WOMEN'S HEALTH 2020:
Beyond the Annual Visit

The Changing Landscape of Contraceptive Trials: Recent Approvals and Future Directions

David J. Portman, MD

omnia EDUCATION

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Faculty

David J. Portman, MD
Director Emeritus, Columbus Center for Women's Health Research
Adjunct Instructor, Obstetrics and Gynecology
The Ohio State University College of Medicine
Columbus, OH

Advisory Board: Evofem
Consulting Fees: Agile Therapeutics, Sebela
Research Grants: Agile Therapeutics
Shareholder: Sermonix Pharmaceuticals

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Learning Objectives

- Review current contraception options, unmet needs, and recent approvals
- Identify information that will overcome the most common misperceptions that clinicians may hold regarding contraceptive patches and other non-Long Acting Reversible Contraception (LARC) methods
- Explain the advantages and drawbacks of contraceptive patches and non-LARC methods
- Discuss the scientific data underlying "typical" and "perfect" use and the "Creeping Pearl Index" demonstrated in contemporary clinical trials of contraception

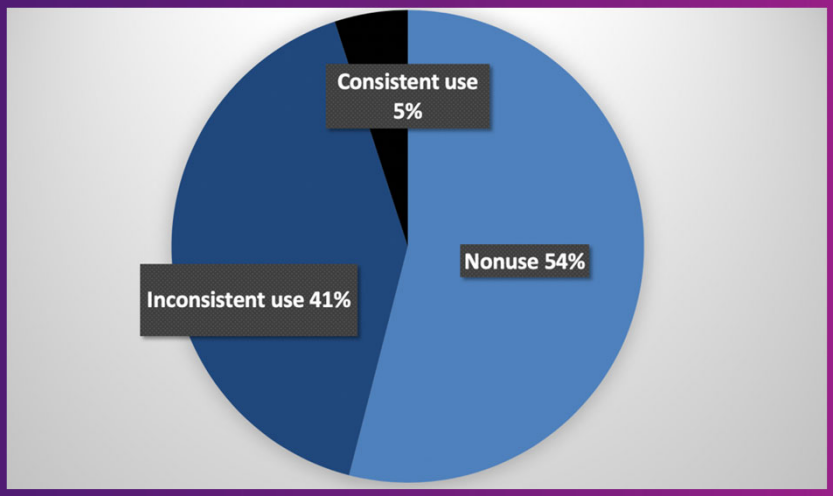
Nearly All US Women Will Use Contraception at Some Point in Their Lifetime[1]

- Women weigh various factors when selecting a contraceptive method[2]
  - Effectiveness
  - Dose
  - Hormonal vs. non-hormonal methods
  - Delivery route and level of invasiveness
  - Frequency of administration
- No single method for all women[3]
  - Choices vary person-to-person within a woman's reproductive years
- Consistency more likely when contraceptive choice fits a woman's lifestyle[4]

1. Daniels K, et al. National Center for Health Statistics. 2013. Available from: http://www.cdc.gov/nchs/data/nhsr/nhsr062.pdf
2. Chen BA, et al. *Contraception*. 2019;99:357-362.
3. Mansour D. *Intl J Womens Health*. 2014;6:367-375.
4. Grady WR, et al. *Perspect Sex Reprod Health*. 2002;34:135-45.

Nearly Half of Pregnancies in the US Are Unintended

Unintended Pregnancy by Consistency of Contraception Use



Sonfield A, Hasstedt K, Gold RB. Moving Forward: Family Planning in the Era of Health Reform. New York: Guttmacher Institute; 2014.

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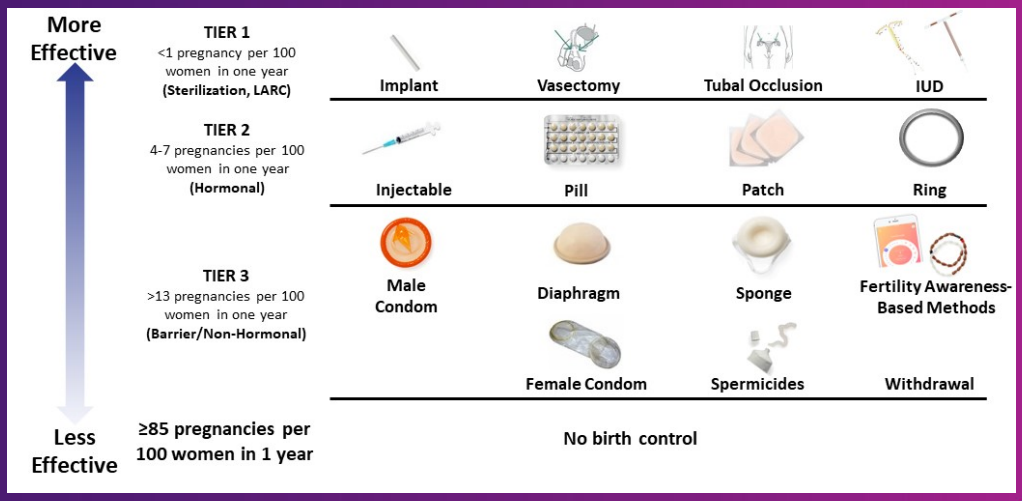
Contraceptive Options Tiered Based on Effectiveness



Adapted from Contraceptive Technology 2018.

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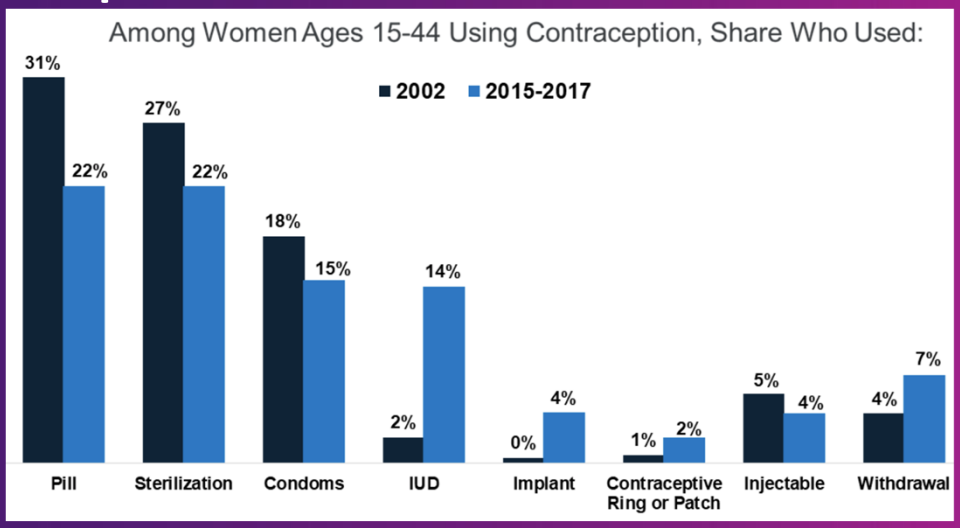
Contraceptive Methods in the US



Note: More than one method may be used by a woman, but these data only reflect the most effective method used.
Source: Kaiser Family Foundation analysis of the National Survey of Family Growth 2002 and 2015-2017

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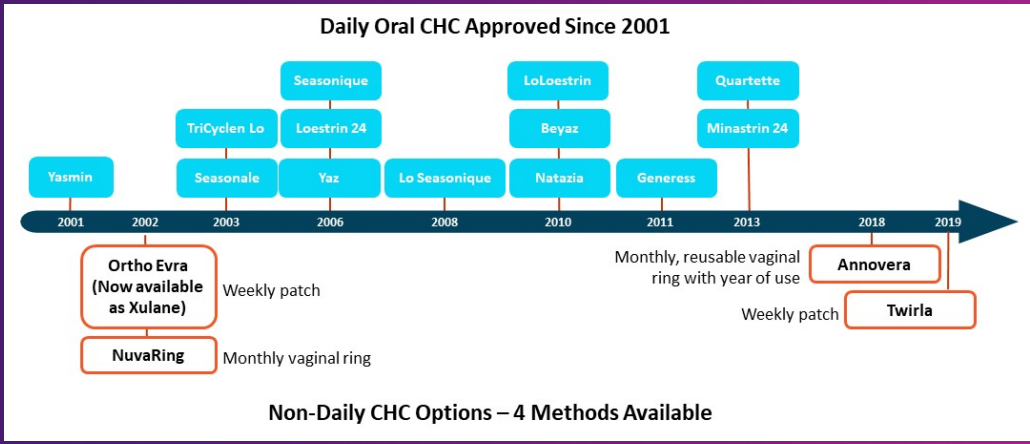
Only Four Non-Daily CHC Methods Available



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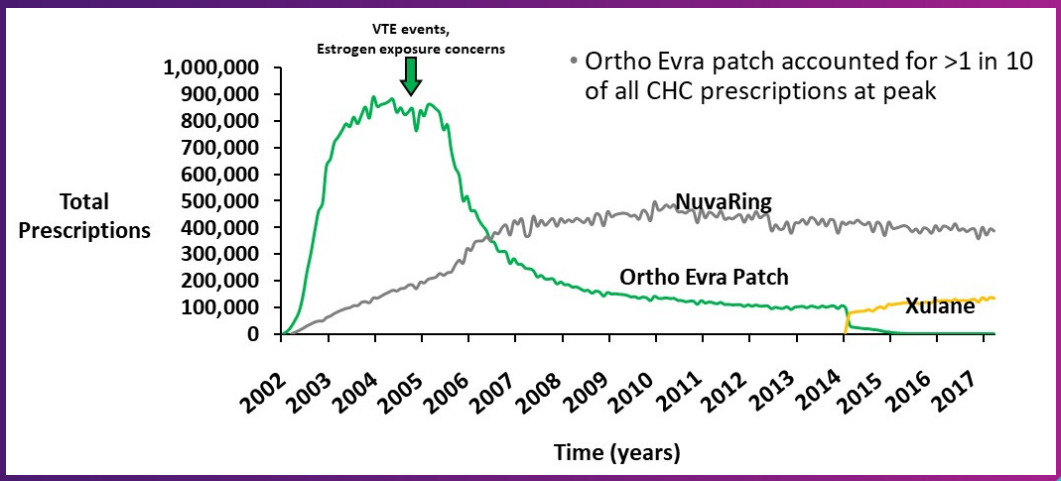
Advantages of Transdermal Drug Delivery

- Controlled-release dosage forms may offer potential to reduce incidence, severity of side effects[1]
- Avoids reduced bioavailability with oral administration[1]
- May be desirable to women who have difficulty or avoid taking oral medication[1]
- Potential to reduce burden associated with daily OCs
  - 49% contraception users prefer non-daily method[2]
  - 52% frustrated with taking pill daily[2]

1. Burkman, 2007
2. Mansour, 2014

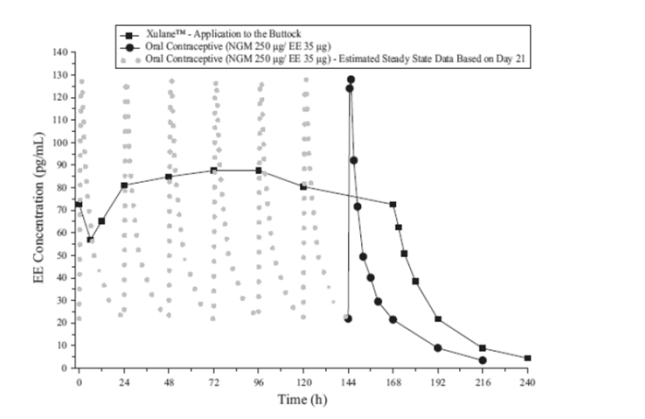
CHC Use Patterns Demonstrate Interest in Non-Oral, Non-Daily Methods



IMS National Prescription Audit

Combination Hormonal Contraceptive (CHC) Norelgestromin (NGMN) + Ethinyl Estradiol (EE)

PK Profiles of Patches vs. Orals



The PK profile of Ortho Evra/Xulane is different from the PK profile for oral contraceptives. AUC and Css for EE are approximately *55% and 60% higher* compared with women using an oral contraceptive containing EE 35 mcg.

Source: Xulane prescribing information

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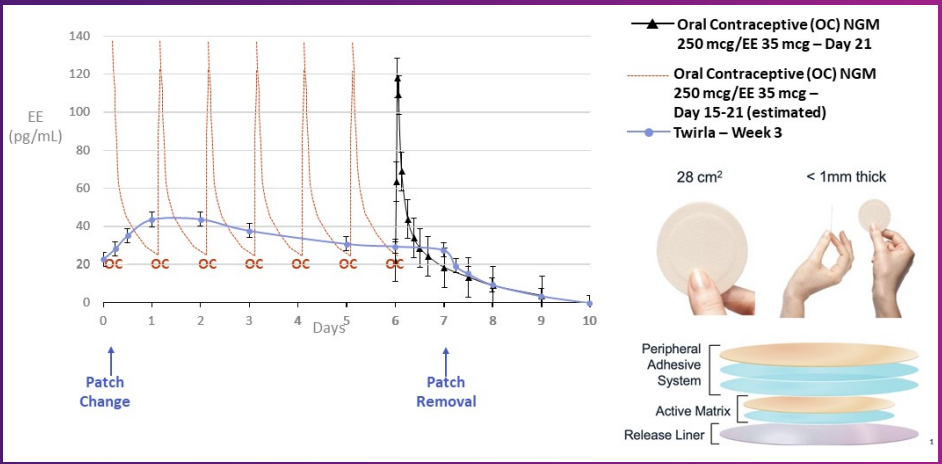
Combination Hormonal Contraceptive (CHC) with Levonorgestrel (LNG) + Ethinyl Estradiol (EE)

A Different PK Profile: Similar to a 30 mcg Pill



Source: Data on file Study ATI-CL14

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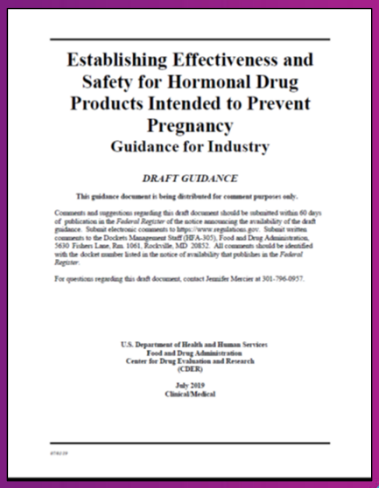
SECURE Trial: Inclusive Study Design to Inform Contraceptive Decision-Making

	FDA Guidance for Contraceptive Clinical Trials (2019)			
Product (Approval date)	Enroll representative patient population relative to the US	No enrollment restrictions on BMI or Weight	Enroll sexually active patients (≥ 1 X per month)	Exclude all sexually inactive cycles
Twirla (Feb 2020)	✓	✓	✓	✓
Annovera (2018)		*	*	
Quartette (April 2013)	✓	✓		
Lo Loestrin FE (Oct 2010)	✓			
Natazia (May 2010)				
LoSeasonique (Oct 2008)	✓	✓		
Lybrel (May 2007)	✓	✓		✓
Ortho Evra/Xulane (November 2001)			✓	



Establishing Effectiveness and Safety for Hormonal Drug Products Intended to Prevent Pregnancy
Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
(CDER)

July 2019
Clinical/Medical

HCP Market Research, MarketVision, February 2020. Data on file.
NDA reviews, *Annovera began excluding participants with BMI > 29 kg/m^2 six months into the study; only 10.6% of the study population were women with BMI > 29 kg/m^2. Per cycle sexual activity was collected at clinic visits but not analyzed in the calculation of the Pearl Index.

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SECURE: Efficacy in a Representative Population: Obesity in 35% of Patients; >25% Women of Color

Population (ITT)	Pearl Index	UB 95% CI
≤35 years of age	5.83	7.21

BMI Category	BMI (kg/m^2)	% of Study Population	Pearl Index	UB 95% CI
Normal	<25	39%	3.46	5.16
Overweight	≥25 - <30	25%	5.69	8.40
Non-Obese	<30	65%	4.34	5.82

ITT, intent to treat; all results shown are based on ITT subjects ≤35 years of age; UB 95% CI, upper bound of the 95% confidence interval.
Source: Nelson, et al. ACOG 2017.

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SECURE: Effectiveness Varied Based on BMI

BMI (kg/m^2) 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 use in women with a BMI <30 kg/m^2 for whom a combined hormonal contraceptive is appropriate. Consider TWIRLA's reduced effectiveness in women with a BMI ≥25 to <30 kg/m^2 before prescribing TWIRLA. TWIRLA is contraindicated in women with a BMI ≥30 kg/m^2.

Data on file Study ATI-CL23

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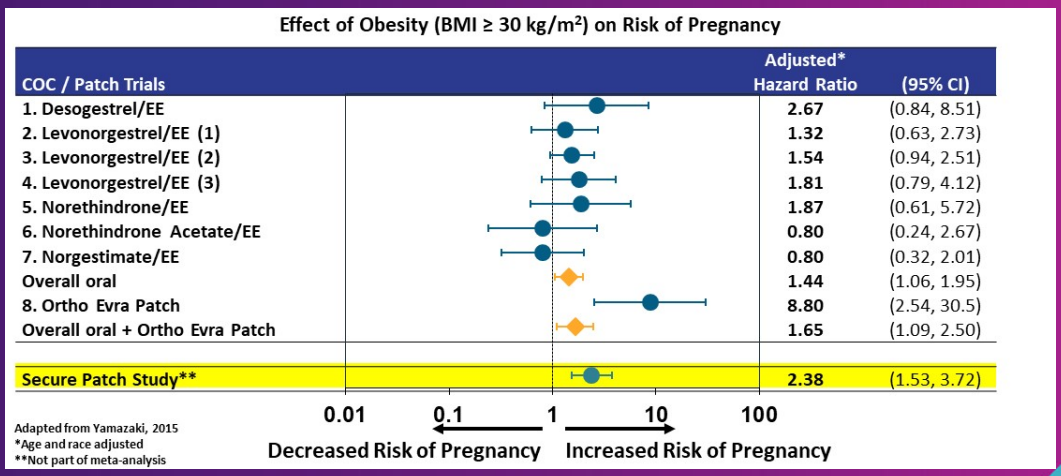
FDA Meta-Analysis: Relationship Between Obesity and Contraceptive Effectiveness



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SECURE: Adverse Events

Adverse Reactions Reported by ≥ 2% of subjects	SECURE N=2031
General disorders and administration site conditions Application Site Disorders	6.2%
Gastrointestinal disorders Nausea	4.1%
Nervous system disorders Headache	3.6%
Reproductive system and breast disorders Dysmenorrhea	2.3%
Investigations Weight increase	2.0%

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SECURE: VTE Serious Adverse Events

Number of Women with Drug-related VTE by BMI BMI Category (kg/m²)	SECURE N=2031
Non-Obese (<30)	0
Normal (<25)	0
Overweight (≥25 to <30)	0
Obese (≥30)	4

Obesity as a risk factor in venous thromboembolism: Stein, et al

	Pulmonary embolism		Deep venous thrombosis	
	Obese vs non-obese		Obese vs non-obese	
Age groups	Relative risk	(95% CI)	Relative risk	(95% CI)
<40 y	5.19	(5.11–5.28)	5.20	(5.15–5.25)
40–49 y	1.94	(1.91–1.97)	2.13	(2.11–2.15)
50–59 y	1.25	(1.23–1.27)	1.67	(1.65–1.68)
60–69 y	1.42	(1.40–1.44)	1.88	(1.87–1.90)
70–79 y	2.07	(2.04–2.10)	1.89	(1.87–1.91)
>80 y	3.15	(3.08–3.22)	2.16	(2.12–2.20)
All ages	2.18	(2.16–2.19)	2.50	(2.49–2.51)

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Contraceptive Clinical Trials and "The Creeping Pearl": Putting Efficacy and Effectiveness into Context

ELSEVIER

Contraception

Contraception 88 (2013) 604–610

Review Article

The creeping pearl: why has the rate of contraceptive failure increased in clinical trials of combined hormonal contraceptive pills?☆,☆☆,★,★★

James Trussell[a,b,*], David Portman[c,d]

[a]Office of Population Research, Princeton University, Princeton, NJ 08544
[b]The Hull York Medical School, Hull, England HU6 7RX
[c]Columbus Center for Women's Health Research, Columbus, OH 43213
[d]Department of Obstetrics and Gynecology, Ohio State University College of Medicine, Columbus, OH 43213

Received 7 February 2013; revised 4 April 2013; accepted 7 April 2013

Abstract

Background: Despite several drawbacks, the Pearl Index continues to be the most widely used statistical measure of contraceptive failure. However, Pearl indices reported in studies of newer hormonal contraceptives appear to be increasing.
Study Design: We searched PubMed and Medical Intelligence Solutions databases for prospective trials evaluating oral contraceptive (OC) efficacy to examine potential factors that could contribute to increasing Pearl indices.
Results: Numerous potential factors were identified, including an increased rate of failures of newer OCs, deficiencies in methods of calculating contraceptive failure rates, differences in study design and changes in patient populations resulting in increased rates of contraceptive failures due to the inappropriate or inconsistent use of the method.
Conclusions: The two most likely important contributors to the increase in Pearl [illegible]

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One-Year Failure Rates: Typical vs. Perfect

Closing the gap?

Method	% of Women Experiencing an Unintended Pregnancy within the First Year of Use		% of Women Continuing Use at One Year[3]
	Typical Use[1]	Perfect Use[2]	
No method[4]	85	85	
Spermicides[5]	21	16	42
Female condom[6]	21	5	41
Withdrawal	20	4	46
Diaphragm[7]	17	16	57
Sponge	17	12	36
Parous Women	27	20	
Nulliparous Women	14	9	
Fertility awareness-based methods[8]	15		47
Ovulation method[9]	23	3	
TwoDay method[9]	14	4	
Standard Days method[9]	12	5	
Natural Cycles[9]	8	1	
Symptothermal method[9]	2	0.4	
Male condom[6]	13	2	43
Combined and progestin-only pills	7	0.3	67
Evra patch	7	0.3	67
NuvaRing	7	0.3	67
Depo-Provera	4	0.2	56
Intrauterine contraceptives			
ParaGard (copper T)	0.8	0.6	78
Skyla (13.5 mg LNG)	0.4	0.3	
Kyleena (19.5 mg LNG)	0.2	0.2	
Liletta (52 mg LNG)	0.1	0.1	
Mirena (52 mg LNG)	0.1	0.1	80
Nexplanon	0.1	0.1	89
Tubal occlusion	0.5	0.5	100
Vasectomy	0.15	0.1	100

Contraceptive Technology 21st Edition 2018

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The Pearl Index

- Used as a measure of contraceptive failure in clinical trials[1]
- Has increased in recent years[1]

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

Number of pregnancies per 100 woman-years of product use

Lower Pearl index = lower chance of unintentional pregnancy

- Difficult to compare rates of contraceptive failure between clinical trials because the Pearl Index is affected by various factors[1]

Clinical trial design and methodology	Study population characteristics
• Duration of clinical trial (likelihood of pregnancy decreases over time) • Frequency and sensitivity of pregnancy testing • Definition of on-study/post-study pregnancies • Lack of uniform trial design	• Frequency of intercourse • Fecundity • Motivation to avoid pregnancy • Sociodemographics • Prior use of hormonal contraceptives • Adherence and correct use

1. Trussell J, Portman D. *Contraception*. 2013;88:604-10.

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

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

BMI, body mass index; EU, European Union.

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, removing sexually inactive cycles
- ✓More frequent pregnancy testing
- ✓More sensitive pregnancy tests

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

BMI, body mass index; CHC, combined hormonal contraception; EU, European Union.
Trussell J, et al. *Contraception* 2013;88:604-610.

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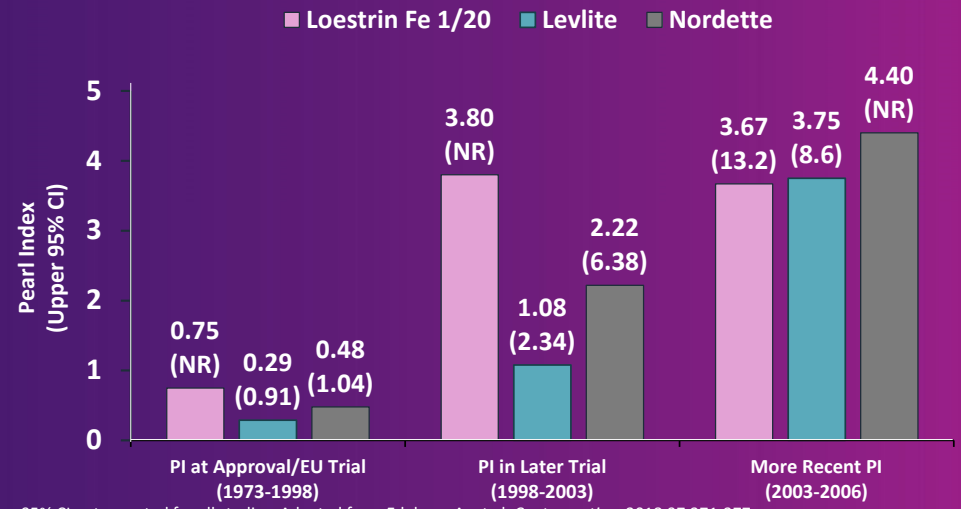
Pearl Indices in Initial FDA Registration Studies Increased in Later Trials



Upper 95% CI not reported for all studies. Adapted from Edelman A, et al. *Contraception.* 2018;97:371-377.
EU, European Union; NR, not reported; PI, Pearl Index.

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Prescribing Information for Recent Contraceptives Include Specific Pearl Index Rates

Contraceptive	Original Approval/ PI updated	Type	Overall Efficacy Data
LNG 120 µg/day and EE 30 µg/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 µg tablets, EE 10 µg tablets and ferrous fumarate 75 mg tablets (Lo Loestrin® Fe)[4]	2010/2017	COC	**PI = 2.92** (95% CI, 1.94–4.21)
LNG 0.15 mg and EE 30 µg tablets (Portia®, generic of Nordette®)[5]	1982; 2002 generic approved/ 2017 label revised	COC	PI Not Reported
Norethindrone acetate 1 mg and EE 20 µg tablets, and ferrous fumarate 75 mg tablets (Junel® Fe 1/20, generic of Loestrin® Fe 1/20)[6]	1973; 2003 generic approved/ 2017 label revised	COC	PI Not Reported
LNG 0.100 mg and EE 0.020 mg tablets (Lessina®, generic of Levlite™)[7]	1998; 2002 generic approved/ 2017 label revised	COC	PI Not Reported

1. TWIRLA (LNG and EE) transdermal system [prescribing information]. Grand Rapids, MI: Corium International, Inc.; 2020. 2. SLYND (drospirenone) tablets for oral use [prescribing information]. Florham Park, NJ: Exeltis USA, Inc.; May 2019. 3. ANNOVERA [prescribing information]. Boca Raton, FL: TherapeuticsMD, Inc.; 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]. North Wales, PA: Teva Women's Health, Inc.; August 2017. 5. NORDETTE®-28 (LNG 0.15 mg and EE 30 mcg tablets) [prescribing information]. North Wales, PA: Teva Women's Health, Inc.; March 2019. 6. JUNEL 21 DAY- norethindrone acetate and EE tablet [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; August 2017. 7. LESSINA® (LNG and EE tablets USP) [prescribing information]. North Wales, PA: Teva Pharmaceuticals USA, Inc.; 2017. COC, combined oral contraceptive; CVR, contraceptive vaginal ring, EE, ethinyl estradiol; LNG, levonorgestrel; PI, Pearl Index; POP, progestin-only pill.

Annovera™ Segesterone Acetate/EE Contraceptive Vaginal Ring FDA Approved 2018 and Factors Impacting PI

Pearl Index **2.98** (95% CI 2.13, 4.06)

Subgroup analyses:

- For women who did not record any episodes of prolonged (> two hours) CVR removal during cyclic use, the PI was **2.10** (95% CI 1.37-3.06).
- For women who did record episode(s) of prolonged CVR removal, the PI was **5.89** (95% CI 3.46-9.27).
- The youngest age group (age 18-19 years): highest PI **8.15** (95% CI 3.5-15.8); PIs declined rapidly in older women.
- Differences in PIs seen between US (**2.87**) and European (**0.47**) subjects; between parous women (**5.43**) and nulliparous women (**1.48**); and between Hispanic women (**6.4**) and non-Hispanic women (**1.41**).
- Education: PI highest for those with only grade school education (**8.50**) versus college graduates (**1.43**).
- BMI did not influence pregnancy rates, but the group with BMI >29 kg/m^2 was modest in size.

Nelson A, 2020. *Contraception* (accepted).

Kaplan-Meier (KM) and Pearl Index (PI)

Pearl Index

- Assumes risk of pregnancy is the same or constant over time[1]
- Can be misleading when comparing pregnancy rates between studies that vary in follow-up; reported pregnancy rates can be driven towards zero by running a trial longer[1]
- Subjects that are most likely to become pregnant tend to at earlier durations of contraceptive use and, thus, discontinue; subjects that use a method for long durations are less likely to become pregnant[1]

Kaplan-Meier

- KM allows for cumulative failure rate for any duration of exposure[1]
- KM estimates have a clinically relevant interpretation (probability of failure over specified number of years of use)[2]
- Estimates can incorporate discontinuation of or use of additional contraceptives for varying intervals of time (known as left or right censoring)[2]

1. Trussell R. *Best Pract Res Clin Obstet Gynaelcol*. 2009;23:199-209.
2. Gilen DL. FDA Repro Presentation. Jan 23-24, 2007. Available at: https://slideplayer.com/slide/4648142/15/images/1/Statistical+Issues+in+Contraceptive+Trials

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Summary of Efficacy Results: 2007-2019

Literature Search of PubMed and ClinicalTrials.gov

	Type of contraception	Number of studies	Typical-use efficacy rates
Hormonal products	Combined oral contraception	5	**PI rates (range):** 1.65 – 3.19
	Combined oral contraception (before 2007)	10	**PI rates (range):** 0.51 – 1.34
	Patch	3	**PI rates (range):** 4.45 – 8.19
	Progestin-only pill	1	**PI rate:** 2.9
Non-hormonal products	Gel	1	**Cumulative pregnancy rate:** 13.7
	Female condom	1	**NR**
	Diaphragm	1	**Cumulative pregnancy rates:** 11.9 (excluding cycles of nonstandard length) 12.4 (adjusted for emergency contraception)

NR, not reported; PI, Pearl Index.

Trussell J, et al. *Contraception*. 2013;88:604-610.
Portman D, et al. *Contraception* (in review). 2020.

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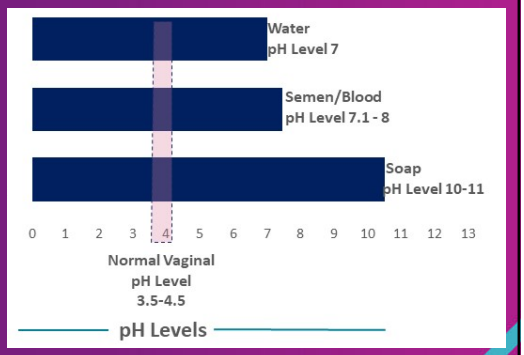
Phexxi™: Mechanism of Action

Phexxi™ acts by maintaining the woman's natural defenses in the vagina[1]

- Has acid-buffering properties[1]

  Maintains an acidic vaginal environment (pH=3.5–4.5) even in the presence of semen[2]
- Highly bioadhesive[1]

  Forms a layer of gel over the vaginal and cervical surfaces[2]
- Initiation of Phase 3 EVO100 for prevention of urogenital chlamydia and gonorrhea to begin 2020, top-line results in 2022
  - Phase 2b study demonstrated
    - 50% RR reduction in chlamydia
    - 80% RR reduction in GC



1. Garg S, et al. *Contraception*. 2001;64:67-75. 2. Data on file, Evofem; Phexxi™ PI.

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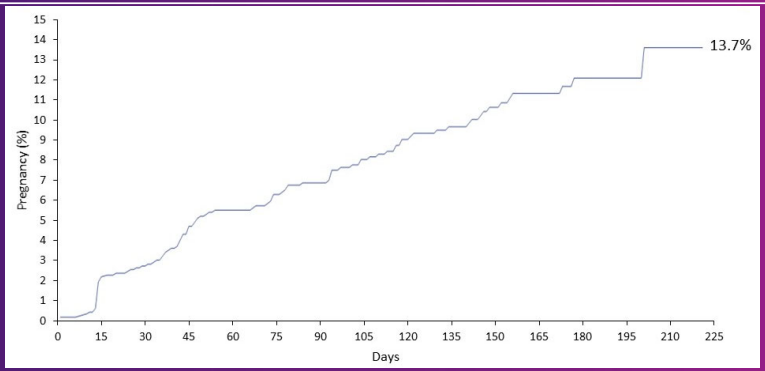
Primary Efficacy Analysis: 7-Cycle Cumulative Pregnancy KM Probabilities*

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



- 100 pregnancies occurred in 1182 subjects and 24,289 acts of intercourse
- 0.4% pregnancy rate per act of vaginal intercourse

*In MITT population
Data on file, Evofem; AMP002 CSR, 2019.

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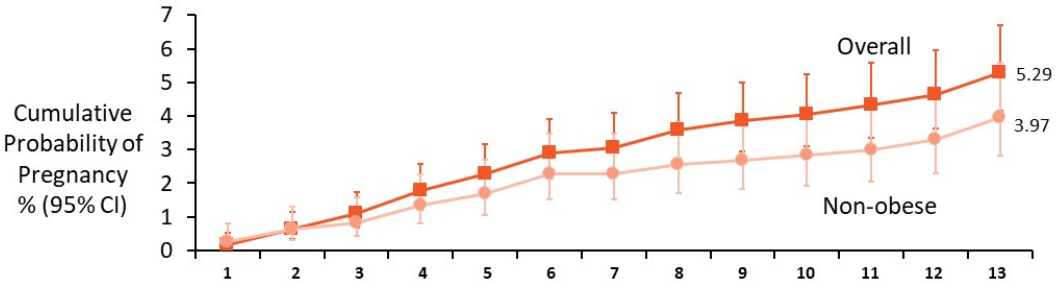
Pregnancy Rates Based on Life Table Analysis: SECURE Trial



Overall Women	1816	1681	1556	1448	1348	1262	1192	1130	1068	1003	966	929	891
Cumulative Pregnancies	3	11	18	28	35	43	45	51	54	56	59	62	68
Non-obese Women	1177	1082	1001	939	872	820	776	740	701	659	633	613	586
Cumulative Pregnancies	3	7	9	14	17	22	22	24	25	26	27	29	33

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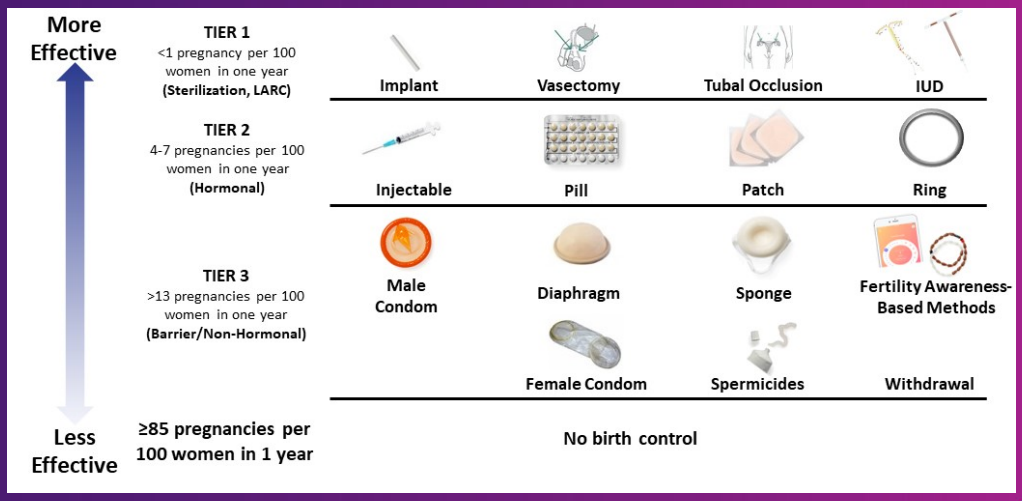
Contraceptive Options Tiered Based on Effectiveness



Adapted from Contraceptive Technology 2018.

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Diverse Population Needs Wide Range of Contraceptive Options to Meet Diverse Needs

- Accurate, generalizable information from inclusive clinical trials
- Labels that fully inform prescribers and users of risks/benefits
- Realize the impact of modern trial design on efficacy and effectiveness endpoints
- Most effective method fits a woman's lifestyle with 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