Expanding Contraceptive Choices for Women:
The Vaginal pH Modulator

WOMEN'S HEALTH:
Beyond the Annual Visit

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Learning Objectives Placeholder

At the completion of this educational activity, learners will be better able to:

- Explain the advantages and drawbacks of vaginal pH modulation contraception
- Identify the strategies that will overcome the most common misperceptions that clinicians and patients have regarding gel-based contraceptives
- Discuss scientific data underlying the increasing pregnancy rate demonstrated in contemporary clinical trials of contraception

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New Hormonal Contraceptives

- Drospirenone (DRSP) 4 mg (Slynd) POP
  - 24/4 formulation
  - Long half-life
- Levonorgestrel (LNG) 150 mcg & Ethinyl Estradiol (EE) (Twirla)
  - 30 mcg patch
  - Similar to other CHCs
  - Less effective BMI >25 (contraindicated BMI ≥30)
- 1-yr Vaginal Ring (Annovera)
  - Segesterone acetate 150 mcg & EE 15 mcg
  - Similar to other CHCs, approved as 21/7 schedule

Annovera™
(segesterone acetate and ethinyl estradiol vaginal system)
Delivers 0.15 mg/0.013 mg per day

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Norethindrone vs DRSP Progestin-Only Pills (POPs)

POP	Bleeding	Ovulation inhibition	Half-life
Norethindrone	May be more likely to have unfavorable bleeding	Does not reliably inhibit ovulation	Due to its short half-life, must take pills at the same time each day
Drospirenone	4-day hormone-free interval allows scheduled bleeding	Reliably inhibits ovulation	Due to its long half-life (30-34 hrs), it is not imperative to take pills at the same time each day

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Comparison of Contraceptive Patches

	Xulane®	Twirla®
Daily release of progestin	Norelgestromin 150 mcg/day	Levonorgestrel 120 mcg/day
Daily release of EE	EE 35 mcg/day per manufacturer but 1.6 times the amount of EE as seen with 35-mcg OCP (60% higher)	EE 30 mcg/day
Size/shape	14 cm^2/square	28 cm^2/round

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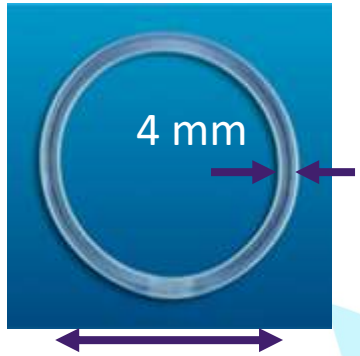
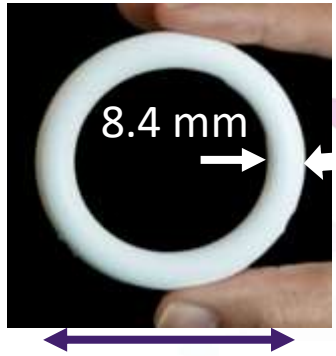
Comparison of Contraceptive Vaginal Rings

	NuvaRing®	Annovera®
Progestin	Etonogestrel 120 mcg/d	Segesterone 150 mcg/d
Estrogen	EE 15 mcg/day	EE 13 mcg/day
Diameter	54 mm	56 mm
Thickness	4 mm	8.4 mm
Lifespan	1 cycle (up to 35 days)	13 cycles (up to 365 days)
Continuous use?	YES, off-label	Highly likely but insufficient data
Appearance	Flexible, transparent	Flexible, opaque, white
Refrigeration	Yes, if stored >4 mo	No

Nuvaring®



Annovera®



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van den Heuvel, et al. *Contraception*. 2005;72(3):168-174.

Vaginal pH Modulation

[Phexxi®]

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Lactic Acid, Citric Acid, and Potassium Bitartrate Vaginal Gel (Phexxi®)

- FDA-approved
- Hormone-free gel
- User-controlled
- Keeps vaginal pH in range of 3.5 to 4.5
- MOA: Maintenance of “normal” vaginal pH = lower sperm motility (vaginal pH increases when semen enters the vagina)

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Lactic Acid, Citric Acid, and Potassium Bitartrate Vaginal Gel (Phexxi®)

- 4-inch prefilled applicator – similar in size to a tampon applicator
- 12 applicators dispensed with each prescription
- Self-administered up to 1 hour before each act of vaginal intercourse
- Can be inserted immediately before intercourse
- Additional dose should be used before each subsequent act of vaginal intercourse

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Mechanism of Action

[Phexxi®]

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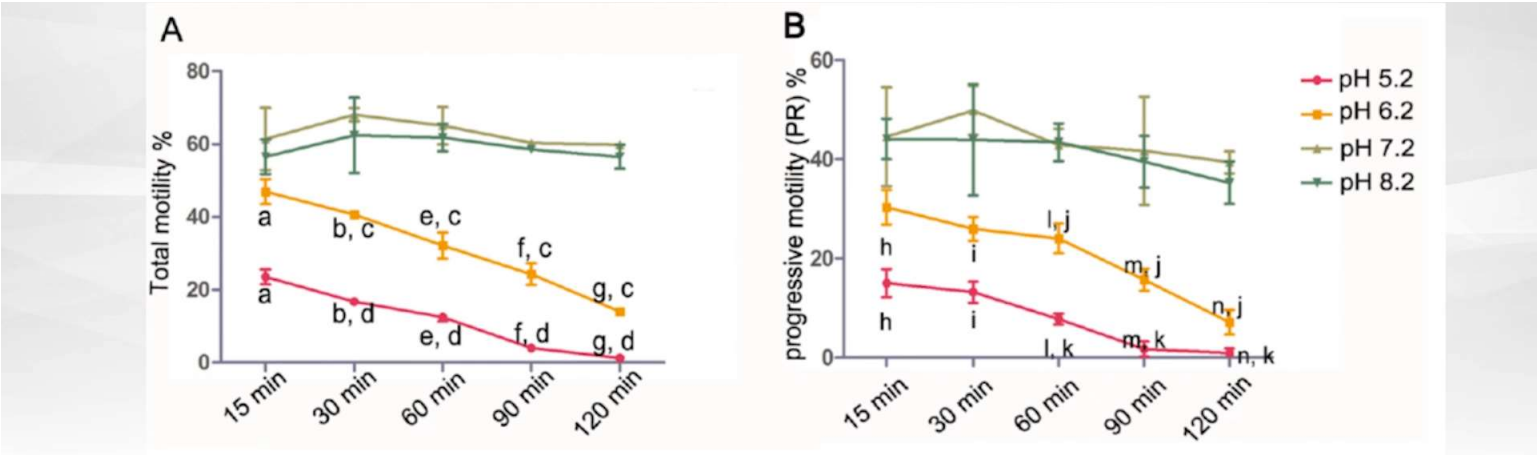
Normal Vaginal pH 3.5-4.5

- Acidic pH between 3.5 and 4.5 maintained by vaginal microbiome
- Lactobacillus ferments glucose, producing lactic acid
- Natural vaginal defense against infections
- Acidic pH is also inhospitable to sperm
- Semen (pH 7.2–8.0) contains buffering proteins to protect sperm from the vaginal environment
- Buffering from ejaculate neutralizes the vaginal defenses for pathogens
- A drug that can maintain an acidic pH in the vagina may provide contraception and potentially reduce risk of STI acquisition

Acidic Environment Can "Neutralize" Sperm

- Total (A) and progressive (B) motility significantly decreased at acidic pH = 5.2



Zhou J, et al. PLoS One. 2015;10(7):e0132974

Vaginal pH Modulator (VPM)

- A successful VPM must:
- Maintain the acidic pH of the vagina
- Have a thick viscosity to prevent dilution due to vaginal secretions, and
- Have bioadhesive properties to persist
- in the vagina for sufficient time to work
- Lactic acid, citric acid, and potassium bitartrate (Phexxi®) is first-in-class, FDA-approved VPM for contraception

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VPM Must "Stick" Around

- Study of 5 vaginal gels showed Phexxi® maintained viscosity 21-271 times better than other 4
- One study demonstrated bioadhesive properties of Phexxi®, meaning it could have spermicidal activity for a prolonged period
- ACIDFORM (precursor product to Phexxi®) was FDA-approved for use as a personal lubricant

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Bayer LL, Jensen JT. *Contraception*. 2014;90(1):11-18. Garg S, et al. *Contraception*. 2001;64(1):67-75. Amaral E, et al. *Contraception*. 2004;70(6):492-497.

Lactic Acid, Citric Acid, and Potassium Bitartrate Vaginal Gel (Phexxi®)

- Prefilled applicator w/5 g of gel at pH 3.55
- Combination of 3 active ingredients:
  - Lactic acid
  - Citric acid
  - Potassium bitartrate
- Inactive ingredients
  - Preservative (benzoic acid)
  - Gelling agents (alginic acid and xanthan gum)
  - Humectant (glycerin)
  - Sodium hydroxide
  - Water

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Bayer LL, et al. *Contraception*. 2014;90(1):11-18. Garg S, et al. *Contraception*. 2001;64(1):67-75.

Lactic Acid, Citric Acid, and Potassium Bitartrate Vaginal Gel (Phexxi®)

- Requires Rx
- User-controlled
- Use prior to each act of vaginal IC
  - NOT postcoital/emergency contraceptive
- Can be used with other contraceptive methods
  - Male/female condoms
  - Diaphragms/cervical caps
  - Hormonal contraceptives (except vaginal contraceptive rings)
  - IUDs

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Source: https://www.empr.com/slideshow/slides/new-drug-product-phexxi/ Accessed on March 23, 2021.

Contraceptive Trial Data

[Phexxi®]

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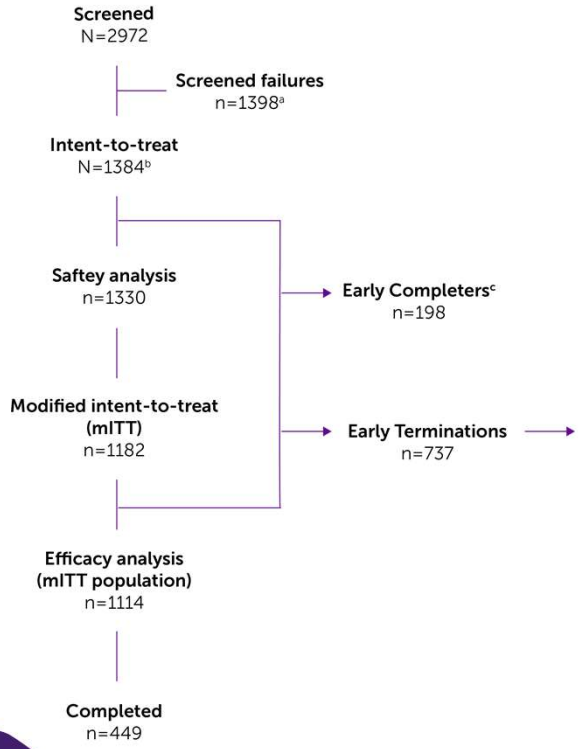
Two Phase 3 Trials: AMPOWER (AMP001)

- 6-mo (7-cycle), open-label, multicenter RCT of VPM vs Conceptrol (4% nonoxynol-9)
  - 4/2011–6/2014
- 18-35 yo
- VPM = 1,665 subjects
  - Cumulative pregnancy rate 10.5% (95%CI, 8.6-12.3)
  - 69% were correct/consistent users → 4.1% pregnancy rate (95% CI, 2.7-5.4)
  - 52.7% discontinued trial <6 mo
- N-9 = 1,659 subjects
  - 54.3% discontinued trial <6 mo
  - Similar pregnancy rates
- <2% in either group cited AEs as reason for discontinuation

Phase 3 Trial: AMPOWER (AMP002)

- 7-cycle, open-label, single-arm, multicenter trial of VPM
- 7/2017-11/2018
- 18-35 yo w/regular menses (21-35 days)
- 1,384 subjects agreed to engage in at least 3 heterosexual acts of vaginal IC/cycle
- Typical-use cumulative pregnancy 13.7% (95% CI, 10.0-17.5)
- Perfect use 6.68% (95% CI, 4.87-8.49)
- Typical use 11.31% (95% CI, 8.92-13.7)
- Pearl Index = 27.5 (95% CI, 22.4-33.5)
- 1.6% of subjects discontinue due to AE

Effectiveness Based on AMP002



Reasons for discontinuation	
Lost to follow-up	250 (18.1%)
Withdrawal by subject	170 (12.3%)
Pregnancy	104 (7.5%)
Non-compliance with study drug	38 (2.8%)
Adverse event	23 (1.7%)
Not sexually active	26 (1.9%)
Physician decision	22 (1.6%)
Protocol deviation	22 (1.6%)
Study method no longer primary method	12 (0.9%)
Study terminated by sponsor	1 (0.1%)
Other	69 (5.0%)
Site scheduled women for final visit before study	54 (3.9%)

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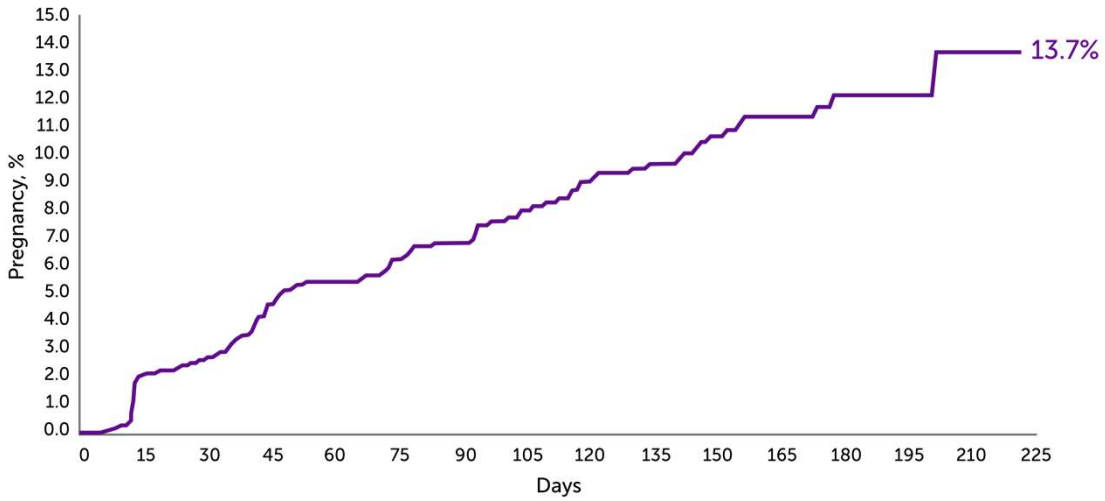
Thomas MA, et al. *Contracept* X. 2020;2:100031. doi:10.1016/j.conx.2020.100031

Effectiveness Based on AMP002*



Risk of pregnancy was 13.7% over 7 cycles of typical use (95% CI: 10.0%, 17.5%) Pearl Index 27.5 (95% CI: 22.4-33.5)

24,289 acts of vaginal IC met inclusion criteria

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*In MITT study
Data on file, Evofem; AMPOO2 CSR, 2019

Adverse Events from AMP001 and AMP002

- 45.2% (601/1330) of women experienced at least one AE
- Most of these adverse reactions were mild
- Only 1.6% discontinued participation in the clinical trials due to an adverse reaction
  - Most common AEs leading to d/c:
    - Vulvovaginal burning sensation 0.7%
    - Vulvovaginal pruritus 0.1%
    - Vulvovaginal discomfort 0.1%
- 0.36% (n = 10) had cystitis, pyelonephritis, or other upper UTI
  - FDA Label: Avoid PHEXXI in women with h/o recurrent UTI or urinary tract abnormalities

Adverse Reactions That Occurred in ≥2% of Subjects Who Used PHEXXI to Prevent Pregnancy (Studies 1 and 2 – United States Population Only)	
Adverse Reaction	**PHEXXI (N = 2480) (%)**
Vulvovaginal burning sensation	18
Vulvovaginal pruritus	14.5
Vulvovaginal mycotic infection*	9.1
Urinary tract infection**,***	9
Vulvovaginal discomfort	9
Bacterial vaginosis	8.4
Vaginal discharge	5.5
Genital discomfort	4.1
Dysuria	3.1
Vulvovaginal pain	2.1

*Includes preferred terms (PTs) vulvovaginal mycotic infection and vulvovaginal candidiasis
**Includes PTs urinary tract infection, streptococcal urinary tract infection, Escherichia urinary tract infection, and urinary tract infection bacterial
***Does not include PTs cystitis, kidney infection, and pyelonephritis (see Warnings and Precautions [5.2])

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Evofem Biosciences. PHEXXI prescribing information. 2020. www.hcp-phexxi.com/core/themes/phexxi/pdf/PhexxiUSPI.pdf

Male Partners

- 9.8% (131 of 1,330) of male partners in AMP002 reported local symptoms
- Burning, itching, pain, and “other”
- 74.7% mild, 21.4% moderate, 3.9% severe
- 2 subjects (N = 1,330) discontinued trial due to male partner symptoms

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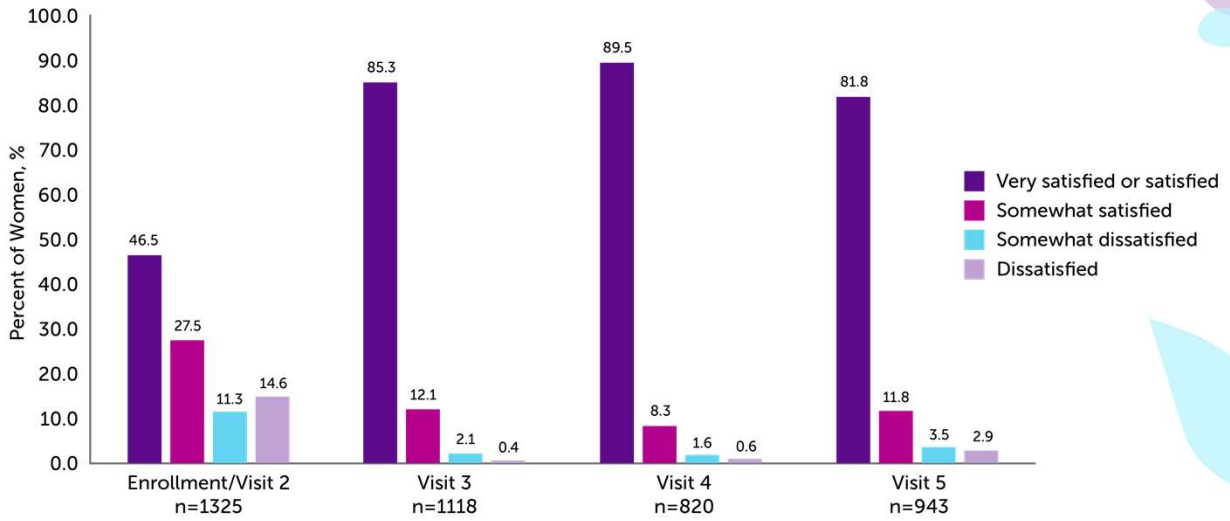
Satisfaction with VPM (AMP002 Trial Data)

Over time in trial

Sexual satisfaction and function 1st cycle compared to baseline

87% of subjects would continue after trial

93% would recommend to a friend



Women's satisfaction with their most recent contraceptive method. At visit 2, women reported satisfaction with their most recent contraceptive method used prior to enrollment. Women reported their satisfaction with the study treatment at every subsequent study visit; visit 3 corresponded to study cycle 2, visit 4 corresponded to study cycles 5 or 6, and visit 5 occurred 14-30 days after study cycle 7. Visit 5 included responses from women who returned 14-30 days after their seventh cycle or from their last use of study product for early termination.

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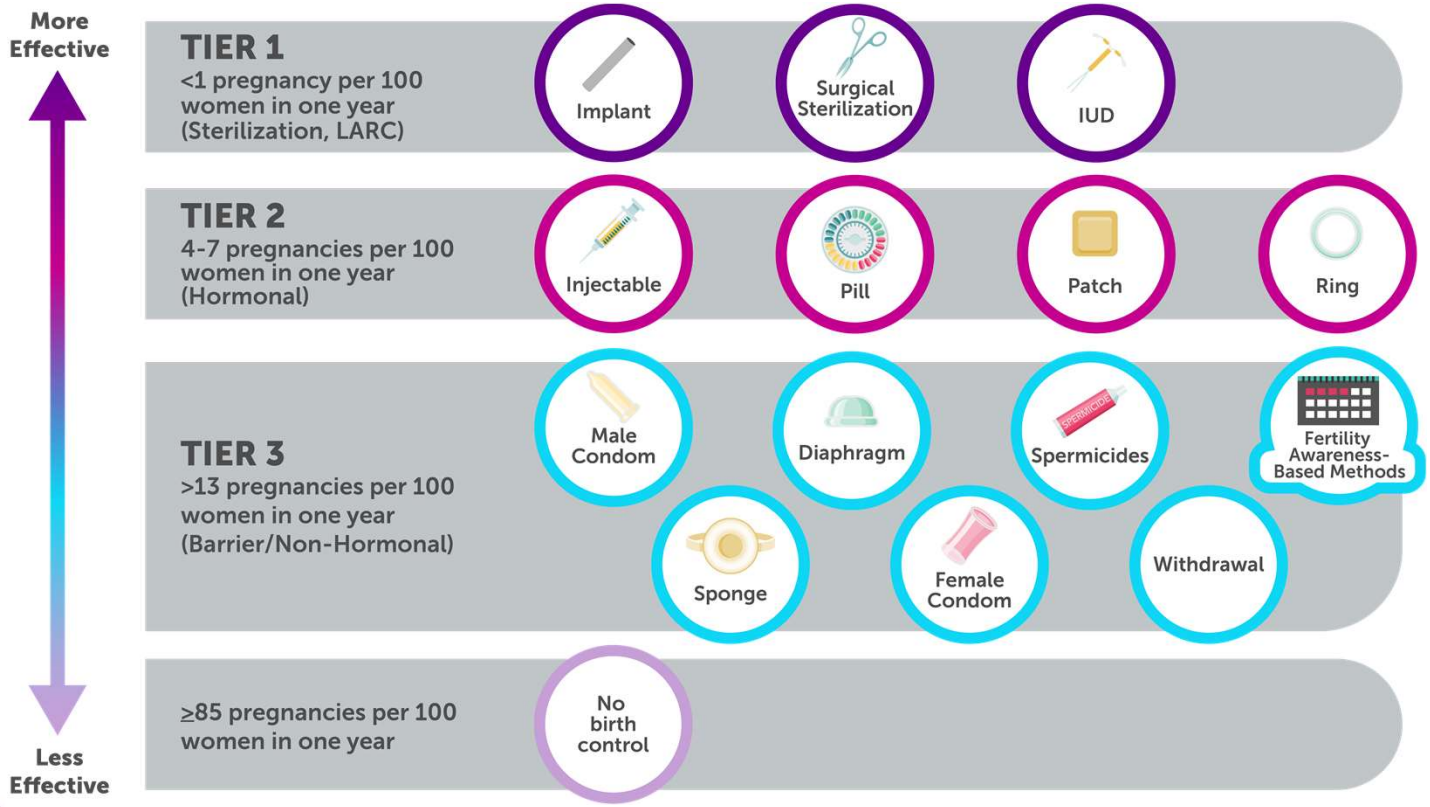
Thomas MA, et al. *Contracept X*. 2020;2:100031. https://doi.org/10.1016/j.conx.2020.100031

Contraceptive Options



Adapted from Hatcher RA. *Contraceptive Technology*. 21st Ed; 2018.

Pearl Index Is Highly Sensitive to Study Design, Duration, and Population Factors

$$\text{Pearl Index} = \frac{\text{Number of Pregnancies}}{\text{Number of Months or Cycles}} \times \begin{matrix}\text{1200 for months}\\ \text{or}\\ \text{1300 for cycles}\end{matrix}$$

Lower Pearl Index = lower chance of unintentional pregnancy

- Used as a measure of contraceptive failure in clinical trials
- Has increased in recent years
- Historical combined hormonal contraception trials include factors known to yield low Pearl Indices:

  - ✓ Enrolling women in EU trial sites
  - ✓ Restricting enrollment based on BMI or weight
  - ✓ Recruiting more affluent, educated women
  - ✓ No requirement to anticipate, record sexual activity
  - ✓ No accounting for lack of sexual activity

- **Produced ungeneralizable results**
- **Wide gap between clinical trial efficacy and actual-use effectiveness**

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Trussell J, et al. *Contraception.* 2013;88(5):604-610.
Gerlinger C, et al. *Contraception.* 2014;90(2):142-146.

Pearl Indices of CHCs Rising in Contemporary Clinical Trials, Referred to as "Creeping Pearl"

Contemporary CHC trials include multiple factors known to increase Pearl indices:

- ✓ Limiting enrollment to women in US
- ✓ Fewer to no restrictions on weight or BMI
- ✓ Documenting and removing sexually inactive and backup method us cycles
- ✓ More sensitive pregnancy tests
- ✓ More frequent pregnancy testing

- More inclusive, representative populations
- Pearl Index more reflective of actual-use effectiveness

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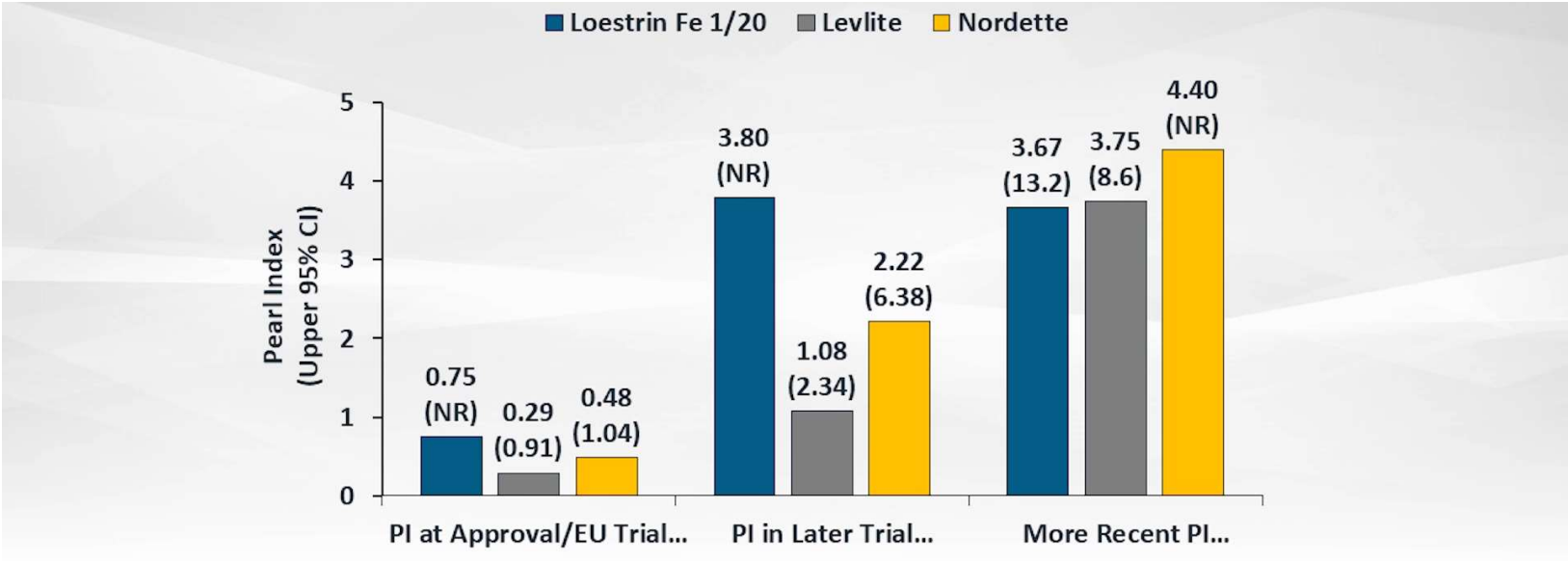
Trussell J, et al. *Contraception.* 2013;88(5):604-610.
Gerlinger C, et al. *Contraception.* 2014;90(2):142-146.
Portman D, et al. *Midwifery Womens Health.* 2021

Pearl Indices in Initial FDA Registration Studies Increased in Later Trials



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Upper 95% CI not reported (NR) for all studies. Adapted from Edelman A, et al. *Contraception*. 2018;97(5):371-377

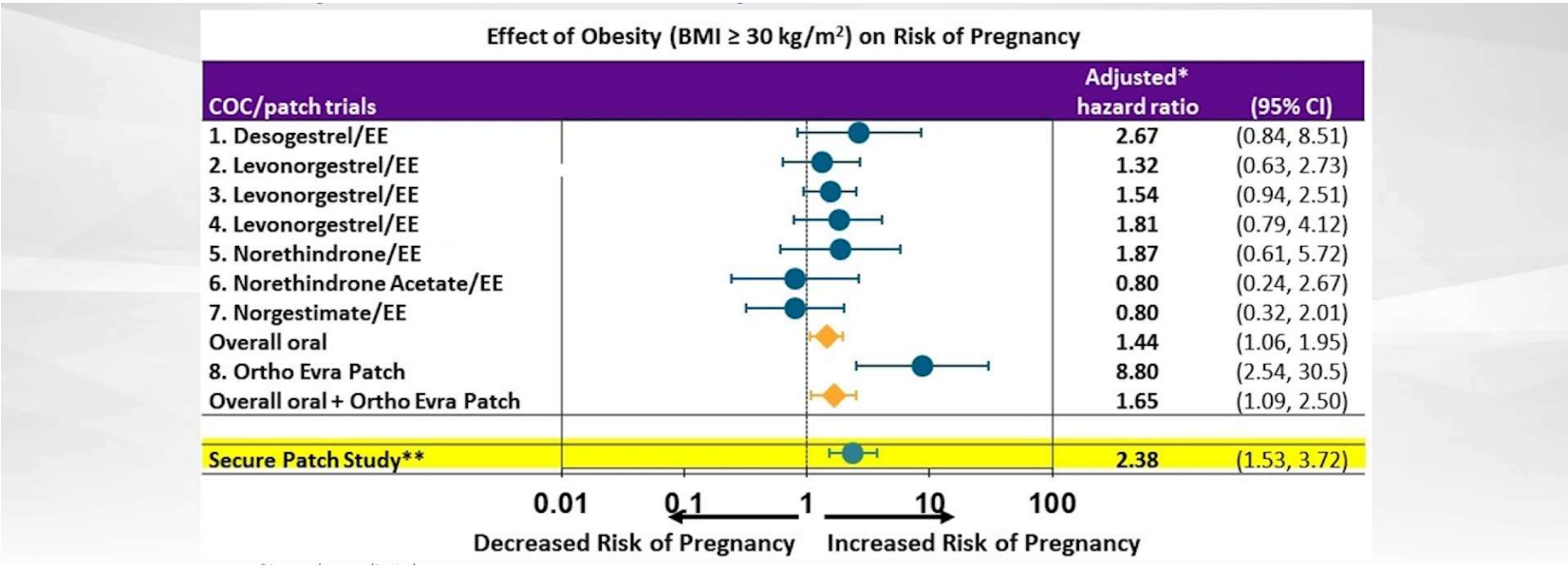
Prescribing Information for Recent Contraceptives Includes Specific Pearl Index Rates

Contraceptive	Original approval/ PI updated	Type	Overall efficacy data
LNG 120 mcg/day and EE 30 mcg/day transdermal system (Twirla®)[1]	2020/2020	Patch	PI = 5.8 (95% CI, 4.5-7.2)
Drospirenone 4 mg tablets (Slynd™)[2]	2019/2019	POP	PI = 4.0 (95% CI, 2.3-6.4)
Segesterone/EE vaginal ring (Annovera™)[3]	2018/2020	CVR	PI = 2.98 (95% CI, 2.13-4.06)
Norethindrone acetate 1 mg and EE 10 mcg tablets, EE 10 mcg tablets and ferrous fumarate 75 mg tablets (Lo Loestrin® Fe)[4]	2010/2017	COC	PI = 2.92 (95% CI, 1.94-4.21)

COC, combined oral contraception; CVR, combined vaginal ring; POP, progestogen-only pill.

1. TWIRLA (LNG and EE) transdermal system. Prescribing information. Corium International, Inc.; 2020. 2. SLYND (drospirenone) tablets for oral use. Prescribing information. Exeltis USA, Inc.; 2019. 3. Annovera. Prescribing information. TherapeuticsMD; 2020. 4. LOESTRIN® 21 Day (norethindrone acetate and EE tablets USP). LOESTRIN® Fe 28 Day (norethindrone acetate and EE tablets USP and ferrous fumarate tablets*). Prescribing information. Teva Women's Health, Inc.; 2017.

FDA Meta-Analysis: Relationship Between Obesity and Contraceptive Effectiveness



*Age and race adjusted
**Not part of meta-analysis

Adapted from Yamazaki M, et al. *Contraception*. 2015;92(5):445-452. FDA Advisory Committee, Sponsor Briefing Document, October 30, 2019

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SECURE: Effectiveness (Life Table) Varied Based on BMI

BMI (kg/m2) of study participants (≤ 35 years old)	Effectiveness (%)
<25 (Normal)	97%
≥ 25 to < 30 (Overweight)	95%
≥ 30 (obese)	93%

TWIRLA is indicated as a method of contraception for us in women with a BMI < 30 kg/m2 for whom a combined hormonal contraceptive is appropriate. Consider TWIRLA's reduced effectiveness in women with a BMI ≥ 25 to < 30 kg/m2 before prescribing TWIRLA. TWIRLA is contraindicated in women with a BMI ≥ 30 kg/m2

Data on file Study ATI-CL23

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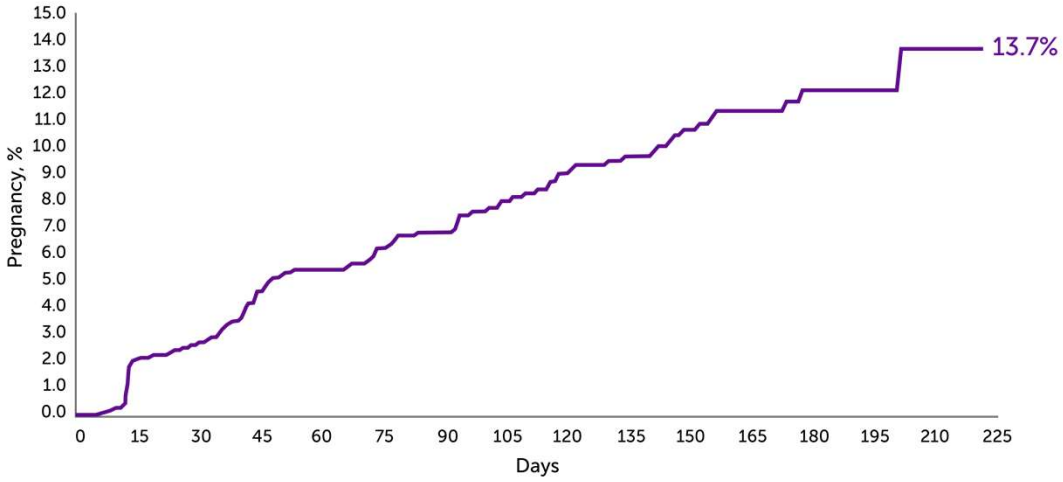
Primary Efficacy Analysis: 7-Cycle Cumulative Pregnancy Kaplan-Meier Probabilities for Phexxi®*



Risk of pregnancy was 13.7% over 7 cycles of typical use (95% CI: 10.0%, 17.5%) Pearl Index 27.5 (95% CI: 22.4-33.5)

- 100 pregnancies occurred in 1,182 subjects and 24,289 acts of intercourse
- 0.4% pregnancy rate per act of vaginal intercourse

Note: The prescribing information lists 101 pregnancies = 1,183 total.

*In MITT study

Data on file, Evofem; AMPOO2 CSR, 2019

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Secondary Efficacy Analysis: Perfect-Use 7-Cycle Cumulative Pregnancy Kaplan-Meier Probabilities

Phexxi® was efficacious in preventing pregnancy

Perfect use	Number of subjects at risk of pregnancy	Number of pregnancies ≤ 7 cycles	7-cycle cumulative pregnancy KM probability %(95% CI)
EE population	941	56	**10.0** (7.2-12.8)
EE population adjusted for subjects with protocol violations †	948	49	**8.4** (5.9-11.0)
MITT population adjusted for subjects with protocol violations †	1100	49	**6.7** (4.6-8.7)

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† including cycles up to 42 days.

Chappell B, et al. ACOG, 2020;135:99S. Data on file, Evofem. AMP002 CSR, 2019

Diverse Population Needs Accurate Effectiveness Information and Wide Range of Contraceptive Options to Meet Diverse Needs

- People need accurate, generalizable information from inclusive clinical trials
- Labels should fully inform prescribers and users of risks/benefits
- Realize that modern trial design impacts efficacy and effectiveness endpoints
- The most effective method fits a woman's lifestyle with an acceptable side effect/risk profile and preferred route of administration
- A wide variety of choices will provide couples with the greatest opportunity for successful contraception, help close the gap between efficacy and effectiveness, and optimize reproductive health goals

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