
<td>0.001</td>
</tr>
<tr>
<td>Pain severity score</td>
<td>5.7 ± 2.4</td>
<td>5.3 ± 2.4</td>
<td>0.018</td>
</tr>
<tr>
<td>Acceptability — % (no., total no.)</td>
<td>83 (83/102)</td>
<td>83 (83/101)</td>
<td>0.95</td>
</tr>
<tr>
<td>Would probably or absolutely recommend this procedure</td>
<td>88 (88/102)</td>
<td>83 (83/101)</td>
<td>0.14</td>
</tr>
<tr>
<td>Would probably or absolutely use this treatment again</td>
<td>78 (78/102)</td>
<td>75 (75/101)</td>
<td>0.34</td>
</tr>
</tbody>
</table>
**Misoprostol**

- Prostaglandin E1 analogue
- FDA approved for prevention of gastric ulcers
- Used off-label for many Ob/Gyn indications:
  - Labor induction
  - Cervical ripening
  - Medical abortion (with mifepristone)
  - Prevention/treatment of postpartum hemorrhage
- Can be administered by oral, buccal, sublingual, vaginal and rectal routes

*Chen B, Clin Obstet Gynecol 2007*

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**Why Misoprostol?**

- Do something while still avoiding surgery
- Cost effective
- Stable at room temperature
- Readily available

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**Misoprostol Dosing Regimens**

*Embyronic Demise & Anembryonic Pregnancy*

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creinin</td>
<td>400 mcg po vs 800 pv</td>
<td>25% vs. 88%</td>
</tr>
<tr>
<td>Ngoc</td>
<td>800 mcg po vs 800 pv</td>
<td>89% vs. 93% (NS)</td>
</tr>
<tr>
<td>Tang</td>
<td>600 mcg SL vs 600 pv</td>
<td>87.5%</td>
</tr>
<tr>
<td>Phupong</td>
<td>600 mcg po x 1 vs. q 4 hrs x 2 doses (SL had more side effects—diarrhea, 70% vs 27.5%)</td>
<td>82% vs 92% (NS)</td>
</tr>
<tr>
<td>Gilles</td>
<td>800 mcg pv saline-moistened vs. dry</td>
<td>83% vs 87% (NS)</td>
</tr>
</tbody>
</table>


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**Pooled Outcomes**

*Medical Management*

<table>
<thead>
<tr>
<th>Success Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
</tr>
<tr>
<td>Single dose misoprostol 400-800 mcg</td>
</tr>
<tr>
<td>Repeat dose x 1 if incomplete at 24 hours</td>
</tr>
</tbody>
</table>

16–60%
25–88%
80–88%

Success rate depends on type of miscarriage

- 100% with incomplete abortion
- 87% for all others

Serum Level Comparison
Misoprostol by Route of Administration

Side Effects and Complications
Misoprostol vs. Placebo

N/V, Diarrhea: Increased with misoprostol

Pain: More pain and analgesics in one study

Hemoglobin Conc: No difference

Infection: No statistical difference placebo vs. misoprostol

- No benefit with repeat dosing within 3–4 hours
- Improved outcome with 1 repeat dose at 24 hours, if incomplete
- 90% found medical management acceptable and would elect same treatment again


Misoprostol Bottom Line
Medical Management

- 800 mcg vaginal or buccal
- Repeat x 1 at 12–24 hours, if incomplete
  - Occasionally repeat more than once for successful completion

Give pain medications
- High dose NSAIDS
- Small number Narcotics

Anti-emetics as needed

Follow Up in 1-2 weeks after treatment

Mifepristone and Misoprostol
Medical Management

- **Mifepristone**: Progestin antagonist that binds to progestin receptor
  - Used with elective medical abortion to “destabilize” implantation site
  - Current evidence-based regimen: 200 mg mifepristone + 800 mcg misoprostol

- Success rates for mifepristone & misoprostol in EPL:
  - 52–84% (observational trials, non-standard dose)
  - 90–93% (standard dose)

- No direct comparison between misoprostol alone and mifepristone/misoprostol with standard dosing

- Mifepristone probably helps, use if you can easily

Methotrexate and Misoprostol
Medical Management

- **Methotrexate**
  - Folic acid antagonist
  - Cytotoxic to trophoblast
- Used in medical management for ectopic pregnancy
- Introduced in 1993 in combination with misoprostol to treat elective abortion medically
  - Success rates up to 98% (misoprostol administered 7 days after methotrexate)
- No data for use in early pregnancy loss

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**Samantha**
26 yo G2P1, CRL of 7mm but no cardiac activity

Samantha returns to the office 7 days after treatment with mifepristone and misoprostol for follow up.

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How do you BEST assess whether or not her treatment is complete?

1. Repeat ultrasound
2. Serial serum beta-HCG tests
3. Urine pregnancy test
4. History and physical

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How do you determine successful completion?
Definitions Used in Studies

- ≤15 mm endometrial thickness (ET)
- 3 days to 6 weeks after diagnosis
- No vaginal bleeding
- Negative urine hCG
Problems with ET Cut-off

- No clear rationale for this cut-off
- Study of 80 women with successful medical abortion
  - Mean ET at 24 hours 17.5 mm (7.6–29 mm)
  - At one week 15% with ET >16 mm
- Study of medical management after EPL
  - 86% success rate if use absence of gestational sac
  - 51% success rate if use ET ≤15 mm

Other problems with follow-up modalities:

- Vaginal bleeding and positive urine pregnancy test are possible for 2–4 weeks
- Poor measures of success at a 1-2 week follow-up visit
- Serial serum HCG tests —
  - Can check 2 to ascertain falling values then stop
  - Don’t need to follow to zero
- Bottom line:
  - Use ultrasound if available
  - If ultrasound not viable option, can check urine pregnancy test
  - If UPT positive, can check serum HCG and repeat ONCE if still elevated.

When to intervene after medical management?

- Continued gestational sac
- Stable/rising/inappropriately falling HCG
- Clinical symptoms
- Patient preference
- Time (?)

Samantha

26 yo G2P1, CRL of 7mm but no cardiac activity

At her follow-up appointment, Samantha says that she had a period of heavy bleeding and is now spotting. Her cramping has resolved. She has noted a marked decrease in breast tenderness and nausea.

Her ultrasound shows a uniform endometrial stripe measuring 30mm in its greatest width.
Samantha
26 y/o G2P1, CRL of 7mm but no cardiac activity

Is Samantha’s pregnancy loss complete?
1. Yes
2. No

Future Risk of Early Pregnancy Loss

<table>
<thead>
<tr>
<th>Outcome</th>
<th>1 SAb</th>
<th>2 SAb</th>
<th>3 SAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>20%</td>
<td>28%</td>
<td>43%</td>
</tr>
</tbody>
</table>

Post EPL Care

- Rhogam at time of diagnosis or treatment
- Pelvic rest for 2 weeks
- No evidence for delaying conception
- Initiate contraception upon verification of completion
- Expect light-moderate bleeding for 2 weeks
- Menses return after 6 weeks
- Negative βhCG values after 2–4 weeks
- Appropriate grief counseling

Grimes D, Cochrane Database Syst Rev 2000
When Women Should Contact Clinician

- Heavy bleeding with dizziness, lightheadedness
- Worsening pain not relieved with medication
- Flu-like symptoms lasting >24 hours
- Fever or chills
- Syncope
- Any questions

For more Information on EPL

- TEAMM website: [www.miscarriagemanagement.org](http://www.miscarriagemanagement.org)
- UCSF website: [www.earlypregnancylossresources.org](http://www.earlypregnancylossresources.org)
- Ipas WomanCare Kit for Miscarriage Management [www.ipaswomancare.com](http://www.ipaswomancare.com)
- Papaya Workshop Videos: [www.papayaworkshop.org](http://www.papayaworkshop.org)

Thanks!

Questions

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