Fetal Loss Update
Fetal Loss

- With the Letter of Amendment, fetal loss is NOT considered an adverse event
  - “Chemical pregnancy”
  - 7 week spontaneous loss
  - 22 week spontaneous loss
  - 34 week stillbirth
- The loss of the pregnancy is NOT an adverse event. Symptoms associated with that loss may be.
Fetal Loss

- Maternal complications or side effects associated with fetal loss that would otherwise be reported as an adverse event are considered adverse events.
Is This an Adverse Event?

- 1st step: take out the fetal loss from consideration
- Would the symptoms or signs that are left be considered an adverse event if the status of the pregnancy hadn’t changed or the woman was not pregnant?
  - N0-> no adverse event
  - YES-> adverse event
Female Genital Grading Table

- Some Pregnancy related AEs are listed on the last two pages of the Female Tox Table
- Examples:
  - Chorioamnionitis
  - Preterm rupture of membranes
  - Preterm contractions
Two Confusing Situations

- When is pain (contraction) an adverse event?
  - What do we call it?

- When is bleeding an adverse event?
  - What do we call it?
Pregnancy Related Pain

- Pain (with the exception of term contractions) is an adverse event
  - Cramping at 8 weeks gestation
    - AE
  - Preterm contractions at 25 weeks
    - AE
  - Contractions at 38 weeks
    - NO AE!!!!!!!!!!
What To Call This?????

- 20 weeks is traditionally the cut off between a “spontaneous abortion” and “preterm labor”
  - “Labor” is delivery of the baby after 20 weeks

- Uterine cramping or contractions
  - “Pelvic Pain” if < 20 weeks
  - Contractions if >20 week

- Preterm Uterine Contractions are graded as follows

<table>
<thead>
<tr>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Preterm contractions which resolve without medical intervention</td>
<td>Preterm contractions with cervical change which result in medical intervention but not resulting in preterm delivery</td>
<td>Delivery at 33-36 weeks’ gestation or 1501-2500 grams birth weight</td>
<td>Delivery &lt; 33 weeks’ gestation or ≤ 1500 grams birth weight</td>
</tr>
</tbody>
</table>
Pregnancy Related Bleeding

- Bleeding prior to labor is an adverse event
  - Bleeding prior to the onset of labor is unexpected and an adverse event
  - Normal bleeding during labor is expected and not an adverse event
- Per LOA#1 Bleeding in pregnancy prior to labor:

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>GRADE 0 NORMAL</th>
<th>GRADE 1 MILD</th>
<th>GRADE 2 MODERATE</th>
<th>GRADE 3 SEVERE</th>
<th>GRADE 4 POTENTIALLY LIFE-THREATENING</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMPLICATIONS OF PREGNANCY</td>
<td>Bleeding during pregnancy prior to the onset of labor</td>
<td>None</td>
<td>Spotting or bleeding less than menses</td>
<td>Bleeding like menses or heavier, no intervention indicated</td>
<td>Profuse bleeding with dizziness or orthostatic hypotension, transfusion indicated</td>
</tr>
</tbody>
</table>
Excessive Bleeding

- Excessive bleeding during labor and delivery is an adverse event
- It is graded using the post partum hemorrhage row in the tox table

<table>
<thead>
<tr>
<th>Postpartum hemorrhage</th>
<th>Grade 0</th>
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<th>Grade 4</th>
</tr>
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<tbody>
<tr>
<td>EBL &lt; 500 cc for vaginal delivery or &lt; 1000 cc after CS or reported as normal</td>
<td>EBL 500-1000 for vaginal delivery or 1000-1500 for CS or reported as slightly increased</td>
<td>EBL &gt; 1000 for vaginal delivery or &gt; 1500 for CS, with or without mild dizziness, no transfusion required</td>
<td>Hemorrhage at a level for which transfusion of 1-2 units of packed cells, but no other blood products indicated</td>
<td>Hemorrhage with shock or coagulopathy, for which transfusion of &gt; 2 units of packed cells or any amount of other blood components is indicated</td>
<td></td>
</tr>
</tbody>
</table>
What To Call it?????

- 20 weeks is traditionally the cut off between a “spontaneous abortion” and “preterm labor”
  - Labor is delivery of the baby after 20 weeks

- For bleeding
  - **Bleeding prior to labor** is an AE
    - Bleeding at 7 weeks, ultimately delivers at term
    - Bleeding at 7 weeks associated with a spontaneous abortion at 7 weeks
    - Bleeding at 22 weeks, ultimately delivers at term
    - Bleeding at 36 weeks, ultimately delivers at 39 weeks
  
  - **Bleeding associated with labor** is not an AE
    - Bleeding at 40 weeks associated with delivery
    - Bleeding at 25 weeks associated with delivery*
    - Bleeding at 21 weeks associated with delivery*

*the adverse nature of this occurrence is captured elsewhere
Some Examples

- Positive pregnancy test at Month 5, negative pregnancy test at Month 6. No bleeding or cramping
  - No AEs
Some Examples

- Pregnant participant at 7 weeks experiences bleeding and cramping but goes on to deliver at term
  - AE for bleeding (not expected)
    - “Bleeding during pregnancy prior to the onset of labor”
  - AE for pelvic pain
    - “Pelvic Pain”
Some Examples

- Spontaneous miscarriage at 7 weeks associated with bleeding and cramping
  - AE for bleeding (not expected)
    - “Bleeding during pregnancy prior to the onset of labor”
  - AE for pelvic pain
    - “Pelvic pain”
Some Examples

- Pregnant participant at 21 weeks experiences bleeding and cramping but goes on to delivery full term
  - AE for bleeding (not expected)
    - “Bleeding during pregnancy prior to the onset of labor”
  - AE for preterm contractions (per tox table)
    - Grade based on the fact that she didn’t deliver
    - Not “pelvic pain” because >20 weeks
Some Examples

- Spontaneous miscarriage at 21 weeks associated with bleeding and cramping
  - Bleeding is part of labor therefore not an AE
    - >20 weeks gestation = labor
  - AE for preterm contractions (per tox table)
    - Delivery after 20 weeks = preterm delivery
# Female Genital Grading Table

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Some Examples

- 28 week delivery of live infant-contractions and normal bleeding
  - AE for preterm contractions

- 28 week delivery of still born baby-contractions and normal bleeding
  - AE for preterm contractions
Some Examples

- Term delivery of live infant associated with contractions and normal bleeding
  - No AEs

- Term delivery of still born baby associated with contractions and normal bleeding
  - No AEs
Some Examples

- Vaginal delivery of term infant complicated by hemorrhage
  - Postpartum hemorrhage= AE

- Vaginal delivery of term still born complicated by hemorrhage
  - Postpartum hemorrhage= AE
Some Examples

- Vaginal delivery of live preterm infant complicated by post partum endometritis
  - Preterm contractions= AE
  - Post partum endometritis= AE

- Vaginal delivery of still born preterm infant complicated by post partum endometritis
  - Preterm contractions= AE
  - Post partum endometritis= AE
Some Examples

- Miscarriage at 7 weeks associated with bleeding, cramping, and infection
  - Bleeding during pregnancy (not expected) = AE
  - Pelvic pain = AE
  - Post abortal endometritis = AE
Questions?