Managing Side Effects and Complications Related to “LARCs”

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Conflict of Interest Disclosure
Anita L. Nelson, MD

<table>
<thead>
<tr>
<th>Grants/Research</th>
<th>Bayer, Merck, Pfizer, Teva</th>
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<tr>
<td>Honoraria/Speakers Bureau</td>
<td>Bayer, Merck, Teva</td>
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<td>Consultant/Advisory Board</td>
<td>Agile, Bayer, Merck, Teva, Watson</td>
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Learning Objectives
At the conclusion of this presentation, the participant will be able to:

- Recognize and treat complications with IUD and implant use
- Counsel women about important side effects and provide treatment

IUD Placement Complications
- Anxious patient
- Stenotic OS
- Extremely verted uterus
- Perforation with sound
- IUD opens too early
- Perforation with IUD
- Vasovagal reaction
- Bleeding from tenaculum site

Anxious Patient
- More apt to experience pain
  - Verbicaine helpful
  - Explain steps to patient
  - Consider premedication, after consent obtained
    - If patient has ride home

Stenotic Os
- Dilate – do not force!
- Pulsating technique at internal os
- Cervical Os finders
- Paracervical block
- Await menses
- ? Misoprostol?
Cervical Stenosis: Coping Strategies

- Stabilize cervix with tenaculum
  - Inject ½ cc local anesthetic agent
- Dilate cervix progressively
  - Lacrimal probes
  - Cervical os finders

Vaginal Misoprostol Prior to IUD Placement

- Double blind, multi-center, randomized, placebo controlled trial
- 400mg misoprostol vs. placebo 3 hours prior to procedure

<table>
<thead>
<tr>
<th></th>
<th>Misoprostol</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failed placement</td>
<td>1.9%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Insertion-related complications</td>
<td>21.8%</td>
<td>19.1%</td>
</tr>
</tbody>
</table>

Side effects statistically higher with misoprostol group with no difference in pain scores.

What Do You Mean “Uterine Depth”??

- Technically: distance between external OS and the fundus
- What if uterine depth is 10 cm, but cervix is 4 cm?
- What if uterine depth is 9 cm, but cervix is 2 cm?

Uterine Challenges; Extremely Verted Uterus

- **Goal**: Place tenaculum on lip that is facing away from introducer to straighten uterine axis
- **Tip**: May need to grasp closer lip first to visualize other lip
- **Real challenge**: Cervix behind symphysis
- **Tip**: Ask patient to push down firmly over bladder (anteverted uterus) or you press forward on upper uterus (retroverted uterus)
**Uterus Challenges: Extremely Verted Uterus**

- Use flexible sound if possible
  - Uterine aspirator
  - Bend metal sound to direction of flexion
  - Bend IUD tubing to conform to direction if possible
  - May flip introducer over for retroverted uterus

**Uterine Challenges: Leiomyomata**

- Fibroids in lower uterine segment can obstruct entry into uterine cavity
  - Possible work around: Place under real time ultrasound imaging
- Fibroids at the fundus can block space for IUD arms
  - Possible tools to evaluate prior to placement:
    - Ultrasound ± saline infusion sonography
    - 3D ultrasound
    - Uterine sound pivoted side to side at fundus
  - **NOTE:** Large submucosal fibroids may bleed more with IUD erosion

**Other IUD Placement Challenges**

- Obese patient – unable to assess uterus on bimanual exam
- Allergy to iodine
- Greater than 5 minute delay after IUD arms folded
- Contaminated IUD

**Vasovagal Reaction**

- Identify at-risk patients
- Try to anticipate and prevent
  - Avoid empty stomach
  - Paracervical block
    - Wait full 5 minutes after injections to enter cervix
    - Encourage flexing arms under tension
- If patient feels prodrome
  - Stop procedure immediately
  - Suggest forceful flexing of legs
  - **NOTE:** Prior treatments (ammonium capsules, alcohol swabs) no longer allowed due to effects on asthma

**Seizures**

- Good reason for always having helper in room during procedure
- Stop procedure immediately – protect site as best as possible
- Call for crash cart and team
- Provide maneuvers to protect tongue, if grand mal seizure
- Assess ABCs, record vitals
- Proceed with usual resuscitation, administering anticonvulsives if needed to break seizure
Nelson: Managing Side Effects and Complications Related to “LARCs”

**IUD Placement Complication: Factors Affecting The Risk Of Uterine Perforation**

- The size, shape and consistency of device.
- The status and configuration of the uterus.
- The technique of placement.
- The skill and experience of the inserter.


**Uterine Perforation LNG-IUS**

- Netherlands, New Zealand, Switzerland and Germany 1990’s – 2007
- 701 cases reported to authorities
- 8.5% detected at time of placement
- Abdominal pain and routine check-ups were most common events leading to detection of perforation
- Change in bleeding patterns was also cardinal sign


**Timing Of Placement And IUD Expulsion**

- Abdominal pain and routine check-ups were most common events leading to detection of perforation
- Change in bleeding patterns was also cardinal sign


**Menstrual Blood Loss**

<table>
<thead>
<tr>
<th>Method</th>
<th>% of Control</th>
<th>ML</th>
</tr>
</thead>
<tbody>
<tr>
<td>No method</td>
<td>100</td>
<td>36.7</td>
</tr>
<tr>
<td>Cu 7</td>
<td>135</td>
<td>47.8</td>
</tr>
<tr>
<td>Lippes Loop</td>
<td>212</td>
<td>78.0</td>
</tr>
<tr>
<td>Oral Contraceptives</td>
<td>55</td>
<td>20.1</td>
</tr>
<tr>
<td>Progestasert</td>
<td>100</td>
<td>35.0</td>
</tr>
</tbody>
</table>

- Control with NSAIDs starting at beginning of cycle


**Management of Heavy Bleeding or Cramping**

- Rule out pregnancy
- Examine to rule out partial expulsion
  - Remove if expelling
- Rule out anemia, offer iron if needed
- Recommend NSAIDs to start with menses
- Consider misplacement
  - 3D transvaginal ultrasound can visualize


**Dimensional Incompatibility:** TCu 200 IUDs (A) in a hysterectomy specimen (B) in vivo. The X-ray does not show the uterus and its cavity (B).

The IUD in vivo (B) caused recurrent painful cramps starting on the left side of the pelvis mainly during the premenstrual and menstrual phases of the cycles. It was replaced by a smaller IUD. The painful cramps disappeared.
Treatments for Bleeding Problems with Copper IUDs

- Metaanalysis: 17 articles from 1470
- Intermenstrual bleeding or spotting
  - 2 studies of poor quality
  - Antifibrinolytic agents/NSAIDs might help


Treatments for Bleeding Problems with Copper IUDs

- Heavy or prolonged bleeding
  - 10 studies fair to poor quality
  - NSAIDs may significantly reduce loss or duration
  - Antifibrinolytics or antidiuretics may reduce loss
  - High dose aspirin increased loss
- New users
  - Antifibrinolytics or NSAIDs may prevent early bleeding.


Side Effects CuT 380A IUD During Menses – 12 Months

<table>
<thead>
<tr>
<th>Level of pain vs. before IUD</th>
<th>0-9 wk</th>
<th>9-19 wk</th>
<th>19-39 wk</th>
<th>&gt; 39 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less</td>
<td>25.3</td>
<td>29.3</td>
<td>27.1</td>
<td>27.7</td>
</tr>
<tr>
<td>Same</td>
<td>36.4</td>
<td>40.1</td>
<td>40.3</td>
<td></td>
</tr>
<tr>
<td>More</td>
<td>38.3</td>
<td>30.6</td>
<td>32.6</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Amount of blood lost vs. before IUD</th>
<th>0-9 wk</th>
<th>9-19 wk</th>
<th>19-39 wk</th>
<th>&gt; 39 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less</td>
<td>11.5</td>
<td>13.1</td>
<td>11.9</td>
<td></td>
</tr>
<tr>
<td>Same</td>
<td>29.4</td>
<td>33.0</td>
<td>30.6</td>
<td></td>
</tr>
<tr>
<td>More</td>
<td>56.3</td>
<td>53.9</td>
<td>48.5</td>
<td></td>
</tr>
</tbody>
</table>


Management Options For Asymptomatic Women with Pap Smears Reporting “Actinomycosis-like organisms”

- Do nothing except to advise women of results and give PID precautions
- Test woman for actinomycosis and treat only positives and do TOC
- Treat all affected women, repeat Pap tests for TOC
- Remove IUD, retest, and insert new IUD after clearance documented

IUD Management Issues: Change in Length of String
- If string is elongated, IUD no longer in contact with fundus
  - Consider ultrasound localization
  - If IUD is anywhere in cavity (not cervix) and woman is not symptomatic, okay to leave in place
- If string is shorter, concern about perforation, twisting, expulsion

Management of Missing Strings: Nonpregnant
- Vaginal exam.
- Endocervical exam with Q-tip, cytobrush, uterine sound, and/or endocervical speculum.
  - If strings tucked into canal but IUD not in canal, gently straighten strings into vagina.
  - If IUD also in canal, remove and replace IUD.

Missing String IUDS Removal
- Do not use IUD hooks except for Lippes Loop IUDs
  - Increase uterine perforation
  - Preprocedure ultrasound can localize, identify embedment, perforation
- With or without ultrasound guidance
  - Use tenaculum, alligator forceps
  - Open, close, tug with forceps
  - Withdraw forceps once something grasped
  - Use rocking motion if some resistance felt

IUDs Move
- IUDs that appear displaced at placement
  - Majority spontaneously move to fundus by 3 months
  - Expulsion rates higher, but still minority of IUDs
- Conclusions:
  - No need to do routine ultrasound imaging at placement to demonstrate "correct" placement (assessment is clinical)
  - No need to remove IUD found to be less than 10th percentile from fundus on ultrasound
  - Note: Endometrial thickness varies with cycle; Estimates of "correct" placement vary.

Management of Pregnancy with IUD: Strings Visible
- First trimester:
  - Advise removal of IUD.
  - Risk of later pregnancy loss about twice as great and certainly more serious if IUD retained.
Management of Pregnancy with IUD: Strings Visible

- Second trimester and later:
  - Perform ultrasound to rule out placenta previa before manipulating IUD
  - Be prepared for extensive blood loss with IUD removed
  - No demonstrated benefits of removal, but need to be alert for early signs of chorioamnionitis if stays in place
  - The only solid indication for removal late in pregnancy is symptomatic partial expulsion (IUD in cervical canal in women with contractions)

Management of Pregnancy with IUD: Missing Strings

- Ultrasound as early in pregnancy as possible to document presence and location
- If IUD is present:
  - Counsel patient about risk of preterm labor
  - Advise her to report any flu-like symptoms (possible septic abortion or chorioamnionitis)
  - Reassure about lack of associated birth defects
  - Plan to remove IUD at delivery

Management of Embedded IUD: Endometrial or Cervical Site

- May attempt gentle traction, rotation, dislodgment maneuvers
- If not successful, traction during sonography or hysteroscopy appropriate

COX-2 Inhibitor for DMPA Related Irregular Bleeding

- 46 subjects, 3-12 months DMPA
- Valdecoxib 20 mg tablet, 2 tabs daily for 5 days

<table>
<thead>
<tr>
<th></th>
<th>Valdecoxib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>% stopped in 7 days</td>
<td>77.3%</td>
<td>33.3%</td>
</tr>
<tr>
<td>Mean # bleeding free days in next 28 days</td>
<td>17.8%</td>
<td>11.5%</td>
</tr>
</tbody>
</table>

Why COX-2 Inhibitor Might Stop Bleeding

- Prostanoids
  - Thromboxane A2 (TXA₂)
    - Synthesized in platelets
    - Promotes vasoconstriction and platelet aggregation
  - Prostacyclin (PGL₂)
    - From vascular endothelial cells
    - Promotes vasodilation, inhibits platelet aggregation
  - COX-2: main enzyme for production of PGI₂

Medical Intervention Prolonged or Frequent Bleeding DMPA: Survey

- Early reinjection
- MPA 5 mg Q d x 14 days (obese)
  - If successful, early reinject
- Estrogen therapies
  1. Continue oral contraceptives 14-21 days
  2. Ethinyl estradiol 50 mcg daily 7-21 days
  3. CEE 1.25-5 mg daily 7-21 days

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WHO Trials of Estrogen Therapies Prolonged Bleeding with DMPA
- 278 women bled > 7 days in first 6 months DMPA given 14 day therapies

<table>
<thead>
<tr>
<th>n</th>
<th>% stopped</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mcg EE</td>
<td>90</td>
</tr>
<tr>
<td>2.5 mg Estrone-S</td>
<td>91</td>
</tr>
<tr>
<td>Placebo</td>
<td>97</td>
</tr>
</tbody>
</table>

EE shortened by 1 day bleeding + 3 days spotting


Possible Treatments for Unscheduled DMPA Bleeding
- Estradiol vaginal ring for first 3 months of DMPA
- Reduced unscheduled bleeding
- Increased continuation rates
- Transitioning from COCs to DMPA
- Reduced bleeding in first 6 months
- 14 day treatment with 50 mcg EE or 2.5 mg ES
- Reduced bleeding in 93% and 78% of cases
- Placebo reduced by 74%
- No long term difference in bleeding or continuation rates

Structured Counseling Lowers Discontinuation Due to Bleeding
- More detailed counseling regarding side effects lowers the discontinuation rate due to irregular bleeding

<table>
<thead>
<tr>
<th>Discontinuation Women [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structured Counseling</td>
</tr>
<tr>
<td>Canto de Cetina, 2001</td>
</tr>
<tr>
<td>Lei, 1996</td>
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Structured Counseling
Routine Counseling
P value

Why Progestin Bleeding with Continuous Progestin?
- Endometrium with:
  - Increased and disorder microvessels (structurally compromised)
  - Decreased stromal and glandular support
  - Reduced epithelial integrity
  - Altered endometrial matrix metalloproteinase (MMP) activity predisposes to:
    - Irregular vessel breakdown and bleeding
    - Vascular fragility


Bleeding Patterns on ENG Implant:
- Women with normal bleeding in first 3 cycles generally do not later discontinue due to bleeding irregularities although bleeding may increase over time
- 50% of women with unfavorable patterns in first 3 cycles will improve with time
- Dysmenorrhea decreased
- 77% complete resolution

NSAIDs for Irregular Implanon Bleeding

- 50 women randomized placebo-controlled study
- Mefenamic acid 500 mg PO TID x 5 days

<table>
<thead>
<tr>
<th></th>
<th>Mefenamic acid</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>% bleeding stopped in 7 days</td>
<td>65.2%</td>
<td>21.7%</td>
</tr>
<tr>
<td>No bleeding &gt; 20 day/28 day</td>
<td>56.5%</td>
<td>21.7%</td>
</tr>
<tr>
<td>Mean # B+S day</td>
<td>10.5</td>
<td>16.8</td>
</tr>
</tbody>
</table>


How Does Anti-Progestin Help?

- Dose dependent effect:
  - 100-200 mg x 2 days – worked but pregnancy risk?
  - 50 mg shortens duration without pregnancy
  - In Morse model mifepristone highly effective
    - Extremely rapid endometrial repair in presence of implanon-like device
    - Estrogen added to maximize the efficacy of estrogen in stimulating endometrial epithelial repair by up regulating estrogen receptors


Tetracyclines: Mechanism of Action

- Inhibit MMPs in dose dependent manner
- Many mechanisms
- Doxycycline:
  - MMP releases
  - Tissue breakdown
- In mouse model – doxycycline not effective in endometrial repair in presence of etonogestrel
- Conclusion:
  - Blocking some MMPs may not be sufficient to prevent or reduce endometrial breakdown and bleeding


Implanon Frequent/Prolonged Bleeding Pilot Study

<table>
<thead>
<tr>
<th>3 Treatments vs. placebo ≥ 3 Months Bleeding</th>
<th>Mean Days to Bleeding Cessation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>Mifepristone 25 mg BID x 1</td>
<td>5.9澄清</td>
</tr>
<tr>
<td>Mifepristone 25 mg BID x 1 + 20 mcg EE x 4d</td>
<td>4.3澄清</td>
</tr>
<tr>
<td>Doxycycline 100 mg BID x 5d</td>
<td>4.8澄清</td>
</tr>
<tr>
<td>Placebo</td>
<td>7.5澄清</td>
</tr>
</tbody>
</table>


Implanon Frequent/Prolonged Bleeding Larger Study (204 Women)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mifepristone 25 mg BID x 1 + doxycycline mg BID x 5d</td>
<td>4.0澄清</td>
</tr>
<tr>
<td>Mifepristone 25 mg BID x 1 + EE 20 mcg x Q x 4d</td>
<td>4.4澄清</td>
</tr>
<tr>
<td>Doxycycline 100 mg BID x 5d</td>
<td>6.4澄清</td>
</tr>
<tr>
<td>Doxycycline 100 mg BID x 5d + EE 20 mcg QD x 5d</td>
<td>6.4澄清</td>
</tr>
<tr>
<td>Placebo BID</td>
<td>6.4澄清</td>
</tr>
</tbody>
</table>

Recommendations for Stopping Unscheduled Bleeding with Implanon

- COC taken cyclically for up to 3 months
- MPA 10mg BID or NETA 5mg BID X 21 days
- POP (desogestrel) for 3 months
- NSAIDs, (esp. Cox-2 inhibitors) for 5-10 days
- Transexamic acid 500mg BTD for 5 days

Prophylaxis to Prevent Early Bleeding with Implanon

- 129 women, 12 week therapies
- Started on day of placement
- Treatment arms
  - Naproxen 500 mg BID x 5 day Q 4 weeks x 3 months
  - Estradiol patch 0.1 mg weekly x 3 months
  - Placebo
- Bleeding diaries
- Median # days B + S

<table>
<thead>
<tr>
<th></th>
<th>Naproxen</th>
<th>E₂</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean # days B + S</td>
<td>27.5</td>
<td>44</td>
<td>32</td>
</tr>
</tbody>
</table>

Etonogestrel Implant: Acne

- Overall, 15% of women reported acne
- 1% had implant removed for acne
- Baseline with no acne
  - 6.1% developed occasional acne
    - 4.7% mild; 0.1% severe
- Baseline with acne
  - 59% disappeared or improved
  - 32% unaffected
  - 3% worsened
- Total testosterone levels reduced by 20%

Difficult Implant Removal Tips

- Apply lubricant to arm before exam to localize
- Try Betadine negative trick
- Reposition arm to thin area around placement scar
- Real time ultrasound-guided removal
- Identify optimal incision site
  - Closest to skin
  - Furthest away from vessels
- Use anesthesia to lift implant
- Use Norgrasp clamps
- Be patient
- Consider needle elevation/stabilization

Test Questions

1. Counselling is the most effective and first line therapy for bleeding irregularities associated with progestin-only methods.
   - True
   - False

2. NSAIDs are first medical intervention for prolonged or heavy bleeding with which of the following.
   - A. Copper T-380A IUD
   - B. LNG-IUS
   - C. ENG implant
   - D. ENG implant
   - E. B, C, D
   - F. All of the above

Correct answers: 1. True 2. F all the above