BOTHERSOME BLEEDING
Evidence based management of bleeding with contraception

OBJECTIVES
- Describe bleeding patterns expected with initiation and continuation of various contraceptive methods
- State 2 interventions to manage irregular bleeding associated with use of COCs, implant, injection, and IUD

I have no disclosures.

CONTRACEPTIVE DISSATISFACTION
- Dissatisfaction with contraceptive method
- Discontinuation of contraceptive method
- Delay in resumption of contraception or adoption of less effective method
- UNINTENDED PREGNANCY
AUDIENCE QUESTION

MATCH EACH CONTRACEPTIVE METHOD WITH ITS MOST COMMON SIDE EFFECT
(appropriate to use each response more than once)

1) COCs
2) Vaginal ring
3) Implant
4) DMPA
5) LNG-IUS

MATCH EACH CONTRACEPTIVE METHOD WITH ITS MOST COMMON SIDE EFFECT
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1) COCs
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4) DMPA
5) LNG-IUS

d) Bleeding

MECHANISM FOR ABNORMAL BLEEDING

Transition from thick to thin endometrium

Fragile and superficial blood vessels in endometrium

Unstable endometrial stroma and glands

Irregular bleeding

Altered endometrial remodeling

INTRODUCTION

Starting contraception is associated with abnormal bleeding

No evidence that unscheduled bleeding is associated with decreased contraceptive efficacy or harmful effects

Consider pregnancy and other etiologies of bleeding including polyps, fibroids, cervicitis, PID, cervical cancer

Reasons for dissatisfaction leading to pill, condom, Norplant or Depo-Provera discontinuation

CASE 1

STUBBORN SPOTTING ON COCs

COCs: SETTING EXPECTATIONS

- Rates of unscheduled bleeding
  - 10-30% in the first month
  - Less than 10% by the third month
- Rates of amenorrhea
  - Less than 2% in the first year
  - Up to 5% after 1 year

COCs: GENERAL COUNSELING

- Take pill at the same time each day
- Inconsistent pill use associated with increased risk of unscheduled bleeding
  - Inconsistent use was associated with 60-70% increased risk of spotting/bleeding in first cycle
  - Inconsistent use over time was associated with up to 600% increased risk of spotting/bleeding in subsequent cycles

COCs: GENERAL COUNSELING

- Stop smoking!
  - Smokers more likely to experience unscheduled bleeding/spotting
  - Among smokers, bleeding more likely to persist through subsequent cycles

COCs: SMOKING & SPOTTING

Figure: Proportion of oral contraceptive users with spotting or bleeding, by smoking status.

COCs: SMOKING & SPOTTING


COCs: STARTING THE PILL

- No significant difference in bleeding patterns between immediate start vs. conventional start of COCs
- Immediate start of vaginal ring was associated with less prolonged bleeding and fewer frequent bleeding episodes in comparison to immediate start of COCs

BACK TO THE CASE: STUBBORN SPOTTING

TREATING BLEEDING ON CYCLIC COCs

- **Supplemental estrogen**
  - Oral CEE 1.25mg x 7 days
  - Oral estradiol 2mg x 7 days

- **Increase dose of estrogen if woman using COC with ≤ 20mcg estrogen**
  - Several COCs containing 20 mcg ethinyl estradiol resulted in:
    - Higher rates of early trial discontinuation
    - Increased risk of bleeding disturbances

- **Switch to vaginal ring**

2. Salio, MF. Cochrane Database of Systematic Reviews, 2013.

TREATING BLEEDING ON EXTENDED COCs

- **Discontinue the COCs for 3-4 consecutive days**
  - A 3-day hormone free interval was associated with greater resolution in breakthrough bleeding/spotting in comparison to continuing active pills
  - After the first 21 days of the hormone

CONTRACEPTIVE RING

- **Overall improved cycle control**
  - Lower rate of breakthrough bleeding and spotting (6%)
  - Lower rate of estrogen-related side effects (nausea, breast tenderness) but higher rates of vaginal symptoms

Figure: Incidence of cycles with irregular bleeding with contraceptive ring or COC


BACK TO CASE 1: STUBBORN SPOTTING

**Talk Today.**

**EE DOSE**

2. Sulak PJ et al. AJOG, 2006
CASE 2

ANNOYING ABNORMAL BLEEDING WITH INJECTABLE CONTRACEPTION

CASE 2

DMPA: SETTING EXPECTATIONS

- Abnormal bleeding is common in the first year
- Rates of unscheduled bleeding:
  - Up to 70% in the first year
  - Approximately 10% after the first year
- Amenorrhea is more likely over time

<table>
<thead>
<tr>
<th></th>
<th>Within 3 months</th>
<th>After 1 year</th>
<th>At 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of amenorrhea</td>
<td>12%</td>
<td>46%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Enhanced pretreatment counseling among DMPA users shown to reduce discontinuation

<table>
<thead>
<tr>
<th>Percentage of women who discontinued DMPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structured Counseling</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Canto De Centina TE et al (2001)¹</td>
</tr>
<tr>
<td>Lei ZW et al (1996)²</td>
</tr>
</tbody>
</table>

Elements of structured counseling include:
- expected bleeding patterns
- reassurance that these irregularities are not harmful


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**NSAIDs AND DMPA**

**Valdecoxib¹**
- Dose: 40mg daily x 5d
- More women in the treatment group had cessation of bleeding (77% vs. 33%)
- Treatment group had a higher mean number of bleeding-free days in the following month (17.8 vs. 11.5 days)*

**Mefenamic acid²**
- Dose: 500mg bid x 5 d
- More women in treatment group had cessation of bleeding in the week following treatment (69% vs. 40%)
- No significant difference in bleeding-free days in the following month (16.1 in treatment grp vs. 12.4 in placebo grp)

*statistically significant


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**ESTROGENS AND DMPA**

RCT of DMPA users with unscheduled bleeding¹

- Ethinyl estradiol 50 mcg
- Estrone sulfate 2.5 mg
- Placebo

**TRANEXAMIC ACID AND INJECTABLE CONTRACEPTIVE**

RCT of DMPA users with unscheduled bleeding¹

- Tranexamic acid 250mg qid x 5 days
- Placebo

% stopped bleeding in 1st wk 88% 8.20%
% stopped bleeding in 4 wk f/u 68% 0%
Mean number of days of bleeding/spotting 5.7 17.5


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**CONCLUSIONS**

- Ethinyl estradiol effective in stopping bleeding during treatment
- Bleeding tended to recur after discontinuation of estrogen

WHAT DOES NOT WORK FOR DMPA?

- Shortening interval between DMPA injections
  - No evidence
  - Not recommended

- Doxycycline
  - Matrix metalloproteinase inhibitor
  - RCT showed doxycycline no more effective than placebo

BACK TO THE CASE: ANNOYING ABNORMAL BLEEDING

Enhanced Counseling
- Bleeding patterns
- Reassurance

Continue DMPA
- More injections, less bleeding

TREAT
- NSAIDs x 5-7 days
- Estrogen (COCs or supplemental estrogen x 10-20 days)
- Tranexamic acid

CASE 3
IRRITATING IRREGULAR BLEEDING WITH IMPLANT
ETONOGESTREL IMPLANT: SETTING EXPECTATIONS

- Most women experience a reduction of menstrual bleeding
  - 1
- Bothersome bleeding reported in 25% of patients
  - 2
  - 6.7% reported frequent bleeding
  - 17.7% prolonged bleeding
- Rates of amenorrhea
  - Approximately 20% in first year
  - 30-40% after 1 year

CONTRACEPTIVE IMPLANT: BLEEDING PATTERNS

- Number of unscheduled bleeding days:
  - Is HIGHEST in the first 3 months
  - DECREASES over the first year
  - PLATEAUS in the second and third year

CONTRACEPTIVE IMPLANT: BLEEDING PATTERNS

- More unpredictable bleeding pattern
  - 1
- Amenorrhea may not be sustained if achieved
- “Favorable” pattern in the first 3 months predicts a continued favorable pattern
- For those with an “unfavorable” bleeding pattern, 50% report improvement over time

CASE 3: IRRITATING IRREGULAR BLEEDING

- EXPECTANT MANAGEMENT for 6-12 months
  - Supplemental estrogen
  - NSAIDs
NSAIDS AND ETONOGESTREL IMPLANT

- Limited data
- Variable efficacy of NSAIDs in LNG implant\(^1,2\)
  - Various regimens
  - Small number of studies and participants
- One RCT evaluated NSAIDs in women with ETG implants\(^3\)
  - Randomized to placebo or mefenamic acid (500mg tid)
  - 65% stopped bleeding within 1 week in NSAID group vs. 21% in the placebo
  - Less bleeding in the subsequent 4 weeks in the women who had received NSAIDs

Recommendations based on studies of LNG implant

- Systematic review of estrogen vs. placebo treatment for irregular bleeding with LNG implant\(^4\)
  - Decreased the days of ongoing bleeding
  - Effect lasted for several months after treatment
  - More side effects in treatment group (nausea, GI upset)

RCT: COCs AND ETG IMPLANT

  - RCT comparing COC vs. placebo for treatment of bothersome bleeding from ETG implant
  - N = 32 women, bothersome bleeding for \(\geq 7\) days
  - Proportion of women who stopped bleeding during treatment and at the end of treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>COCP (n=16)</th>
<th>Placebo (n=16)</th>
<th>(P^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporary interruption of bleeding during therapy</td>
<td>14 (87.5)</td>
<td>6 (37.5)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>No. of days until temporary interruption of bleeding during therapy(^1)</td>
<td>5.0 (1-13)</td>
<td>9.0 (5-14)</td>
<td>.05</td>
</tr>
<tr>
<td>No. of days without bleeding during therapy</td>
<td>9.0 (1-15)</td>
<td>3.5 (1-11)</td>
<td>.06</td>
</tr>
<tr>
<td>No. of days to recurrence of bleeding after discontinuation of therapy(^2)</td>
<td>5.5 (1-131)</td>
<td>5.0 (1-57)</td>
<td>.14</td>
</tr>
</tbody>
</table>

COCP: oral contraception pill.
Data are n (%) or median (range) unless otherwise specified.
\(^1\) Patients' worst test used for categorical variables and non-parametric independent samples used for continuous variables.
\(^2\) Cases with temporary interruption of bleeding included in analysis used contraception pills for 41, placebo included in ETONOGESTREL

ESTROGEN AND LNG IMPLANT

- Recommendations based on studies of LNG implant

PRAGMATIC APPROACH

First choice
- COC taken daily x 21 with a 7-day break (up to 3 months)
- Minimal

Second choice
- Cyclic progestin – medroxyprogesterone acetate 10 mg bid x 21 days with a 7-day break (up to 3 months)
- Anecdotal

Third choice
- POP daily (up to three months)
- Anecdotal

Fourth choice
- NSAIDS, especially COX-2 inhibitors, daily for 5-10 days
- Minimal

Fifth choice
- Tranexamic acid 500 mg twice daily for 5 days
- Minimal
CASE 4
LASTING LIGHT BLEEDING WITH LEVONORGESTREL IUS

Unscheduled spotting or light bleeding is common, especially during the first 3–6 months.

For LNG 52/5, spotting was present in 25% of the users at 6 months and decreased over time.

LNG IUS: SETTING EXPECTATIONS

- 79-97% reduction in bleeding
- 33% developed oligo/amenorrhea in first 3 months, 70% at 2 yrs
- Amenorrhea at 1 yr: 20%
- Amenorrhea at 2 yrs: 30-40%

- Amenorrhea at 1 yr: 6%
- Amenorrhea at 2 yrs: 12%

LNG 13.5/3 & LNG 52/5: BLEEDING AND SPOTTING OVER TIME

A/B Mean number of bleeding or spotting days by 30-day reference period during the first year of LNG-IUS

C/D Mean number of bleeding or spotting days by 90-day reference period during the 3 years of LNG-IUS

LNG-IUS: INTERVENTIONS FOR BOTHERSOME BLEEDING

- Estrogen
  - Estradiol patch weekly x 12 weeks
  - Greater number of bleeding/spotting days compared to placebo (non-significant)
  - More dissatisfaction with treatment

- NSAIDs
  - Naproxen 500mg bid x 5 days every 4 weeks for 12 weeks
  - Fewer number of bleeding/spotting days compared to placebo (non-significant)
  - More dissatisfaction with treatment

“No direct evidence was found regarding therapeutic treatments for bleeding irregularities during LNG-IUD use.”

-US SPR, 2013

BACK TO THE CASE: LASTING LIGHT BLEEDING

- Provide excellent counseling pre-insertion
  - Discuss bleeding/spotting in first 3-6 months
  - Discuss amenorrhea

- Provide reassurance as bleeding likely to improve

- Confirm appropriate location of IUD
**SUMMARY**

**MANAGING BOTHERSOME BLEEDING ASSOCIATED WITH CONTRACEPTION**

**GENERAL GUIDANCE**
- Reinforce and encourage continuation
- If appropriate, reinforce consistent use and decrease missed doses
- If appropriate, advise tobacco cessation
- Evaluate for pregnancy, cervicitis, and pathology of cervix and uterus

**Rates of irregular bleeding**

<table>
<thead>
<tr>
<th>Contraceptive Type</th>
<th>Within 1st year</th>
<th>At 1 year</th>
<th>Beyond</th>
</tr>
</thead>
<tbody>
<tr>
<td>COCs</td>
<td>10-30%</td>
<td>&lt;10%</td>
<td>6%</td>
</tr>
<tr>
<td>Vaginal Ring</td>
<td>Similar to COCs</td>
<td>6%</td>
<td></td>
</tr>
<tr>
<td>Patch</td>
<td>Similar to COCs</td>
<td>70%</td>
<td>10%</td>
</tr>
<tr>
<td>Injectable</td>
<td>70%</td>
<td>12%</td>
<td>40%</td>
</tr>
<tr>
<td>Implant</td>
<td>70%</td>
<td>12%</td>
<td>40%</td>
</tr>
<tr>
<td>Cu-IUD</td>
<td>25%</td>
<td>12%</td>
<td>40%</td>
</tr>
<tr>
<td>LNG-IUS</td>
<td>25%</td>
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**Rates of amenorrhea**

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<th>Beyond</th>
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</thead>
<tbody>
<tr>
<td>COCs</td>
<td>&lt;2%</td>
<td>Up to 5%</td>
<td></td>
</tr>
<tr>
<td>Vaginal Ring</td>
<td>Similar to COCs</td>
<td>6%</td>
<td>12%</td>
</tr>
<tr>
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<td>Similar to COCs</td>
<td>12%</td>
<td>40%</td>
</tr>
<tr>
<td>Injectable</td>
<td>12%</td>
<td>40%</td>
<td>80%</td>
</tr>
<tr>
<td>Implant</td>
<td>21%</td>
<td>30-40%</td>
<td>0%</td>
</tr>
<tr>
<td>Cu-IUD</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>LNG-20</td>
<td>20%</td>
<td>30-40%</td>
<td>0%</td>
</tr>
<tr>
<td>LNG-14</td>
<td>6%</td>
<td>12%</td>
<td>0%</td>
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Dissatisfaction with contraceptive method → Discontinuation of contraception → Delay in resumption of contraception or adoption of less effective method → Unintended Pregnancy

- Address dissatisfaction & manage bleeding
- Continue contraception

Thank you