Contraception Update

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Conflict of Interest Disclosure
Anita L. Nelson, MD

Grants/ Research
Bayer, Merck, Pfizer, Teva

Honoraria/ Speakers Bureau
Activas, Bayer, Merck, Pfizer, Teva

Consultant/ Advisory Board
Agile, Agile, Bayer, ContraMed, Merck, Teva

Learning Objectives
At the end of this presentation, the participant will be able to:
- Identify women who are candidates for each of the methods.
- Discuss ways to counsel women on currently available methods.
- Enhance women’s success with fertility control.

Worldwide Perspective
• 1 million conceptions occur every day worldwide
  - 50% are unintended
  - 150,000 are terminated
  - 1,000 women die

Maternal Mortality: US
- Pregnancy-related mortality in US 1998-2005¹
  - Higher than any other period in prior 20 years
  - 1.5 deaths per 100,000 live births
  - African American women: 3-4 times higher rates
  - 4693 pregnancy-related deaths reported to CDC
- Another 34,000 “near misses” each year
- Healthy, nonsmoking women’s (age 15-34) has chance of dying from OC use less than 1:1 million²

Environmental Impacts

- Unwanted pregnancy pollutes the environment
- World population projection
  - 1950: 2.5 billion
  - 2011: 6.9 billion
  - 2050: 9.3 billion
  - 2100: 10.1 - 27 billion


High Typical Use Failure Rates: First Year Estimates

- Injectables: 6.7%
- Oral contraceptives: 8.7%
- Condoms: 17.4%
- Withdrawal: 18.4%
- Fertility awareness methods: 25.3%


Tiers of Contraceptive Efficacy

| Longer Term | Implants, IUDs |
| Combined Hormonal | DMPA Injections |
| | Vaginal Rings, Transdermal Patches |
| | Oral Contraceptive Pills |
| Barriers and Behaviors | Male Condoms |
| | Diaphragms, Withdrawal, FAM, NFP |
| | Caps, Female Condoms, Shield |
| | Spermicides |

New Developments

- Pill – Obesity, formulations, supplies
- DMPA – Grace period, No BMD issues
- IUDs – Quick start, lower dose LNG, teens
- Implants – New introducer
- Male condoms – More sizes needed
- Female condoms – new options coming
- EC – New option, impact of obesity
- Patches – new version pending
- Vaginal ring – new version pending
- Spermicide – new version pending

Etonogestrel Contraceptive Implant

- Single implant rod (4 cm x 2 mm) made of ethylene vinyl acetate
- Contains 68 mg of etonogestrel (3-keto-desogestrel)
- Effective for 3 years
- 6 pregnancies in 20,648 cycles in U.S. trials
- Inhibits ovulation and thickens cervical mucus
- Rapid return of fertility
ENG Implant Update

- Efficacy not diminished by obesity.1,2
- Immediate postpartum use safe and effective with no adverse effects on breastfeeding.
- Reduced teen pregnancy at 12 months (2.6% vs. 18.6%).3
- 0% pregnancy at 12 months
- < 5% frequent and prolonged bleeding
- 0 discontinuation5


Immediate postabortal placement high continuation rate (81%)1
- No impact on CHO metabolism2
- Bleeding patterns now more predictable3
- Prophylactic NSAIDs (not estrogen) help minimize irregular bleeding4


Copper IUD Updates

- Place same day as visit, during elective C-section, post partum, post-abortal.1,2,3,4,5,6
- Most effective emergency contraceptive
- Very appropriate for nulliparous women7,8
- 30% clinicians have misconceptions8


Condition of Ova Recovered From Fallopian Tubes at Ovulation

<table>
<thead>
<tr>
<th>Group</th>
<th>Normal Development</th>
<th>No Development</th>
<th>Uncertain Or Abnormal Development</th>
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<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>All IUDs</td>
<td>0</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Lippes loop</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>TCu 200</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Progestin IUD</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

**Levonorgestrel-Releasing Intrauterine System (LNG IUS)**

- Steroid reservoir
- Levonorgestrel 20 mcg/day

**Cervical Mucus**


**Median Menstrual Blood Loss (MBL)**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 Month</th>
<th>6 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBL (mL)</td>
<td>150</td>
<td>130</td>
<td>100</td>
</tr>
</tbody>
</table>


**LNG IUS-20 Updates**

- Place same day as visit, but need 7-days of backup
- Place postpartum, post abortal
- Can be used by nulliparous women
- Most effective medical treatment for heavy menstrual bleeding:
  - 5 year follow-up HMB: LNG-IUS 20 vs thermal balloon. IUS better efficacy and satisfaction
- US-guided hysteroscopy for removal in early pregnancy experimental


**LNG IUS-13.5**

- Smaller device 30 x 28mm
- New and narrower introducer 3.8mm
- Silver ring at top of vertical stem
- Barium sulfate in device to make radio opaque
- Approval for 3 years use
- First year failure rate: 0.41%
- Cumulative 3 year failure rate: 0.9%

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**Skyla™ T-body**

- LNG-IUS 13.5mg T-body
- No component of the IUD or its packaging contains latex
DMPA Contraceptive Formulations
- DMPA 150mg 1M every 11-13 wks
  - Branded product
  - Generic version
- DMPA – SQ 104 mg/0.65mL
- Synthetic analog of 17α-hydroxyprogesterone
- Microcrystals suspended in an aqueous solution

DMPA Developments
- May safely be given immediately post partum to breastfeeding women
  - No increase in postpartum depression
- Need to choose needle size and injection site by patient’s BMI
- Improves health-related quality of life
- Slow return to fertility (esp. obese women)

DMPA Developments
- Does temporarily (and reversibly) reduce bone mineral density
  - 2008 ACOG states that should not influence practices
  - DMPA may decrease ovarian cancer risk but increase breast
  - Doxycycline 100mg BID doesn’t stop DMPA bleeding
  - No weight change difference from CuT IUD after adjustments

DMPA-SC
- Highly effective contraceptive option
  - 0 pregnancies in 20,607 woman-cycles of exposure
  - Immediate suppression of ovulation
  - Efficacy not affected by BMI
- Safe and well tolerated
  - Similar safety profile to DMPA-IM
  - Similar bleeding pattern to DMPA-IM
  - Improved tolerability profile versus DMPA-IM

DMPA Noncontraceptive Health Benefits
- Reduces risk of ectopic pregnancy
- Reduces risk of corpus luteal cysts
- Sickle cell crises:
  - 70% eliminated entirely for 1 year
  - 14% had significant reductions in pain
- Reduces risk of endometrial hyperplasia and endometrial cancer
- DMPA-SQ 104 is FDA approved for treatment of endometriosis pain

References:
Progestin-Only Pills Features

- Very safe
  - Virtually every women can use
  - 1 absolute contraindication (US MEC Cat 4)
  - More susceptible to drug-drug interactions
- Few complications
  - No risk of VTE/ATE
  - No cosmetic issues
  - Lower metabolic impacts than COCs
- Easy to use
  - One tablet every day
  - No need to buy extra packs to close time gaps

“Birth control pills are not dangerous, but there are dangerous women out there. Find them and keep them away from the pill, and the pill will do its work well.”

Paul Brenner, M.D.
Professor, OB-GYN
USC

Pregnancy is hazardous to a woman’s health

Prerequisites for Prescribing Combined Hormonal Contraceptive (CHCs)

- What is needed before prescribing CHCs?
  a. History
  b. History, BP
  c. History, BP, breast exam
  d. History, BP, breast exam, pelvic exam
  e. History, BP, breast exam, pelvic exam, pap smear, STD tests

Starting Contraceptive Methods: Anytime if Not Pregnant

<table>
<thead>
<tr>
<th>Method</th>
<th>Exams/Tests Needed</th>
<th>Back-up Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper IUD</td>
<td>Bimanual exam &amp; cervical inspection</td>
<td>None</td>
</tr>
<tr>
<td>LNG-IUSs</td>
<td>Bimanual exam &amp; cervical inspection</td>
<td>7 days**</td>
</tr>
<tr>
<td>Implant</td>
<td>None</td>
<td>7 days*</td>
</tr>
<tr>
<td>Injection</td>
<td>None</td>
<td>7 days**</td>
</tr>
<tr>
<td>Combined hormonal contraceptives</td>
<td>BP</td>
<td>7 days*</td>
</tr>
<tr>
<td>Progestin-only pills</td>
<td>None</td>
<td>2 days*</td>
</tr>
</tbody>
</table>

* If >5 days since LMP        ** If >7 days since LMP


Oral Contraceptive Pills

- Safe and well-tested -- the gold standard:
  - 50 years of clinical experience in US
  - Best studied medication in history
- Failure rate with consistent and correct use < 1%
- Typical first year failure rate is 9%
- Rapidly reversible:
  - Only 2 week average delay in fertility
- Extensive non-contraceptive benefits

COC Updates

- High failure rates seen in obese women due to behaviors
  - Noncompliance related to poverty
- Provision of 13 cycles halves pregnancy and abortion rates
- Pelvic exams still demanded by > 33% FP
- New E₂V/DNG formulation approved for heavy menstrual bleeding (HMB)

COC Updates

- Postpartum initiation must be delayed 42 days in at risk women (US MEC 2012)
- Flexible extended cycle regimens: less bleeding
- Doxycycline 40mg SR shortens time to amenorrhea with extended cycle COCs
- FDA published DVT risks of pregnancy in DRSP pill package inserts


VTE Risk and COCs

- When is time of VTE risk highest with COC?
  a. Initial months
  b. At 3-6 months
  c. After 12 months
- How long does a woman have to discontinue pills to be considered a new start from VTE risk?
  a. 9 months
  b. 6 months
  c. 3 months
  d. 1 month

Recommended Actions After Late or Missed COC

If one hormonal pill is late (<24 hours since a pill should have been taken):
Take the late or missed pill as soon as possible. Continue taking the remaining pills at the usual time (even if it means taking two pills on the same day). No additional contraceptive protection is needed. EC should be considered.

If one hormonal pill has been missed (24 to <48 hours since a pill should have been taken):
Take the most recent missed pill as soon as possible. (Any other missed pills should be discarded.) Continue taking the remaining pills at the usual time (even if it means taking two pills on the same day). Use back-up contraception (e.g., condoms) or abstinence until hormonal pills have been taken for 7 consecutive days. EC should be considered.

If two or more consecutive hormonal pills have been missed (>48 hours since a pill should have been taken):
Take the most recent missed pill as soon as possible. (Any other missed pills should be discarded.) Continue taking the remaining pills at the usual time (even if it means taking two pills on the same day). Use back-up contraception (e.g., condoms) or abstinence until hormonal pills have been taken for 7 consecutive days. EC should be considered.

If the Evening News Carries a Story: Messages to Patients

Do not stop your pill until we talk
Whatever pill you are taking is safer than pregnancy
When you stop taking your pill for only 4 weeks and then restart it
You experience the risks as large as those that happen at the time of pill initiation
Keep on letting your pill work for you until the dust settles

Management of Bothersome Unscheduled or Prolonged, Heavy Bleeding*

NSAIDS (5-7 days)
Cu-IUD
Implants
DMPA
Hormone holiday 3-4 days
CH after first 21 days (once per 28d cycle)
COCs or estrogen for 10 days if medically eligible
Consider method change if problem persists

Note: no recommendation for LNG-IUS
* May need to evaluate for non-contraceptive causes
Impact of Inappropriate Warning 
Nocebo or Noise?

- In original OC trials for menstrual irregularity, counseling women about OC side effects increased their incidence in placebo users

"Because Level 1 evidence documents no important increase in nonspecific side effects with oral contraceptives, counseling about these side effects or including those in package labeling is unwarranted and probably unethical."


Contraceptive Vaginal Ring

- Very low dose
  - 120 mcg/day etonogestrel
  - 15 mcg/day ethinyl estradiol
- Flexible
- Transparent
- Outer diameter: 54 mm
- Thickness: 4 mm
- One ring per cycle: 3 weeks ring-in, 1 week ring-free

Contraceptive Ring Update

- Extended cycle (once a month) effective
- Prolonged use of single ring up to 6 weeks
- Concern with BV vaginal pH changes
- Obese women same efficacy as normal weight, but lower systemic EE levels
- AT/VTE risk with ring not higher with COCs


New Contraceptive Rings

- New ring with EE and nesterone tested
  - 1 year ring used 3 weeks in/1 week out
- Progestin only ring for breastfeeding women
- Selective progesterone receptor modulators in future

Continuation Rates: Hormonal Methods

<table>
<thead>
<tr>
<th>Percent</th>
<th>Ring</th>
<th>Pill</th>
<th>Patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never started</td>
<td>14.7</td>
<td>13.6</td>
<td>19.2</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>13.0</td>
<td>16.1</td>
<td>11.8</td>
</tr>
<tr>
<td>Discontinued: total</td>
<td>30.0</td>
<td>23.9</td>
<td>43.0</td>
</tr>
<tr>
<td>% cycle control</td>
<td>3.6</td>
<td>3.0</td>
<td>3.4</td>
</tr>
<tr>
<td>Side effects</td>
<td>9.7</td>
<td>11.5</td>
<td>16.1</td>
</tr>
<tr>
<td>Pregnancy wanted</td>
<td>2.6</td>
<td>2.5</td>
<td>3.6</td>
</tr>
<tr>
<td>Change in mind</td>
<td>4.1</td>
<td>3.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Failure</td>
<td>0.3</td>
<td>0.1</td>
<td>0.1</td>
</tr>
<tr>
<td>Other</td>
<td>9.2</td>
<td>3.9</td>
<td>15.6</td>
</tr>
<tr>
<td>12 month continuation</td>
<td>42.3</td>
<td>46.9</td>
<td>26.0</td>
</tr>
</tbody>
</table>

3,443 new starts. Methods not covered by Spanish insurance

“Ten months ago, I would have called this (the condom) an invention of the devil, but now I find that its inventor must have been a man of good will …”

Jacques Casanova, 1758

Condom Use and Remaining Need
- Worldwide, 6-9 billion condoms used each year
- 24 billion condoms needed
- Under-utilization not only from non-using couples but also from intermittent, inconsistent use by “condom users”


Male Condom
- Typical first year failure rate: 17.4%; range 2-20%
- Advantages:
  - Male participation
  - Inexpensive
  - Protects well against STDs
  - Readily available
  - Cervical dysplasia reduced
  - Special applications:
    - Premature ejaculation
    - Antisperm antibody
    - Female allergy to sperm


Male Condom Update
- Inconsistent use common
- Many new sizes needed
- New materials: polyisoprene
- New incentives: ribbing, scents, vibrating rings
- New market strategies: to women
- New barriers: removed to locked cases
- New biomarkers for failure
- Addition of condoms to COCs could reduce STDs, unintended pregnancies and abortions


Female Contraceptive sponge variably available
- Female condom FC2 (nitrile)
- Use of female vs. male condom
  - Less ejaculation, less active coitus, shorter coital duration
- New female condoms under development
- SILCs diaphragm
- 2 day method
- Standard days method with beads


THE EVENING AFTER THE DAY FOLLOWING THE MORNING AFTER THE NIGHT BEFORE PILL
EMERGENCY CONTRACEPTION
**LNG EC Products**

- Single pill
  - 1.5 mg levonorgestrel in 1 tablet to be taken within 72 hours
  - Available without a prescription to people aged 17 and older with government identification
  - Available with prescription to women of all ages
- 2 pill product
  - Available without a prescription to people age 17 and older with government identification
  - Available with a prescription to women of all ages

**How Long After the Morning After? WHO Pooled Data (Yuzpe and LNG), 1998**

- Pregnancy Rate
  - 0.5% to 5.0%
  - 0-12 13-24 25-36 37-48 49-60 61-72


**LNG-EC Update**

- Works by ovulation suppression only
  - No effect after ovulation
- Failure rates strongly impacted by weight
  - 1.3% normal; 2.5% over; 5.8% obese
- Biggest contributor to failure – unprotected coitus following use


**Ulipristal Acetate for Emergency Contraception**

- 1553 treatments of women 48-120 hours after unprotected intercourse
- 30 mg Ulipristal acetate orally
- Pregnancy rate
  - Overall 2.1%
  - 48-72 2.3%
  - 72-96 2.1%
  - 96-120 1.3%
- Cycle length increased a mean of 2.8 days
- Duration of bleeding did not change


**Overweight and Obese Women Have Higher EC Failure Rates with LNG-EC**

<table>
<thead>
<tr>
<th>BMI</th>
<th>LNG-EC</th>
<th>UPA-EC</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 25 kg/m²</td>
<td>1.3%</td>
<td>1.1%</td>
</tr>
<tr>
<td>25 - 29.9 kg/m²</td>
<td>2.5%</td>
<td>1.1%</td>
</tr>
<tr>
<td>≥ 30 kg/m²</td>
<td>5.8%</td>
<td>2.6%</td>
</tr>
<tr>
<td>Further coitus</td>
<td>7.3%</td>
<td>5.6%</td>
</tr>
</tbody>
</table>


**LNG-EC Update**

- Meloxicam 15mg boosts efficacy LNG EC
- Can be used in combination with hormonal contraceptive Quick Start
- Safety, but not cost effectiveness, of advance prescription shown

Role of Ulipristal Acetate in Quick Start Protocols

- Ulipristal acetate is a selective progesterone receptor modulator (SPRM)
- Binds to progesterone receptor to block progesterone action
- May start hormonal contraception immediately following UPA use. (QuickStart®)
- Some experts recommend 3 day delay/5 days since unprotected intercourse

1. Jensen J, et al. XXXXX; XXXX; XX: XX-XX

Contraception and Health

- Increasing contraceptive use in developing countries
- Reduced maternal deaths by 40% in 20 years
- Most impact on high risk women and those pregnancies that would end in unsafe abortion
  - 26% reduction in maternal mortality in 10 years
- Estimates: another 30% reduction can be achieved by fulfilling current unmet need for contraception