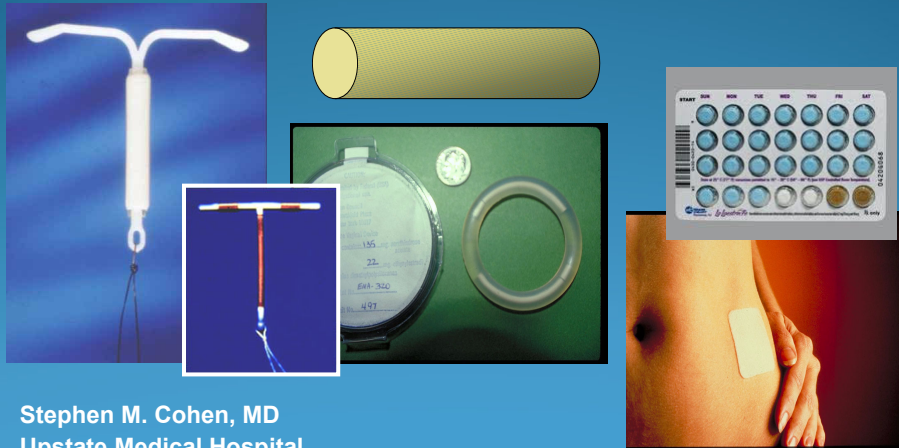


Women's Fertility Control: What's New



Stephen M. Cohen, MD
Upstate Medical Hospital
The Women's Wellness Place

1

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

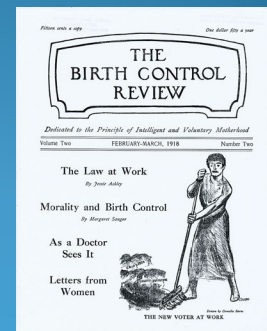
2

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



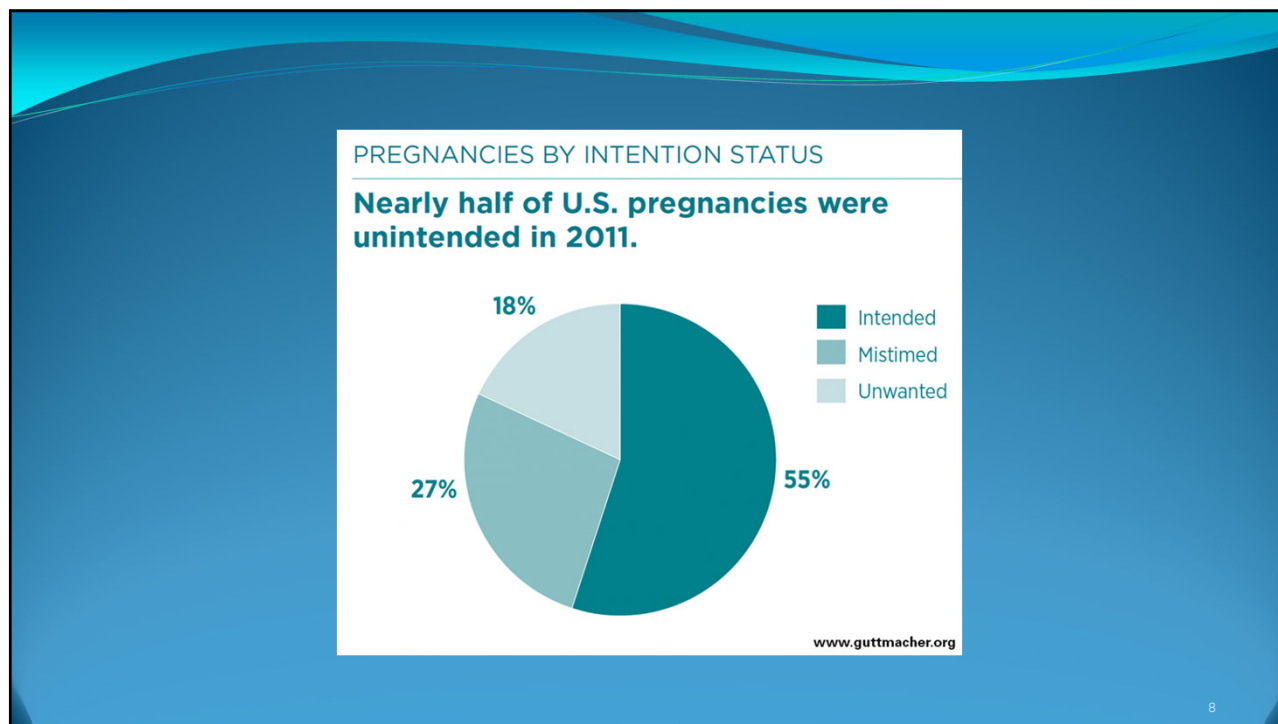
3

First birth control clinic: Margaret Sanger (1916)

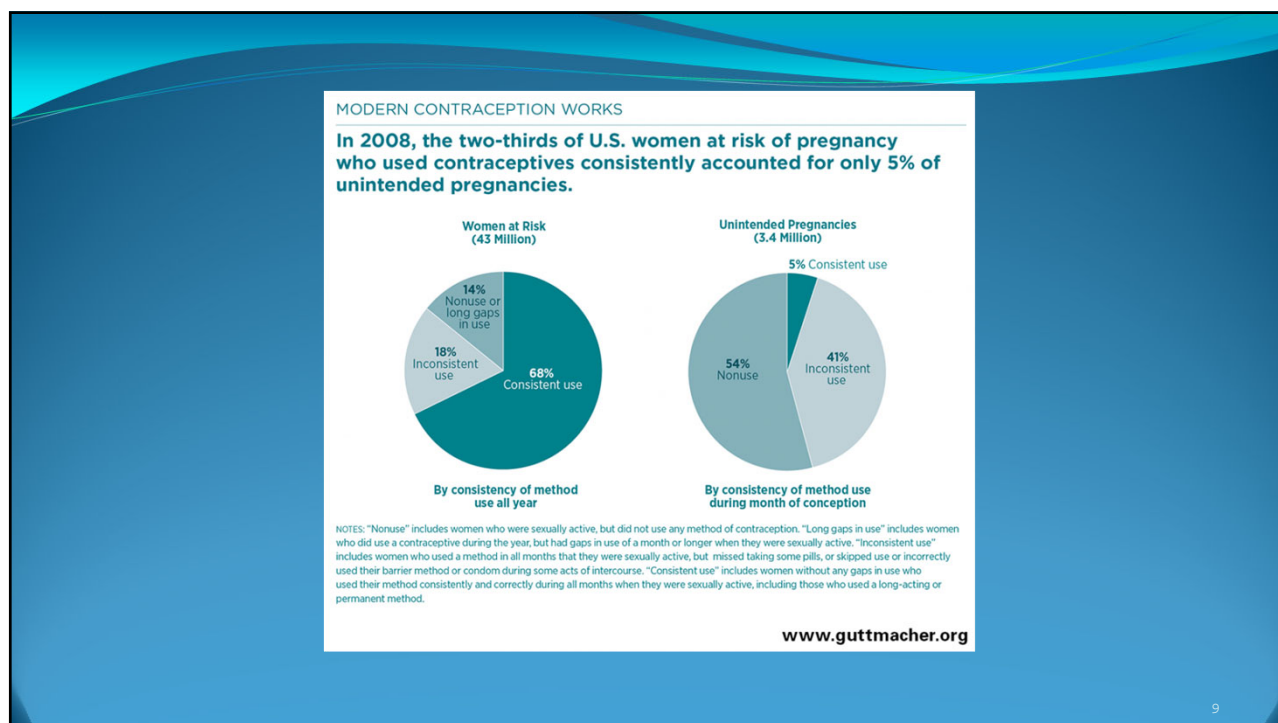


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“Contraception” Can There Really be Anything New to Know?

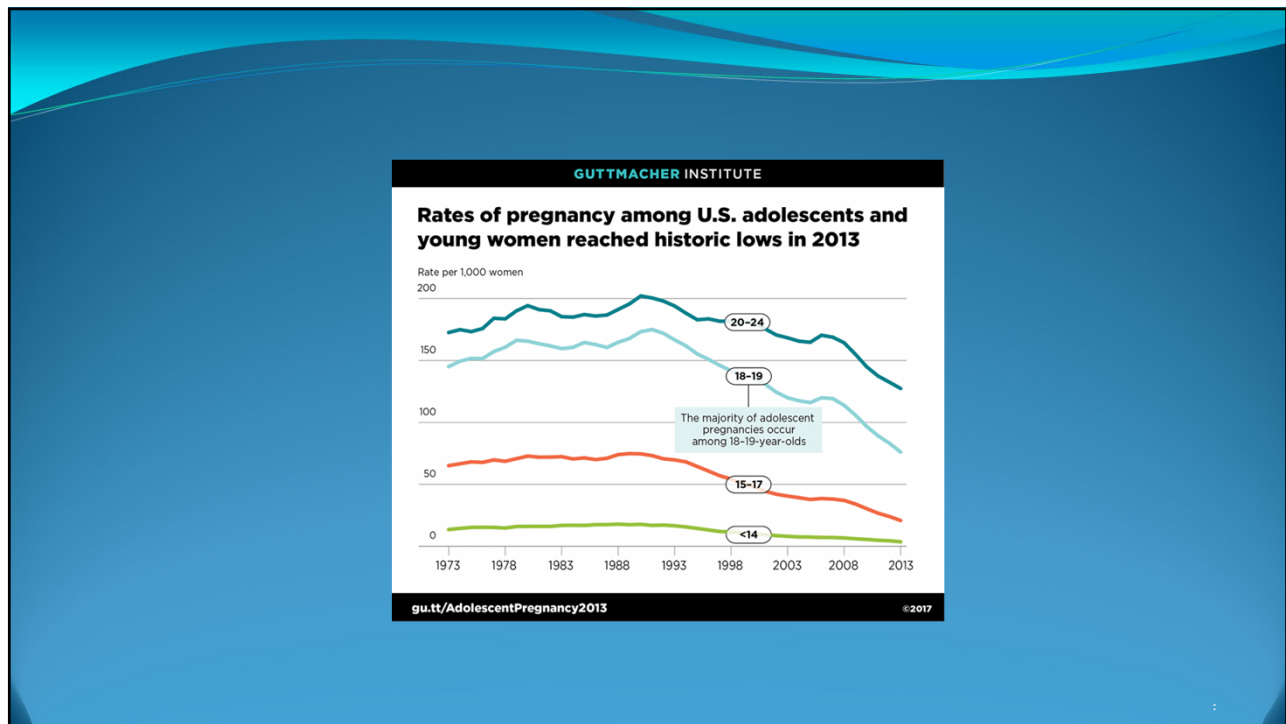


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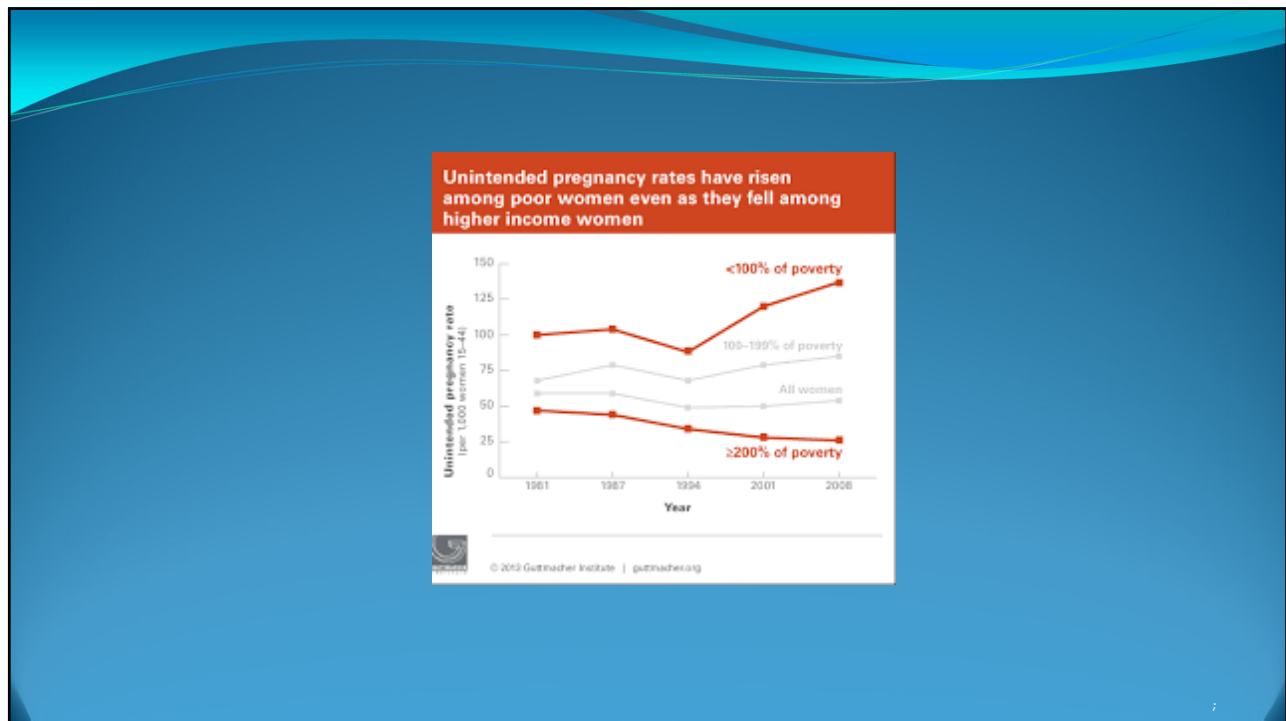


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“Contraception” Can There Really be Anything New to Know?

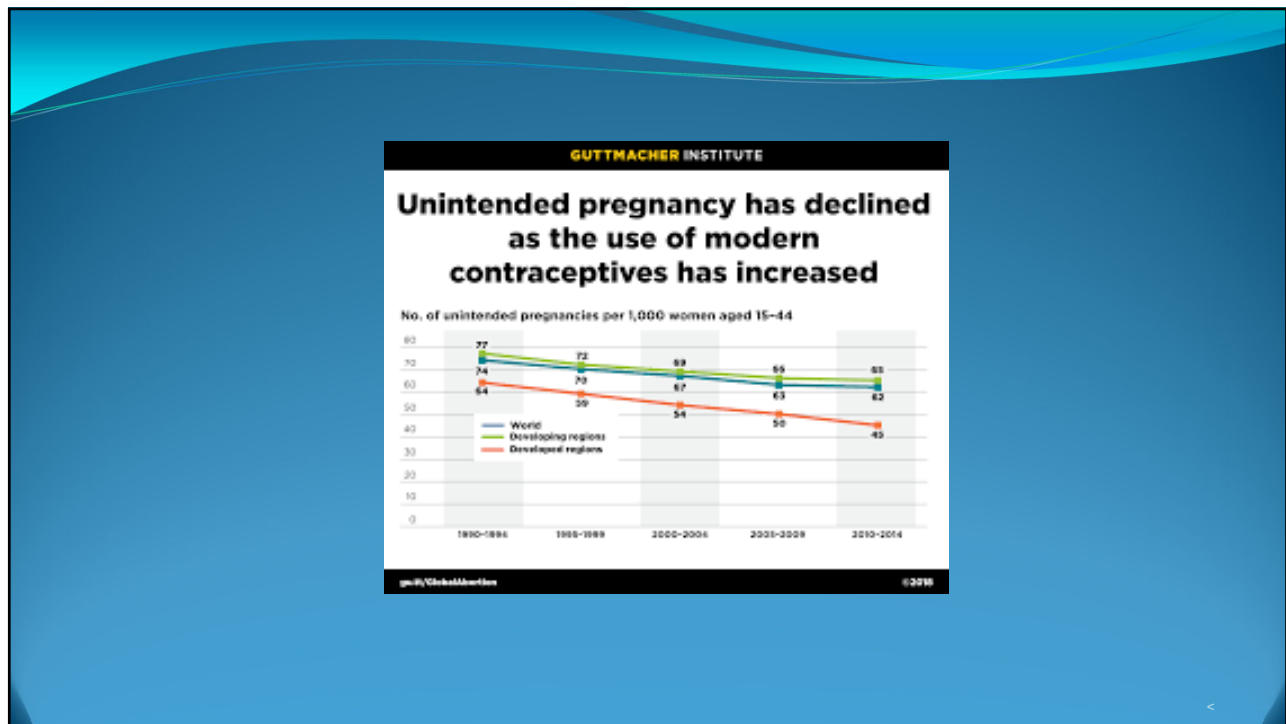


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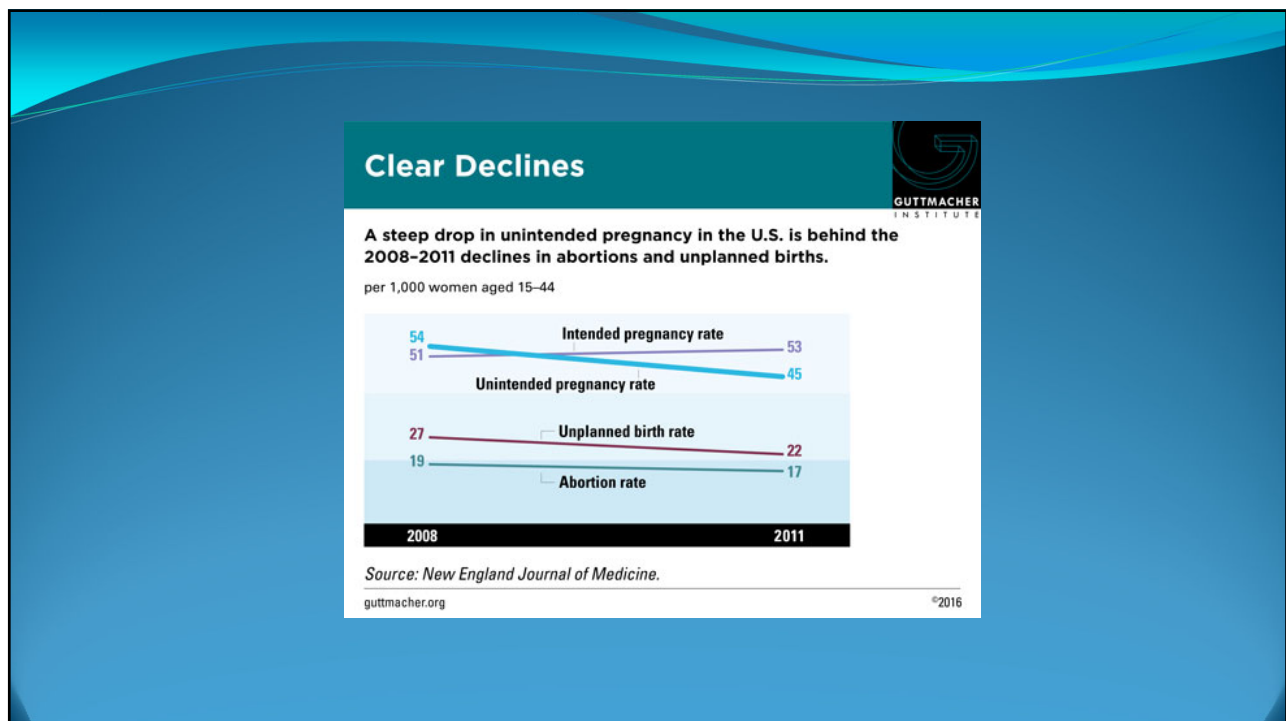


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“Contraception” Can There Really be Anything New to Know?

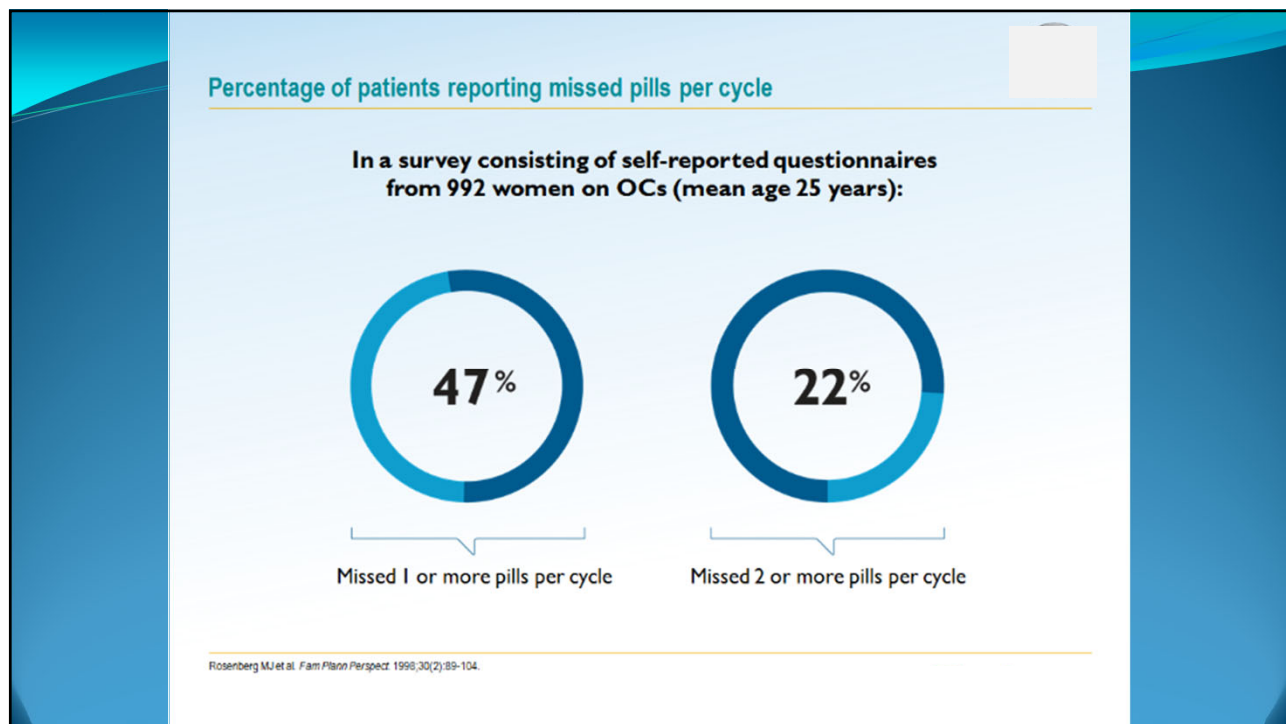


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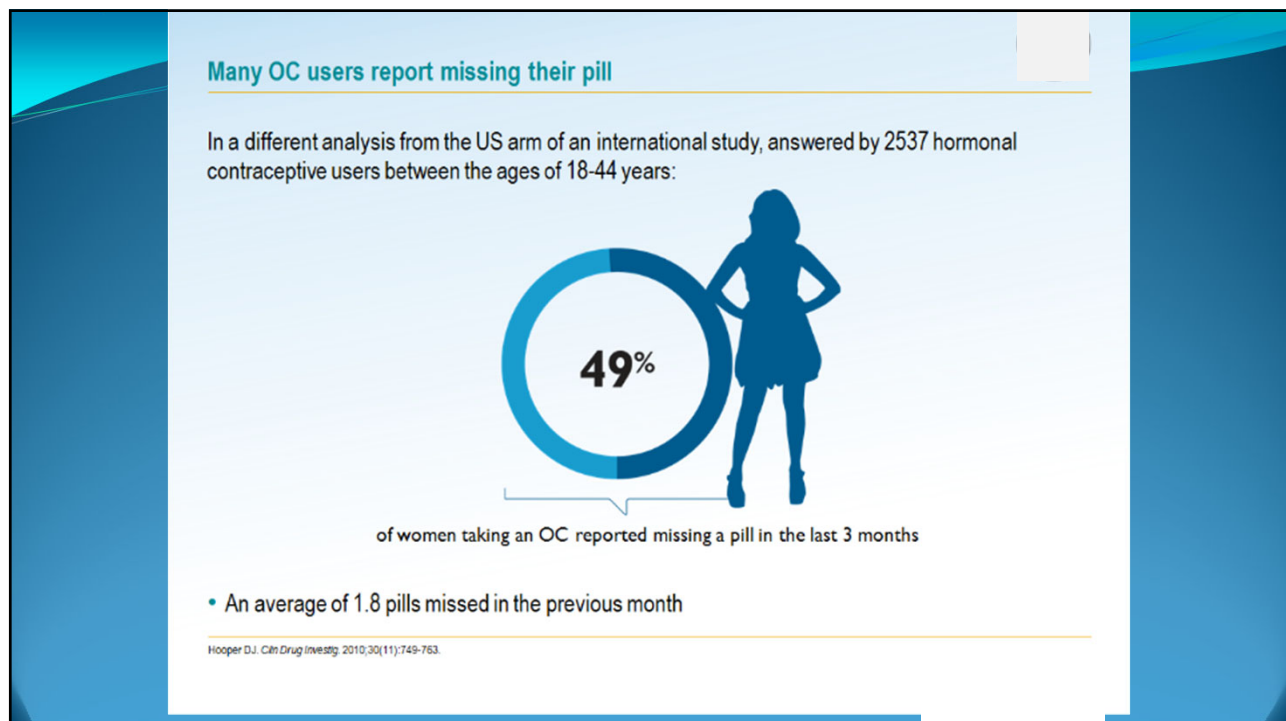


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“Contraception” Can There Really be Anything New to Know?

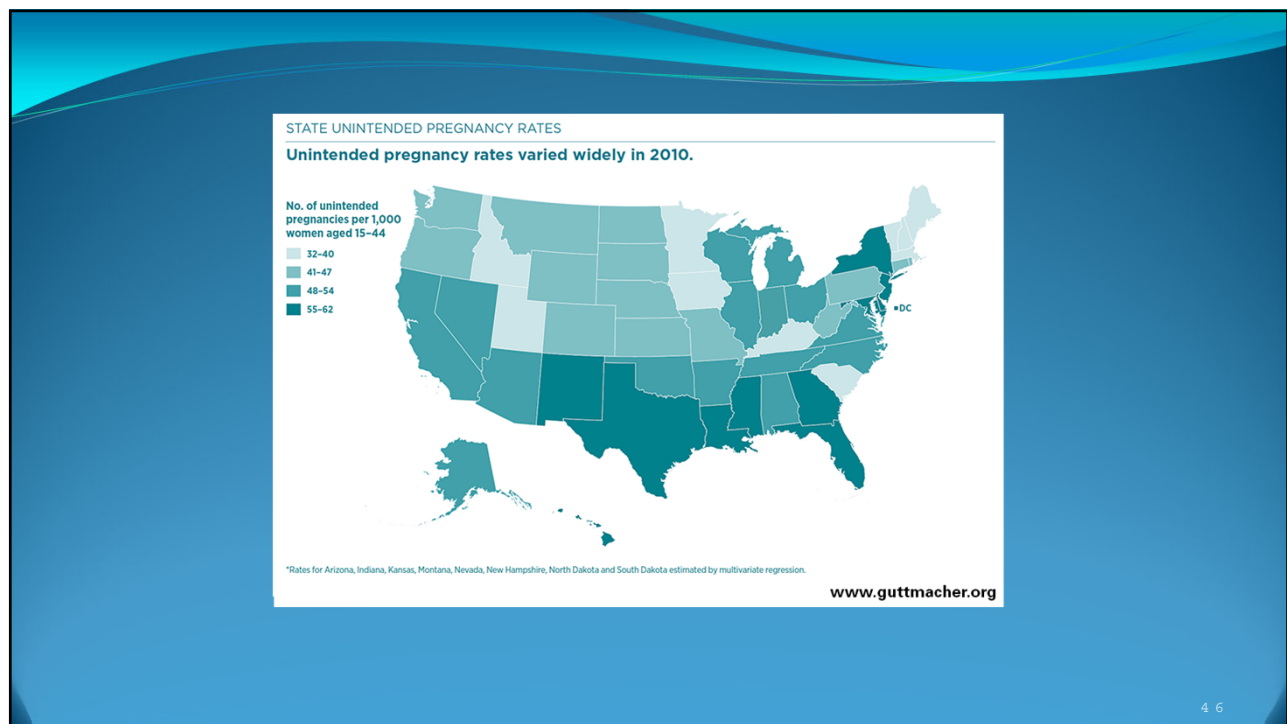


11



12

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



13

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

Jones RK and Kavanaugh ML, *Changes in abortion rates between 2000 and 2008 and lifetime incidence of abortion*, *Obstetrics & Gynecology*, 2011, 117(6):pp-pp.

14

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

Contraception Options

The collage displays several contraceptive options:

- Yaz:** A box and blister pack of Yaz birth control pills, which contain drospirenone and ethinyl estradiol.
- Hand with Pill:** A close-up of a hand holding a small, white, round pill.
- NuvaRing:** A box and individual packaging for NuvaRing, a vaginal ring that releases hormones.
- Plan B:** A box of Plan B One-Step emergency contraception.
- Condom:** A hand holding a condom, with a large blue 'X' overlaid on it, indicating it is not the correct answer for this specific question.
- IUD:** An image of an intrauterine device (IUD) with its insertion string.
- Diaphragm:** A diaphragm shown inside its blue plastic storage case.
- Today Sponge:** A box of Today Sponge, a non-hormonal contraceptive sponge.

15

Options for Sexual Health in 2019

16

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

Oral Contraceptives



17

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.

4 ;

18

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

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).

19

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.

20

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

Hormonal contraception has other significant health benefits.

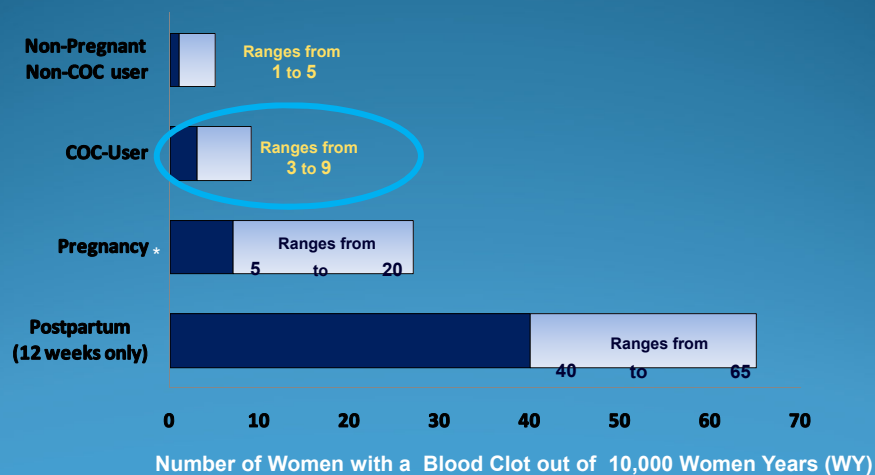
The small increased risk of breast cancer identified in this study needs to be interpreted in the context of the benefits of hormonal contraceptive use. The non contraceptive benefits of hormonal contraception are well-established and include decreased risk of ovarian, endometrial, and colon cancer (4).

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).

21

Likelihood of Developing a VTE



* Pregnancy data based on actual duration of pregnancy in the reference studies. Based on a model assumption that pregnancy duration is nine months, the rate is 7 to 27 per 10,000 WY. Contraception. 2007; Obstet Gynecol 2011; Ann Intern Med. 2005; USPI

22

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

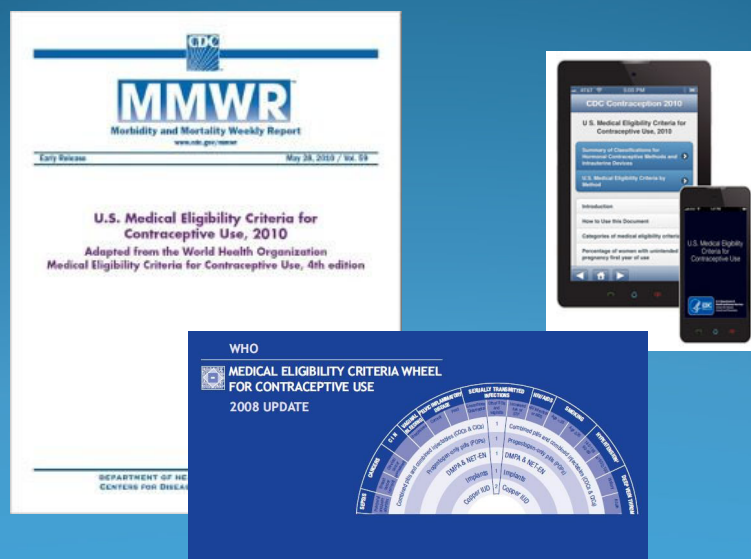
Green Journal Article Summary

• 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

23

CDC /WHO Publications for Contraception Use



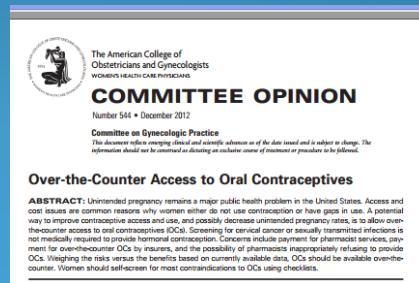
24

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

OTC Oral Contraceptives

The New York Times

Sunday Review | The Opinion Pages



25

Contraceptive Patch



59

26

“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.*

27

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

5 ;

28

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

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.

5 <

29

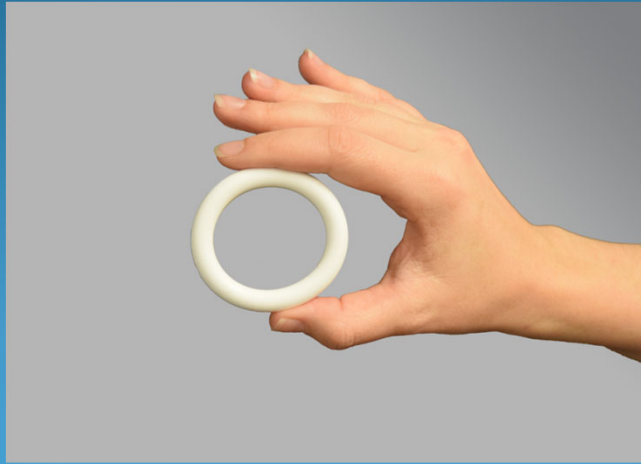
Intravaginal Contraception

63

30

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

Vaginal Ring:Nuvaring



31

Intravaginal Contraceptive

- 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 approved by the FDA in August 2019.

32

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

Intravaginal Ring

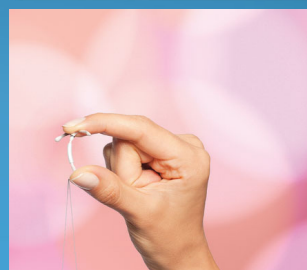
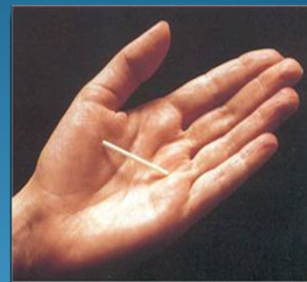
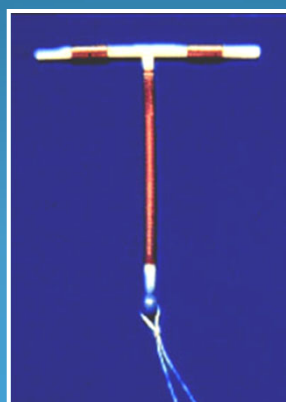
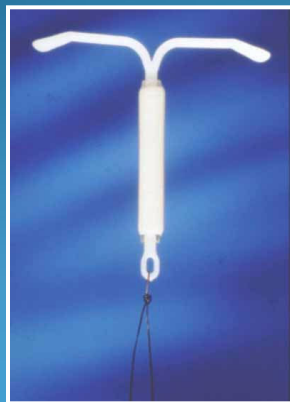
- ⌘ The FDA approved **Annovera** (segesterone acetate and ethinyl estradiol vaginal system), which is a combined hormonal contraceptive for women of reproductive age used to prevent pregnancy and is the first vaginal ring contraceptive that **can be used for an entire year**.
- ⌘ Annovera is a reusable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

66

33

Long Acting Reversible Contraception (LARC)



34

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

The IUD



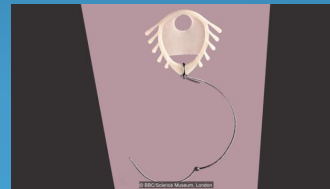
This 'wishbone pessary', developed in Germany around 1880 (Credit: BBC/Science Museum, London)



Ernst Grafenberg designed this IUD in the 1920s



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



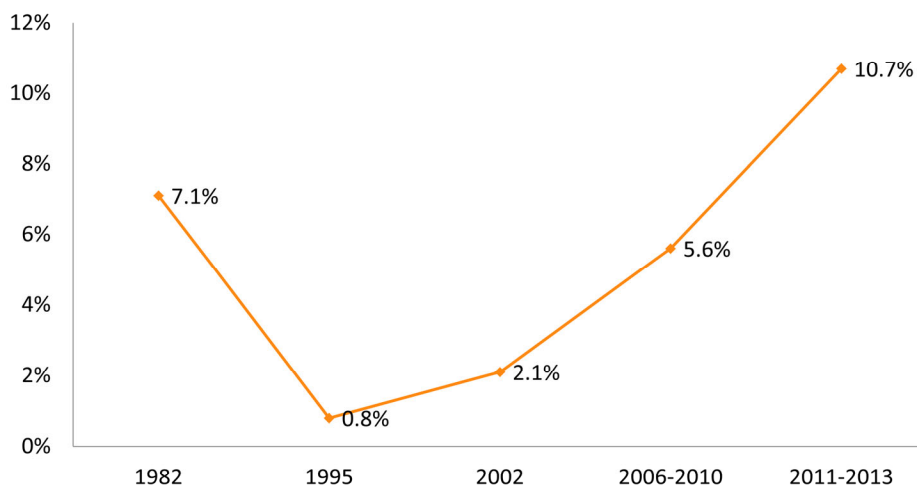
Dalkon Shield had a high risk of pregnancy – and of infections

68

35

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 9.*

THE HENRY J.
KAISER
FAMILY
FOUNDATION

69

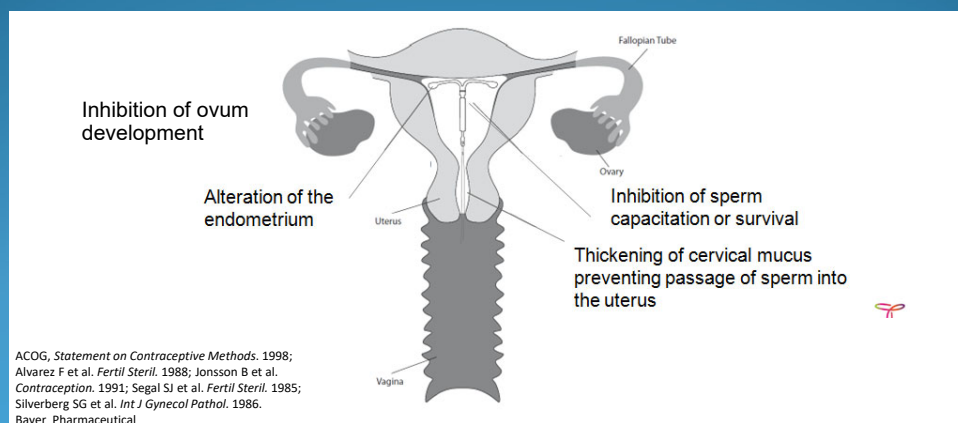
36

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

<u>Copper T IUD</u>	<u>LNG IUS 52mg</u>	<u>LNG IUS 13.5mg</u>	<u>LNG IUS 19.5mg</u>
• Approved in 1984	• Approved in 2000	• Approved in 2012	
• Copper ions	• Releases 20 µg of LNG/day	• Releases 10 µg of LNG/day	Releases 17.5 µg of LNG/day
• Approved for 10 years of use	• Approved for 5 years of use	• Approved for 3 years	• Approved for 5 years of use
• Inserter 4.1 mm	• Inserter 4.4 mm	• Inserter 3.8 mm	• Inserter 3.8 mm
• Indicated for contraception	• Indicated for contraception HMB, PMDD	• Indicated for contraception	
• Specific contraindications: Wilson's disease	• Specific contraindications: Breast cancer, acute liver disease	• Specific contraindications: Breast cancer, acute liver disease	• Specific contraindications: Breast cancer, acute liver disease
Sivin I. <i>Contraception</i> . 2007			

37

Mechanism of Action

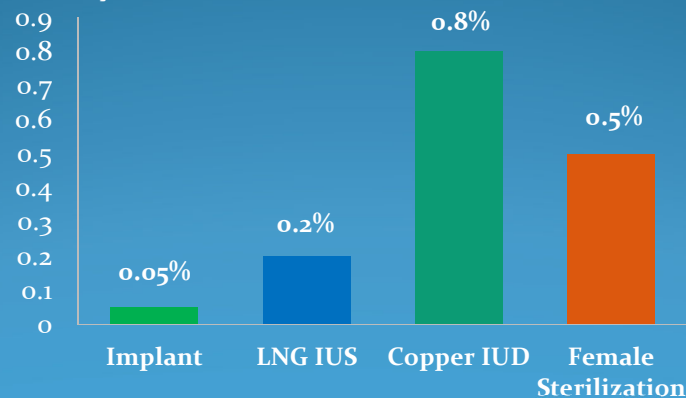


38

“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



Trussell J. Contraceptive failure in the United States. Contraception 2011;83(5):397-404. Epub 2011 Mar 12.

39

LARC in Adolescents

Age and Parity	LNG-IUD	Cu-IUD	Implants
Menarche to <20 years	2	2	1
≥20 years	1	1	1
Nulliparous	2	2	1
Parous	1	1	1

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.

40

“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

Suhonen S, Haukkamaa M, Jakobsson T, Rauramo I. Clinical performance of a levonorgestrel-releasing intrauterine system and oral contraceptives in young nulliparous women: a comparative study. *Contraception* 2004;69:407-12.

Hubacher D. Copper intrauterine device use by nulliparous women: review of side effects. *Contraception* 2007;75(6 suppl):S8-11.

Paterson H, Ashton J, Harrison-Woolrych M. A nationwide cohort study of the use of the levonorgestrel intrauterine device in New Zealand adolescents. *Contraception* 2009;79:433-8.

41

Insertion Timing

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

www.acog.org 2012

42

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

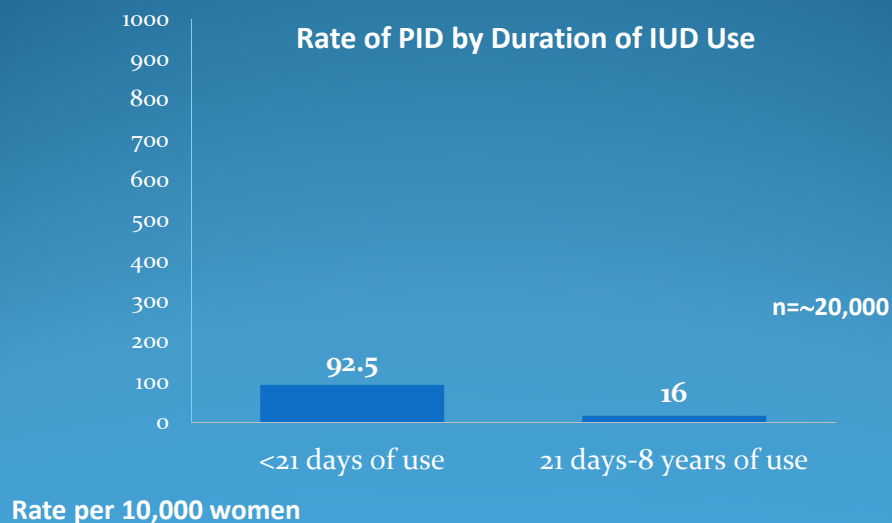
Insertion Protocols - Infection

- ⌘ 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 2012

43

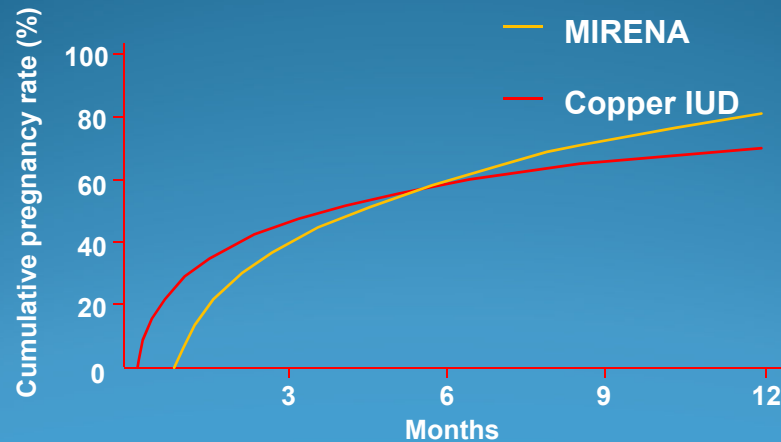
IUDs Do Not Cause PID



44

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

IUD: Return to Fertility



Dqghuvrq#1#0#Frgwdfhswrq#4<<5>79-8:8
Ehkdgr#1#0#Frgwdfhswrq#<;9>67-594

45

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”

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

Postpartum – IUD Controversy

Postpartum	LNG- IUD	Cu- IUD
< 10 minutes	2	1
10 minutes – < 4 weeks	2	2
> 4 weeks	1	1
Puerperal Infection	4	4

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

47

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

48

“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

www.acog.org 2012

49

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

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

Varma R, Sinha D, Gupta JK. Non-contraceptive uses of levonorgestrel-releasing hormone system (LNG-IUS)--a systematic enquiry and overview. Eur J Obstet Gynecol Reprod Biol 2006;125:9–28

50

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

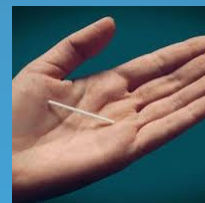
Nexplanon



51

Single-Rod Implant

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



52

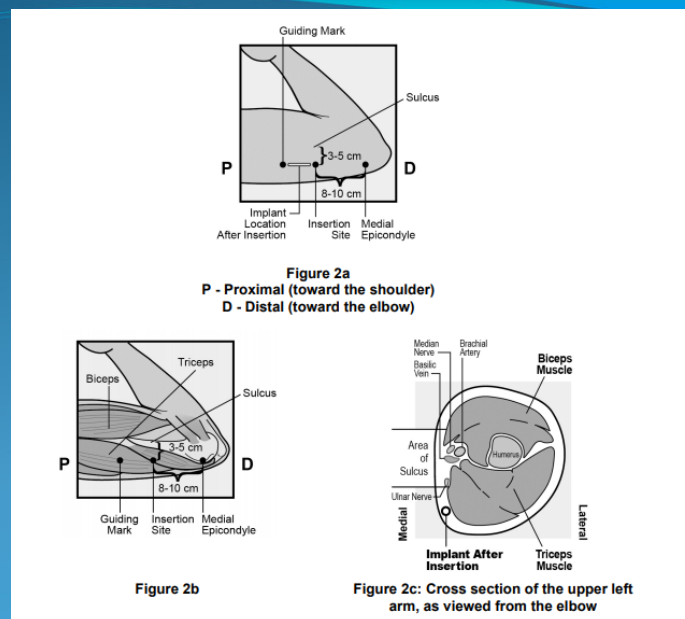
“Contraception” Can There Really be Anything New to Know?

New Location

- Step 2. Identify the insertion site, which is at the inner side of the non-dominant upper arm.
- 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.
- This location is intended to avoid the large blood vessels and nerves lying within and surrounding the sulcus.

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8 7

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

Emergency Contraception

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Many Women Are Unaware of Emergency Contraception or How to Use It

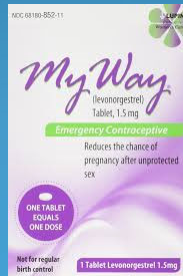
- ⌘ Among women at high risk for unintended pregnancy, 64% have never heard of emergency contraception
- ⌘ Only 7% were aware that the method must be used within 72 hours after intercourse.
- ⌘ Fewer than half (44%) of the women who had heard of emergency contraception believed that it is safe.
- ⌘ A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

Family Planning Perspectives
Volume 33, Number 1, January/February 2001

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

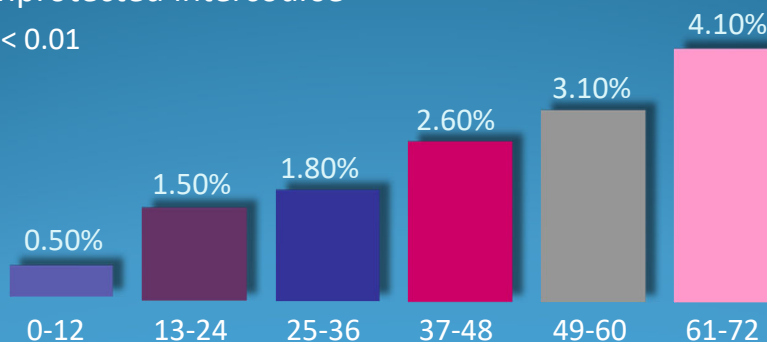
ECPs “Over-the-Counter” in the US



57

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

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



Piaggio G, et al. *Lancet*. 1999.

58

“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

59

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

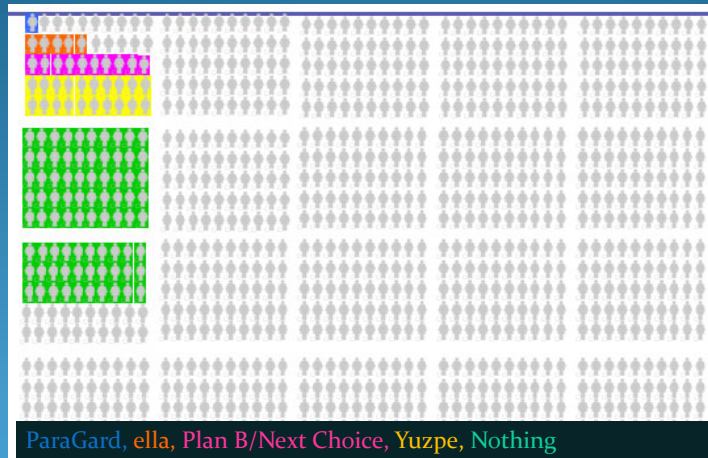


Trussell J, Raymond EG. 2011.

60

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

Pregnancies per 1000 Episodes of Unprotected Intercourse



Trussell J, Raymond EG. Emergency Contraception: A Last Chance to Prevent Unintended Pregnancy. November 2011. Available at <http://dx.doi.org/10.1186/1475-2875-10-100>. 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

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ECP Safety

Safe

- 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. 2011; Trussell J, Schwarz EB. *Contraceptive Technology* 2011; CDC *MMWR* 2010.

62

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