Contraceptive Update
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Disclosure
I am on the Scientific Advisory Board of M360.
• M360 is a non-profit pharmaceutical company that is working on bringing another IUD to market in the US.

Half of All Pregnancies in the US Each Year Are Unintended

Each year, half of U.S. women are not fully protected from unintended pregnancy

Women report a variety of reasons for contraceptive nonuse

Half of women with gaps in use report coinciding life changes

The Alan Guttmacher Institute: Fulfilling the Promise, 2000

*Data from: Alan Guttmacher Institute, In Brief 2008 Series No 1

Guttmacher Institute: Improving Contraceptive Use in the U.S., Jan 2009
http://www.guttmacher.org/presentations/ICU_ARHP-CORE.html
Inconsistent method use is elevated among women not satisfied with their method.

![Graph showing % who used their method inconsistently in the past 3 months](http://www.guttmacher.org/presentations/ICU_ARHP-CORE.html)

**Contraceptive Use and Unintended Pregnancy**

- 53% of unintended pregnancies occur in contraceptive users¹
- The majority of contraceptive failures come from inconsistent or incorrect use²
- An estimated 1 million unintended pregnancies in the U.S. are related to OC method failures (5%), inconsistent or incorrect use or discontinuation²

¹ The Alan Guttmacher Institute, Facts in Brief: Contraceptive Use, 2004
² Rosenberg et al., J Reprod Med 1995; 40:355

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**Contraceptive Effectiveness**

<table>
<thead>
<tr>
<th>Method</th>
<th>% experiencing unintended preg. in 1st yr</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Typical Use</td>
</tr>
<tr>
<td>No method</td>
<td>85</td>
</tr>
<tr>
<td>Diaphragm</td>
<td>16</td>
</tr>
<tr>
<td>Condom (male)</td>
<td>15</td>
</tr>
<tr>
<td>Combined pill and minipill</td>
<td>8</td>
</tr>
<tr>
<td>Combined patch (Evra)</td>
<td>8</td>
</tr>
<tr>
<td>Combined ring (NuvaRing)</td>
<td>8</td>
</tr>
<tr>
<td>DMPA (Depo-Provera)</td>
<td>3</td>
</tr>
<tr>
<td>IUD</td>
<td></td>
</tr>
<tr>
<td>ParaGard (Copper T)</td>
<td>0.8</td>
</tr>
<tr>
<td>Minua (LNG-IUS)</td>
<td>0.1</td>
</tr>
<tr>
<td>Implants</td>
<td>0.05</td>
</tr>
<tr>
<td>Female Sterilization</td>
<td>0.5</td>
</tr>
<tr>
<td>Male Sterilization</td>
<td>0.15</td>
</tr>
</tbody>
</table>


**Adherence**

**Combined Hormonal Methods**

(contain estrogen + progestin)

- The pill (combined oral contraceptives - COC)
- The patch (Evra™)
- The ring (NuvaRing®)

**Patch and ring versus the pill**

- Patch vs. COC (5 trials)
  - Similar contraceptive efficacy
  - Similar cycle control
  - Patch: better adherence
  - Patch: more breast discomfort, dysmenorrhea, nausea, and vomiting
  - Patch: more early discontinuation

- Ring vs. COC (10 trials)
  - Similar contraceptive efficacy
  - Similar cycle control
  - Ring: similar adherence in 2 trials, less in 1 trial
  - Ring: less nausea, acne, irritability, and depression
  - Ring: more vaginitis and leukorrhea, less vaginal dryness
  - Similar discontinuation rates

Reminder systems for COC users

- RCT: text message reminders and daily pill-taking\(^1\)
  - Electronic monitoring device for pill pack (N=82)
  - Mean # missed pills per cycle: 4.9 (±3.0) vs. 4.6 (±3.5)
  - No benefit to daily text message reminders
  - Despite high # of missed pills, no pregnancies
  - Highly educated population, use of condoms and EC
- RCT: educational text messages and COC continuation\(^2\)
  - 962 women enrolled, 683 with 6 month follow-up
  - Continuation, 64% vs 54% (p=.005)
  - Continuation 74% if final interview while pt receiving txts.

Controversy over the patch

- Pharmacokinetic study showed 60% higher estradiol levels with patch than 35 mcg pill\(^1\)
- Epidemiologic studies of VTE risk (patch vs COC)
  - Two studies, conflicting results
  - One showed increased VTE risk with patch\(^2\)
    - Compared new patch users to ongoing pill users
    - The other showed no difference\(^3\)
  - Both studies showed the absolute VTE risk with patch (~40/100,000) is lower than with pregnancy (57/100,000)\(^4\)

Controversy over drospirenone

- 2 studies published in BMJ 2009\(^1,2\)
  - 1.5-2 x increased VTE risk with drospirenone
- 2 company sponsored (phase 4) studies show no increased risk\(^3,4\)
- 2 more studies published in BMJ 2011\(^5,6\)
  - 2-3 x increased VTE risk, drospirenone vs. levonorgestrel
  - 12 VTE/100,000 woman/yrs vs. 31/100,00 (levon vs. drosp)\(^6\)
  - New users or re-starters\(^5\), different durations of use\(^6\)
  - One controlled for BMI\(^5\)

FDA panel reviews data

- FDA panel concluded (15 vs. 11): Benefit still outweighs risk, keep on market
- Voted to change label (21 vs. 5)
  - Warning: drospirenone has greater VTE risk than other OCPs
- Dr. Kessler (former FDA commissioner)
  - Expert witness for patients suing Bayer
  - Says Bayer knew drospirenone has increased clot risk long before BMJ studies published

Controversy over drospirenone

**My opinion**

- Drospirenone not first-line for new starts
- Reasonable for switchers, unable to find another tolerable pill
- Those happy on drospirenone, stay on drospirenone
  - If higher than average baseline VTE risk (i.e. obese) might consider switch

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\(^1\) Hou MY et al., Obstet Gynecol 2010
\(^2\) Castano et al., Obstet Gynecol 2012
\(^3\) van den Heuvel MW et al., Contraception 2005
\(^4\) Jick et al., Contraception 2006
\(^5\) Cole JA et al., Obstet Gynecol 2007
\(^6\) Phelps and Kelver, Obstet Gynecol 2009
The Case for Long-Acting Reversible Contraception (LARC)

- Need for effective contraceptive methods that are “forgettable”.
- Traditionally, sterilization has been very popular in the U.S. (approximately 1/3 of U.S. contraceptive users)
- 20% of women selecting sterilization at age ≤30 years later express regret.

Hillis et al. Obstet Gynecol 1999
Stanwood, NL. Obstet Gynecol 2002

Intrauterine Contraceptive Devices Available in the United States

CuT380A (Paragard®)
Copper ions
Approved for 10 years use

LNG IUS (Mirena®)
20 mcg levonorgestrel /day
Approved for 5 years use

Intrauterine Contraception

Efficacy

- LNG IUD (Mirena)
  - Typical first-year failure rate: 0.1 per 100 women¹
  - Cum. pregnancy rate, 1.1 per 100 women over 7 years²
  - Pregnancy very rare, but if pregnant ~50% ectopic³
  - Ectopic incidence, 1 per 1000 per year³

- Cu-T380A (Paragard)
  - Typical first-year failure rate: 0.8 per 100 women²
  - Cum. pregnancy rate, 2.2 per 100 women over 12 years⁴
  - Pregnancy very rare, but if pregnant 11% ectopic⁵

² Sivin I, Fertil Steril 1994
⁵ Mirena Package Insert
Levonorgestrel IUS: Side Effects

• Disrupted bleeding patterns
  – Extra bleeding and spotting for first 3-6 months
  – After 8 months ~50% of women have no menstrual bleeding, but occasional spotting
  – 20% of women have amenorrhea in the first year

• Overall decrease in bleeding

Lahteenmaki et al., Steroids 2000; 65:693

Cu T380-A (Paragard®)

• Side effects
  – No hormonal side effects (no hormones)
  – Heavier menstrual bleeding
    • Most women experience increased blood loss
    • Approximately 50% increase in blood loss
    • Especially heavy in first few months post insertion
  – More cramping and/or pain
    • Dysmenorrhea, dyspareunia, backache
    – Anemia

Risk of Pelvic Inflammatory Disease

• PID with IUD associated with
  – Insertion process
    • Risk greatest in first 20 days after insertion
      (1-10 / 1000 women)
    • Rare after that (1.4 / 1000)
  – After insertion, risk of PID based on risk of acquiring an STI.
  – Around insertion, if infection occurs usually polymicrobial including anaerobes from vagina/cervix.

Dean and Goldberg, Up to Date 2009

Non-contraceptive Uses of IUD

LNG-IUS (Mirena®) specific uses
• Evidence-based, but not currently FDA approved
• Long term endometrial suppression
  – Fibroids, idiopathic menorrhagia
  – Endometriosis, adenomyosis, dysmenorrhea
• Post-menopausal women with uterus
  – Permits use of estrogen-only HT regimens

Cu-IUC (Paragard®) specific uses
Emergency contraception
  – The Cu-T380A can be inserted within 5 days of a single act of unprotected intercourse as emergency contraception.
  – IUD expulsion, bleeding, and pain are slightly more likely among nulliparous women

Li C. Contraception 2004;69:247-250


IUD: Use in Nulliparous Women

• Use of IUCs by nulliparous women with low risk of PID is safe and effective.1-4
• LNG-IUS is appropriate for nulliparous women with menorrhagia and/or dysmenorrhea
• IUC expulsion, bleeding, and pain are slightly more likely among nulliparous women

Suhonen S. Contraception 2004;69:507-512
Li C. Contraception 2004;69:247-250
IUDs: Summary

• IUDs provide highly effective contraception with minimal user compliance requirements.
• IUDs are ideally suited for long term contraception, including women who have not been pregnant
• Women who do not engage in risky sexual behaviors may use an IUD, regardless of age, parity, or a history of PID

Etonogestrel Implant (IMPLANON)

• Progestin-only subdermal implant effective for up to 3 yrs
• Inserted subdermally in the groove between the biceps and triceps muscles
• Can only be inserted and removed by clinicians completing FDA mandated training program
• Highly effective, 0.38 pregnancies/100 woman-years (in clinical trials, no pregnancies with implant in situ)
• Very few absolute contraindications to use.

Adverse Experiences Associated with Implanon

Irregular bleeding is expected and patterns are unpredictable

• Acne 14 %
• Headache 13 %
• Weight increase 10 %
• Breast Pain 9 %
• Emotional Lability 5 %
• Abdominal Pain 5 %
• Decreased Libido 3 %
• Nausea 3 %

Greater use of long-acting reversible contraception holds great promise as a means to reduce unintended pregnancy in the United States.

New Emergency Contraceptive

• Ulipristal acetate
• Selective progesterone receptor modulator
• Large RCT (N=1696) and Meta-analysis
  – Ulipristal (30 mg) vs. levonorgestrel (1.5mg)
    • Large trial: pregnancy rates
      – 1.8% vs. 2.6% (OR 0.68, 0.35-1.31) <72 hours after UPI
    • Meta-analysis: pregnancy rates
      – 0.9% vs. 2.5% (OR 0.35, 0.11-0.93), <24 hours after UPI
      – 1.4% vs. 2.2% (OR 0.58, 0.35-0.99), 0-72 h after UPI
      – 1.3% vs. 2.2% (OR 0.55, 0.32-0.93), 0-120 h after UPI

Glasier et. al, Lancet 2010

New Emergency Contraceptive

• August 2010, ulipristal FDA approved as EC
• For use up to 5 days after UPI
• Marketed as “Ella” by Watson
• Prescription required
• Cost (Partners pharmacy)
  – Ella ~$38
  – Plan B $47
  – Next choice $26
• Not too late.com (Office Pop Research + Princeton)
  – Plan B, Next Choice $35-60 in pharmacy
  – Ella $55 in pharmacy, $77 on-line
• UK-NHS analysis, ulipristal is cost-effective*

Thomas CM et. al., J Fam Plann Reprod Health Care. 2010
Contraceptive Eligibility

Which patients are eligible for which methods?

WHO Medical Eligibility Criteria for Contraceptive Use


World Health Organization
Medical Eligibility Criteria 2008

• Recommendation Grading System
  – Category 1: No restrictions
  – Category 2: Generally use (Benefits usually outweigh risks)
  – Category 3: Not recommended, unless other methods not available or appropriate. (Risks usually outweigh benefits-use requires careful clinical judgment and access to clinical services)
  – Category 4: Absolute contraindication

WHO Medical Eligibility Criteria for IUD Use in Women with Certain Medical Conditions

<table>
<thead>
<tr>
<th>Medical Conditions</th>
<th>TCu-380A WHO Risk Category</th>
<th>LNG-IUS WHO Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension (controlled)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Multiple cardiovascular risk factors</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>History of DVT or pulmonary embolism</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Stroke</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Severe valvular heart disease (complicated)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>HIV infection</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>AIDS (clinically well on antiretroviral therapy)</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>


What’s different?

• Same classification system
• Recommendations unchanged for most conditions
• U.S. guidelines modified from WHO for:
  – Venous thromboembolism
  – Valvular heart disease
  – Ovarian cancer
  – Fibroids
  – Postpartum and breastfeeding

CDC adaptation of WHO guidelines

MMWR, June 18, 2010
What’s different?

- New CDC guidelines for contraceptive use in women with:
  - Rheumatoid Arthritis
  - h/o Bariatric Surgery
  - Peripartum cardiomyopathy
  - Endometrial hyperplasia
  - Inflammatory bowel disease
  - h/o solid organ transplantation

Examples from CDC MEC

<table>
<thead>
<tr>
<th>Medical Conditions</th>
<th>COC patch, ring CDC Risk Category</th>
<th>TCu-380A CDC Risk Category</th>
<th>LNG-IUS CDC Risk Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On immunosuppressive tx</td>
<td>2</td>
<td>2(i), 1(c)</td>
<td></td>
</tr>
<tr>
<td>Not on immunosuppressive tx</td>
<td>2</td>
<td>2(i), 1(c)</td>
<td></td>
</tr>
<tr>
<td>History of Bariatric Surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restrictive procedure</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Malabsorptive procedure</td>
<td>COC: 3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>2/3*</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Uterine fibroids</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Question 1

Which carries the greatest risk of deep vein thrombosis?

- a) combined oral contraceptives
- b) the contraceptive patch (Ortho EVRA)
- c) the contraceptive ring (NuvaRing)
- d) pregnancy

Question 2

A healthy 27 year old nulliparous, monogamous woman with heavy periods and severe dysmenorrhea desires contraception. Good methods for her would include all the following EXCEPT:

- a) Combined oral contraception
- b) The vaginal ring (NuvaRing)
- c) The copper IUD (Paragard)
- d) The levonorgestrel IUD (Mirena)

References

- WHO. Medical Eligibility Criteria for Contraceptive Use. 4th ed. 2008