Women’s Fertility Control: What’s New

Objectives

- Review the history of contraception
- Understands the current unmet needs regarding contraceptives
- Learn about the non contraceptive aspects of contraceptives
- Learn about what is new in the contraceptive arena

“Contraception” Can There Really be Anything New to Know?
First birth control clinic: Margaret Sanger (1916)
“Contraception” Can There Really be Anything New to Know?
“Contraception” Can There Really be Anything New to Know?
“Contraception” Can There Really be Anything New to Know?
“Contraception” Can There Really be Anything New to Know?
Why the Need for New Contraceptives

- Endemic rate of unintended pregnancies

- **30%** of all U.S. women will have had an induced abortion by age 45

---

“Contraception” Can There Really be Anything New to Know?
On December 7, 2017, a cohort study analyzing the risk of invasive breast cancer in women who used hormonal contraception was published in the *New England Journal of Medicine* (1).

Compared with women who never used hormonal contraception, the overall relative risk of invasive breast cancer among women who were current or recent users of any hormonal contraception was 1.20 (95% confidence interval [CI], 1.14–1.26).

Relative risk increased with duration of use, ranging from 1.09 (95% CI, 0.96–1.23) for less than 1 year of use to 1.38 (95% CI, 1.26–1.51) for use longer than 10 years.

In general, risk was similar among different formulations or preparations of combined oral contraceptives. The results among progestin-only methods were inconsistent, with no statistically significant increased risk with some progestin-only methods but an increased risk with other.

Among women who used the levonorgestrel-releasing intrauterine device (LNG-IUD), the relative risk of breast cancer was 1.21 (95% CI, 1.11–1.33) compared with never-users of hormonal contraception, but the risk did not increase with duration of use.
This study found that the overall risk of breast cancer among hormonal contraceptive users is low.

Because of the low baseline risks in the age groups using hormonal contraception (premenopausal women), the risk difference between hormonal contraception users and nonusers is small.

The relationship between oral contraceptive use and breast cancer has been the subject of a number of studies. Meta-analyses of these studies have shown a slight increased risk, ranging from 8–24% (2–4), which is similar to the risk observed in the current study.

The increased relative risk observed in the current study translates into 1 additional case of invasive breast cancer for every 7,690 women using hormonal contraception (1).

This risk varied with age: for women younger than 35 years, there was 1 additional case of invasive breast cancer for every 50,000 women using hormonal contraception (1).

The relationship between progestin-only contraceptives and breast cancer risk warrants further study.

The risks for different progestin-only formulations were inconsistent and dose-response and duration-response relationships were not present, making it very difficult to interpret these findings.

In this study, the LNG–IUD had a relative risk of breast cancer similar to that of combined hormonal oral contraception, whereas contraceptive implants and injectables had no observed increased risk.

Methods with higher systemic levels of progestin, particularly injectables, did not seem to be associated with increased risk.

The LNG–IUD had increased risk, but this risk was unchanged with duration of use.
Hormonal contraception has other significant health benefits.

The small increased risk of breast cancer identified in this study needs to be interpreted in the context of the benefits of hormonal contraceptive use. The non contraceptive benefits of hormonal contraception are well-established and include decreased risk of ovarian, endometrial, and colon cancer (4).

Because of protection against these cancers, overall cancer risk may be slightly lower in hormonal contraceptive users compared with nonusers, even with the small increased breast cancer risk observed in this study (5).

The benefits of hormonal contraceptives in preventing pregnancy are also important. In 2015, the maternal mortality rate in the United States was 26.4 deaths per 100,000 women (6), which is double the risk of developing invasive breast cancer (13 additional breast cancers per 100,000 users) found among women in the current study who used hormonal contraception (1).

“Contraception” Can There Really be Anything New to Know?
**Green Journal Article Summary**

- The important message for patients, clinicians, and policy makers is that the **benefits of all contraceptive methods markedly outweigh their risks**, primarily because they prevent pregnancy, an inherently hazardous condition.

Raymond et al, Obstet Gynecol, Vol 119(50), **May 2012**, pg 1039

---

**CDC /WHO Publications for Contraception Use**

---

“Contraception” Can There Really be Anything New to Know?
“Contraception” Can There Really be Anything New to Know?
Contraceptive Patch

- Ortho Evra patch – gone
- Generic version of Ortho Evra = Xulane
- Twirla – Not FDA Approved, but
  1. It offers lower ethinyl estradiol levels (instead of being similar to a 60 mcg type of product, it is more like a 30 mcg pill).
  2. A 2nd generation progestin (levonorgestrel) replaces 3rd generation progestin.
  3. The surface is best described as being fuzzy, so that women cannot put decals on it or mess up the absorption.

Contraceptive Patch

- Failure rates were similar in the pill and patch group = 4-5% annual failure rate at 1 year.
- 10% of clinical trial participants in both groups, were not taking their study contraceptive
- Normal weight failure rate < 2.6%.
- Overweight failure group = 5.0%.
- Obese >30 = 5.5%.

Dr. Andrew Kaunitz and Dr. Anita Nelson; Reach MD 2017
Twirla

- Agile Therapeutics Announces FDA Acceptance of the NDA Resubmission of Twirla®
- FDA Assigns Prescription Drug User Fee Act (PDUFA) Goal Date of November 16, 2019
- A combined hormonal contraceptive (CHC) patch that contains the active ingredients ethinyl estradiol (EE), and levonorgestrel (LNG)
- Twirla is designed to be applied once weekly for three weeks, followed by a week without a patch.

Intravaginal Contraception

“Contraception” Can There Really be Anything New to Know?
Population Council researchers have developed Annovera™ (segesterone acetate/ethinyl estradiol vaginal system).

- Provides an entire year of protection against unintended pregnancy while fully under a woman’s control.
- Annovera was approval was approved by the FDA in August 2019.
Intravaginal Ring

The FDA approved Annovera (segesterone acetate and ethinyl estradiol vaginal system), which is a combined hormonal contraceptive for women of reproductive age used to prevent pregnancy and is the first vaginal ring contraceptive that can be used for an entire year.

Annovera is a reusable donut-shaped (ring), non-biodegradable, flexible vaginal system that is placed in the vagina for three weeks followed by one week out of the vagina for one year

August 2018

Long Acting Reversible Contraception (LARC)

“Contraception” Can There Really be Anything New to Know?
The IUD

This ‘wishbone pessary’, developed in Germany around 1880 (Credit: BBC/Science Museum, London)

Ernst Grafenberg designed this IUD in the 1920s

Catgut loop and bone, used in the early 20th Century

Dalkon Shield had a high risk of pregnancy – and of infections

Figure 2

IUD Utilization over time among women ages 15-44 who used contraception within previous 30 days, 1982-2013

Note: 61.7% of women ages 15-44 used contraception in previous 30 days. Source: CDC. (2015). Health, United States, 2014: Table 8.
### Copper T IUD
- Approved in 1984
- Copper ions: Releases 20 µg of LNG/day
- Approved for 10 years of use
- Inserter: 4.1 mm
- Indicated for contraception
- Specific contraindications: Wilson’s disease

### LNG IUS 52mg
- Approved in 2000
- Approved for 5 years of use
- Inserter: 4.4 mm
- Indicated for contraception
- Specific contraindications: Breast cancer, acute liver disease

### LNG IUS 13.5mg
- Approved in 2012
- Approved for 3 years
- Inserter: 3.8 mm
- Indicated for contraception
- Specific contraindications: Breast cancer, acute liver disease

### LNG IUS 19.5mg
- Approved in 2012
- Releases 17.5 µg of LNG/day
- Approved for 5 years of use
- Inserter: 3.8 mm
- Indicated for contraception
- Specific contraindications: Breast cancer, acute liver disease

#### Mechanism of Action
- Inhibition of ovum development
- Alteration of the endometrium
- Inhibition of sperm capacitation or survival
- Thickening of cervical mucus preventing passage of sperm into the uterus

---

**REFERENCES**
- ACOG, Statement on Contraceptive Methods. 1998;
- Jonsson B et al. Contraception. 1991;
- Segal SJ et al. Fertil Steril. 1985;
- Bayer Pharmaceutical.
Contraception: Can There Really be Anything New to Know?

Reversible Contraception that Works as Well as Sterilization

% of women experiencing an unintended pregnancy within the first year of use

- Implant: 0.05%
- LNG-IUS: 0.2%
- Copper IUD: 0.8%
- Female Sterilization: 0.5%


www.cdc.gov/mmwr/preview/mmwrhtml/rr5904a13.htm.

LARC in Adolescents

<table>
<thead>
<tr>
<th>Age and Parity</th>
<th>LNG-IUD</th>
<th>Cu-IUD</th>
<th>Implants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menarche &lt; 20 years</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>≥ 20 years</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nulliparous</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Parous</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Clinical considerations:
- Insertion difficulty for IUD (smaller os and uterus than in parous woman)
- Insertion pain – consider misoprostol, NSAIDs, lidocaine instillation into endometrial cavity, paracervical block
- Possible increased risk of STIs (chlamydia) and PID (because of age <25 years) with IUD; can conduct chlamydia testing on same day with normal exam.
- Still needs to use condoms for STI protection

US Centers for Disease Control and Prevention. MMWR 2010;59(RR04):76-81.
www.cdc.gov/mmwr/preview/mmwrhtml/rr5904a13.htm.

“Contraception” Can There Really be Anything New to Know?
Nulliparous Patients

- All IUD’s, except Mirena, are approved by the FDA for nulliparous women. But Mirena is not contraindicated, it was just not studied.
- The U.S. Medical Eligibility Criteria for Contraceptive Use classifies use in nulliparous women and adolescents for both IUDs as Category 2.
- More effective and higher rates of continuation and satisfaction than OCs
- Expulsion rates similar in nulliparous vs. parous women

Hubacher D. Copper intrauterine device use by nulliparous women: review of side effects. Contraception 2007;75(suppl):S8–11.

Insertion Timing

- Any time during the menstrual cycle
- Reasonably exclude pregnancy
- No major advantage to insertion during menses

www.acog.org 2012

“Contraception” Can There Really be Anything New to Know?
**Insertion Protocols - Infection**

- Routine antibiotic prophylaxis is not recommended before insertion.
- Current data do not support routine screening for STIs prior to insertion for women at low risk.
- Treat mucopurulent discharge or known STI before insertion.

[www.acog.org](http://www.acog.org) 2012

---

**IUDs Do Not Cause PID**

**Rate of PID by Duration of IUD Use**

- Rate per 10,000 women
  - <21 days of use: 92.5
  - 21 days-8 years of use: 16

n=~20,000

---

“Contraception” Can There Really be Anything New to Know?
IUD: Return to Fertility

Cumulative pregnancy rate (%)

- **MIRENA**
- **Copper IUD**

Months

- 0
- 20
- 40
- 60
- 80
- 100

Cumulative pregnancy rate (%)

FDA PI: IUD Insertion Postpartum

- **Mirena, Lyletta, Kyleena & Skyla** – “Should be delayed a minimum of 6 weeks after delivery”

- **Paraguard** – “Can be placed immediately after delivery; if delayed, must then wait 2 months”
Postpartum – IUD Controversy

<table>
<thead>
<tr>
<th>Postpartum</th>
<th>LNG- IUD</th>
<th>Cu- IUD</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 minutes</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>10 minutes – &lt; 4 weeks</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 4 weeks</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Puerperal Infection</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>


Expulsion Rates

- Higher with immediate postpartum insertion (up to 24%)
  - May be lower after Cesarean delivery
  - Benefits may outweigh risk of expulsion

www.acog.org 2012

“Contraception” Can There Really be Anything New to Know?
Ectopic Pregnancy

- IUDs may be offered to women with a history of ectopic pregnancy (off label)
- IUD use does not appear to increase absolute risk

LNG IUD 52 mg (Mirena) as Treatment for Heavy Menstrual Bleeding

- Menstrual blood reduction: 79–97%
- High rates of patient satisfaction and continuation

Nexplanon

Single-Rod Implant

- Trade name: Nexplanon®
- One rod 40 mm x 2 mm
- Effective for 3 years
- 99+% effective
- Radiopaque / Improved inserter
- Core:
  - 40% ethylene vinyl acetate (EVA)
  - 60% etonogestrel (68 mg)
- Rate-controlling membrane:
  - 100% EVA

“Contraception” Can There Really be Anything New to Know?
New Location

1. Step 2. Identify the insertion site, which is at the inner side of the non-dominant upper arm.
2. The insertion site is overlying the triceps muscle about 8-10 cm (3-4 inches) from the medial epicondyle of the humerus and 3-5 cm (1.25-2 inches) posterior to the sulcus (groove) between the biceps and triceps muscles.
3. This location is intended to avoid the large blood vessels and nerves lying within and surrounding the sulcus.

“Contraception” Can There Really be Anything New to Know?
Many Women Are Unaware of Emergency Contraception or How to Use It

- Among women at high risk for unintended pregnancy, 64% have never heard of emergency contraception.
- Only 7% were aware that the method must be used within 72 hours after intercourse.
- Fewer than half (44%) of the women who had heard of emergency contraception believed that it is safe.
- A third (32%) believed that the method induces abortion.
ECPs “Over-the-Counter” in the US

How Long After the Morning After?
WHO Studies: Combined or POPs

Pregnancy rates based on hour of treatment after unprotected intercourse
p < 0.01

0-12 13-24 25-36 37-48 49-60 61-72
0.50% 1.50% 1.80% 2.60% 3.10% 4.10%


“Contraception” Can There Really be Anything New to Know?
Ulipristal Acetate (Ella)

- Progesterone antagonist-agonist whose likely main effect is to inhibit or delay ovulation.
- One 30mg ulipristal acetate pill
- Ulipristal effectiveness does not decline with delay in treatment
- Rx required for all ages
- May be ordered from online prescription service - https://www.ella-kwikmed.com/
  - Pill mailed the next day

Glaser, Moreau, Trussell; www.nor-2-late.com; www.rhtp.org

Paragard® (Copper-T IUD)

- Off label use
- Placed within 5 days after intercourse
- Effectiveness does not decline with delay
- Placed by a trained clinician
- Most effective EC method, remains underutilized

Trussell J, Raymond EG. 2011.
Pregnancies per 1000 Episodes of Unprotected Intercourse

ParaGard, ella, Plan B/Next Choice, Yuzpe, Nothing

ECP Safety

- Benefits outweigh risks
- Safer than pregnancy
- Short duration of exposure and low total hormone content
- No increased risk of birth defects
- No increase in ectopic pregnancy
- Breastfeeding women may use progestin-only ECPs and IUDs

Trussell J, Raymond EG. Emergency Contraception: A Last Chance to Prevent Unintended Pregnancy. November 2011. Available at http://ec.princeton.edu/questions/ec-review.pdf Original content for this slide submitted by ARHP’s Clinical Advisory Committee for New Approaches to Unintended Pregnancy Prevention in December 2011. This project is funded through an educational grant from Watson Pharma, Inc. This slide is available at www.arhp.org/core

Trussell J, Raymond EG. Contraceptive Technology 2011; CDC MMWR 2010.