

HORMONAL CONTRACEPTION FOLLOW-UP: Management of Side Effects and Discussion of New Hormonal Contraception Options

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New Mexico Pharmacists Association Conference
January 22, 2022



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FINANCIAL DISCLOSURES

None

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LEARNING OBJECTIVES

Pharmacists and pharmacy technicians:

- Describe common side effects of hormonal contraception, including approaches for management and referral
- Identify new FDA-approved hormonal contraceptives
- Discuss indications for and considerations when counseling patients on new FDA-approved hormonal contraception options

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ROADMAP

- *Review of Combined Hormonal Contraception Methods
- *Common side effects and management options
- *New FDA approved hormonal contraceptives
 - * Drospirenone tablets (Slynd)
 - * Drospirenone and estrol tablets (Nextstellis)
 - * Segesterone acetate and ethinyl estradiol vaginal system (Annovera)
- *Other methods


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BUT FIRST . . .

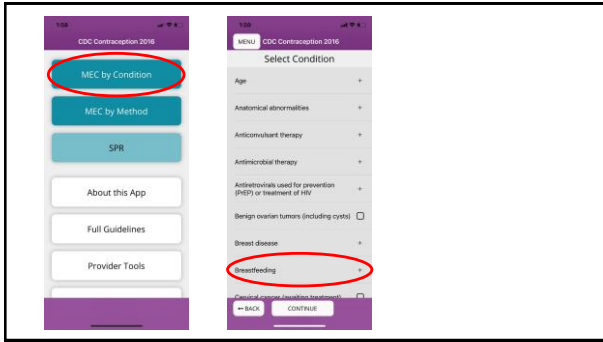
CDC US Medical Eligibility Criteria App



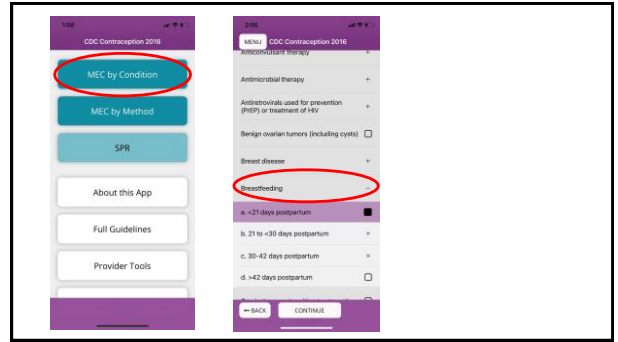

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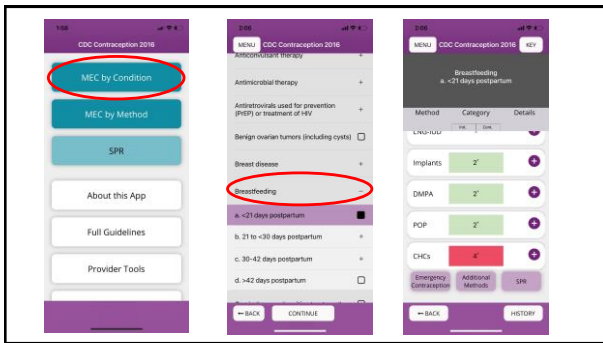
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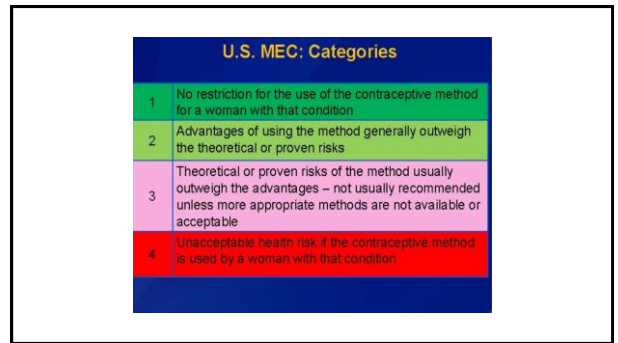
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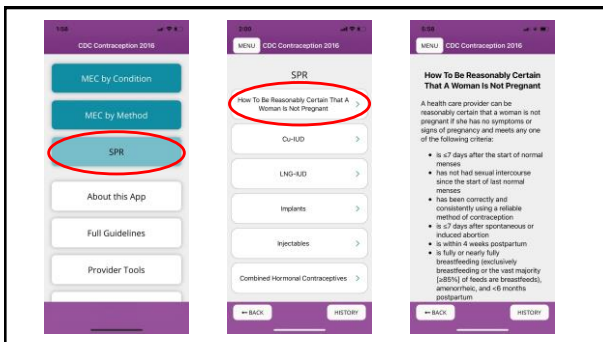
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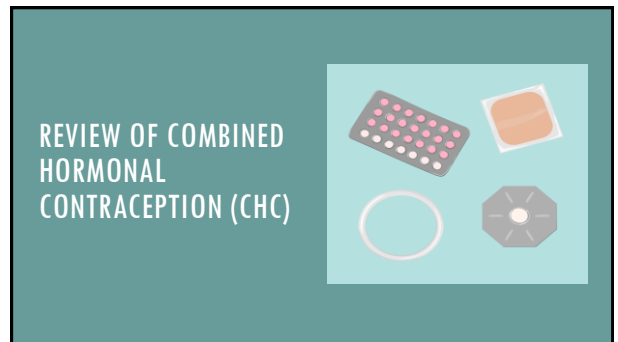
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METHODS

Oral Contraceptive Pill



Ethinyl Estradiol + progestin
Estrelol + Drospirenone

Progestin only methods
Norethindrone
Drospirenone

Transdermal Patch



Ethinyl Estradiol + norelgestromin

Ethinyl Estradiol + levonorgestrel

Vaginal Ring



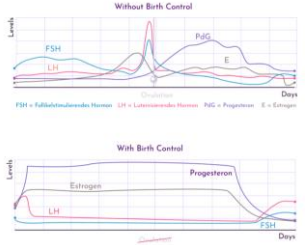
Ethinyl Estradiol + etonogestrel

Ethinyl Estradiol + segestosterone acetate

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HOW DO CHC WORK?

- Suppression of ovulation
- Progesterone
 - Suppression of LH surge
 - Primary contraceptive benefit
- Estrogen
 - Suppression of FSH
 - Potentiates progestin effects
 - Cycle control

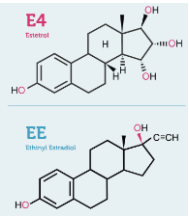


https://www.pearlyfertility.com/blog/entry/how-does-the-pill-work
Contraceptive Technology, 21st ed.

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ESTROGEN COMPONENT

- Ethinyl Estradiol (EE) -
 - Found in most CHCs in the United States
 - "Low dose" = 10-35 mcg
- Estretol (E4) -
 - Naturally occurring estrogen produced by the fetal liver
 - Less potent than estradiol
 - Minimal liver metabolism



Clinical Guide to Contraception, 6th ed.

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PROGESTIN COMPONENT

- Chemical structures vary widely
- Dose to suppress ovulation varies from type to type

Parent Steroid	19-Testosterone	17 α -Hydroxyprogesterone	19-Nortestosterone	17 β -Spiroacetone
Class name	Androgens	Androgens	Androgens	Androgens
Product name	Norethindrone, Norgestrel, Norgestimate, Norgestimate	Norethindrone, Norgestrel, Norgestimate	Norethindrone, Norgestrel, Norgestimate	Norethindrone, Norgestrel, Norgestimate
Other names				

Clinical Guide to Contraception, 6th ed.

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PROGESTIN COMPONENT

Table 1
Activity of Progestin Agents

Generation	Progestin	Estrogenic	Progestational	Androgenic
First	Norethindrone	++	+++	++
	Ethinyl diacetate	++	+++	+
	Norgestrel	-	+++	+++
	Norethindrone acetate	++	+++	++
Second	Levonorgestrel	-	+++	++++
Third	Norgestimate	-	++	++
	Desogestrel	+/-	++++	++
Fourth	Drospirenone	-	+/-	-

+/- indicates low to no activity
- indicates no activity
Source: References 3, 8, 18.

https://www.uptodate.com/links/selecting-and-monitoring-hormonal-contraception-an-overview-of-available-products
Clinical Guide to Contraception, 6th ed.

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MONOPHASIC VS MULTIPHASIC PILLS

- **Monophasic** – same combination of estrogen and progesterone in each active pill
- **Multiphasic** – active pills with differing doses of estrogen and progesterone
 - Pill doses increase as cycle progresses
 - Biphasic – two different dose combinations
 - Triphasic – three different dose combinations

Contraceptive Technology, 21st ed.

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PILL DOSING REGIMENS

- Standard cyclic regimen
 - 21 days active pill + 7 days placebo
- Extended cyclic regimen
 - 24 days active pill + 4 days placebo
- Extended cycle
 - >28 days active pill, placebo pill as desired

Contraceptive Technology, 21st ed.

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SIDE EFFECTS

SIDE EFFECTS

- Side effects may be a part of life rather than actual "side effect" of methods
- O'Connell et al.
 - Double blinded, placebo-controlled trial of adolescents
 - Similar types and numbers of side effects in both groups of participants
- Westhoff et al.
 - 1,600 US COC users
 - 50% reported at least one side effect
 - If reported side effect, more likely to discontinue COC at 6 months
 - 34% reported side effect as main reason for discontinuing

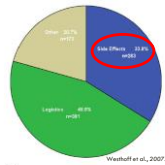


Figure 1. Main reason for discontinuing COC.
Clinical Guide to Contraception, 6th ed
Contraceptive Technology, 21st ed.
O'Connell et al., Contraception, 2007
Westhoff et al., Am J Obstet Gynecol, 2007

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RESPONDING TO SIDE EFFECTS

- Set expectations up front
- Reassurance
- Validate the experience
- Educate the patient
- Support their decision if decide to switch methods
- Reinforce that patient can safely stop method any time
- Counsel about rapid return to fertility

Clinical Guide to Contraception, 6th ed
Contraceptive Technology, 21st ed.
Grimes & Schultz, Contraception, 2011.

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MARINA

- 32 yo G3P3 who presents to the pharmacy to discuss concerns about combined hormonal contraceptives. Two months ago, you prescribed her an 100 mcg levonorgestrel and 20 mcg ethinyl estradiol combination pill for 3 months with 1 refill.
- Her concerns today:
 - Irregular bleeding since starting pills
 - Persistent breast tenderness
- Medical history unremarkable. Used pills previously, but doesn't remember prior experience.
- BMI 32, BP today 122/86

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BREAKTHROUGH BLEEDING

- Common
 - Up to 50% of patients initiating cyclic CHCs, but decrease to < 10% by third month of use
 - 40% of women on progestin only pills (POPs)
 - Slightly higher with lower dose pills (20 mcg EE versus 30-35 mcg EE)
 - Extended cycle regimens
- Evaluation
 - Compliance with method
 - Other causes of bleeding?

Clinical Guide to Contraception, 6th ed.
Contraceptive Technology, 21st ed.

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BREAKTHROUGH BLEEDING – MANAGEMENT

- Cyclic Regimen
 - Observation and Reassurance
 - Consider increasing EE dose, particularly if on < 20 mcg EE
- Extended Cycle Regimen
 - Trial a 4 day hormone free interval
 - Consider increasing EE dose, particularly if on < 20 mcg EE
 - Consider changing from levonorgestrel to norethindrone acetate formulation
- POPs
 - Observation, NSAIDs
 - Change methods

Contraceptive Technology, 21st ed. Edelman et al., Obst. Gynaecol. 2006

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MASTALGIA

- Breast tissue is dynamic and responsive to hormone exposure
- Overall volume of the breast varies by 76 mL during the menstrual cycle
- Common with initiation
- Management
 - Proper fitting bra
 - Change in formulation – Cochrane Review
 - Desogestrel-containing pills users complained of less breast tenderness than drospirenone containing pills
 - Lower EE component (20 mcg) reported less pain than higher EE pills
 - Consider extended cycle

Contraceptive Technology, 21st ed. Lawrie et al., Cochrane Database, 2011.

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NAUSEA

- Estrogen can induce nausea/vomiting
- Management
 - Reassurance – resolves from 1-3 months of use
 - Take with food or at night
 - Switch to progestin-only formulation
 - Consider lowering the EE dose

Contraceptive Technology, 21st ed.

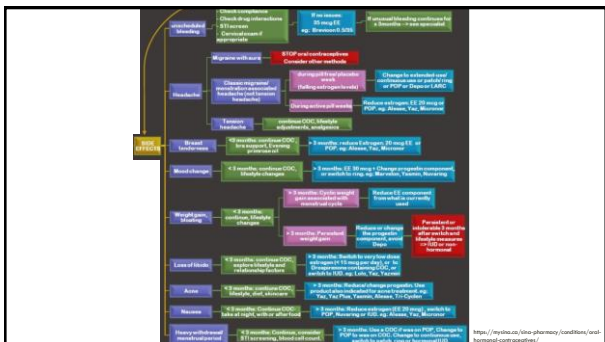
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OTHER COMMON SIDE EFFECTS

- Decreased libido
- Multifactorial
- Consider reduction in EE dose
- Weight gain/bloating
 - Cochrane Review – 49 trials met inclusion criteria
 - Insufficient evidence to determine effect of CHCs on weight, but no large effect was evident
- Listen to concerns, review evidence and discussion of pro/cons of changing methods

Contraceptive Technology, 21st ed. Gallo et al., Cochrane Database, 2014.

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WHEN IN DOUBT? REFER!

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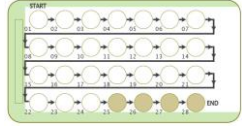
NEW FDA APPROVED HORMONAL CONTRACEPTIVE METHODS

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DROSPIRENONE TABLETS

Slynd

- * Drospirenone 4 mg
- * 24 active pills + 4 inactive pills
- * Antimineralocorticoid and antiandrogenic properties
- * Half life of 25-30 hours
- * Ovulation suppression



Clinical Guide to Contraception, 6th ed. Duljers et al, Contraception, 2016.

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DROSPIRENONE TABLETS

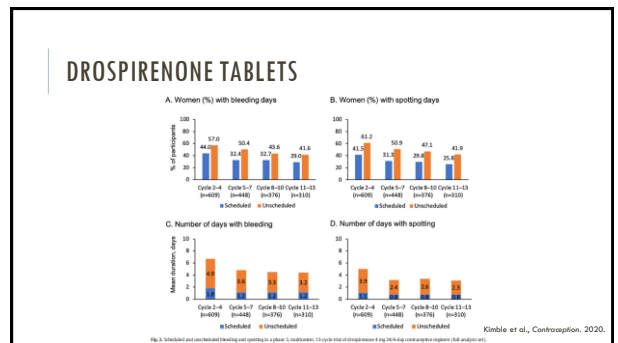
Single arm, multicenter, clinical trial in the US
953 women (35% BMI > 30 and 18% BMI > 35)

- * 1.8% pregnancy rate (Pearl Index 4.0)
- * Few adverse reactions
- * No cases of VTE reported
- * 0.5% asymptomatic hyperkalemia
- * Widely accepted

Adverse Reaction	Total n (%)
Any adverse reaction	627 (64.1)
Acne	98 (3.8)
Melancholia	72 (2.8)
Headache	71 (2.7)
Breast pain	57 (2.2)
Weight increased	50 (1.9)
Dysmenorrhea	49 (1.9)
Nausea	47 (1.8)
Vaginal hemorrhage	43 (1.7)
Libido decreased	33 (1.3)
Breast tenderness	31 (1.2)
Menstruation irregular	30 (1.2)

Clinical Guide to Contraception, 6th ed. Kimble et al., Contraception, 2020. Slynd Prescribing Information

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DROSPIRENONE TABLETS

Slynd[®] Savings Program

ELIGIBLE PATIENTS MAY PAY AS LITTLE AS

\$25 * PER 1-MONTH OR 3-MONTH PRESCRIPTION FILL

3-MONTH FILL MAY COST PATIENT **\$8.33 PER MONTH**

- * Contraindications
 - * Kidney disease or kidney failure
 - * Adrenal insufficiency
 - * Liver disease
- * Cost
 - * Cost saving program on website


Kimble et al., Contraception, 2020. Slynd Prescribing Information.

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DROSPIRENONE / ESTETROL TABLETS

Nextstellis

- * Estetrol 14 mg / Drospirenone 3 mg tablets
- * 24 active pills + 4 inactive pills
- * Estetrol is a natural estrogen
- * Mixed agonist and antagonist activities
- * Low impact on hemostasis biomarkers, triglycerides and breast tissues



https://bitcoormpharmaceutical.com/2021/09/20/nextstellis

Crehin et al., Contraception, 2021. Grandi et al., 2020.

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DROSPIRENONE / ESTETROL TABLETS

Multicenter, open-label, 13-cycle, phase 3 trial

- 1674 women enrolled; 899 completed trial
- aged 16-35 yo, 23% BMI > 30
- Pearl index 2.65 (CI 1.73, 3.88)
- BMI > 30 Pearl Index 2.94
- 7.1% reported adverse events leading to discontinuation of study
- No cases of VTE

Adverse event	54 mg DRO/1 mg EE (n=894)
Any adverse event	94 (10.5)
Headache	89 (10.0)
Nausea/vomiting	48 (5.4)
Diarrhea	39 (4.4)
Abuse	33 (3.7)
Urinary tract infection	34 (3.8)
Weight increased	32 (3.6)
Vaginal erythema/itch/irritation	32 (3.6)
Vaginal/vulvovaginal yeast infection	31 (3.5)
Breast tenderness	34 (3.8)
Acne	40 (4.5)
Edema	40 (4.5)
Fatigue	42 (4.7)
Vaginal hemorrhage	42 (4.7)
Menorrhagia	39 (4.4)
Abnormal uterine bleeding	39 (4.4)
Head injury	38 (4.3)
Menstrual cycle altered	38 (4.3)
Menstruation	82 (9.2)
Headache	85 (9.5)
Abuse	73 (8.2)
Diarrhea	52 (5.8)
Breast tenderness	51 (5.7)
Weight decreased	46 (5.1)
Nausea	46 (5.1)
Adverse event leading to discontinuation	18 (2.0)
Menorrhagia	14 (1.6)
Vaginal hemorrhage	10 (1.1)
Weight increased	9 (1.0)

Crainin et al., Contraception, 2021.

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DROSPIRENONE / ESTETROL TABLETS

- Unscheduled bleeding
 - 30.3% in cycle 1 to 22.1% during cycle 4 and remained stable
- Amenorrhea
 - 10% of users per cycle

Crainin et al., Contraception, 2021.

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SEGESTERONE ACETATE AND ETHINYL ESTRADIOL VAGINAL SYSTEM

Anovera

- 103 mg segesterone acetate → 150 mcg released daily
- 17.4 mg ethinyl estradiol → 13 mcg released daily
- Soft, flexible ring inserted in the vagina
- 56 mm in diameter, 8.4 mm in cross section diameter
- 3 weeks in / 1 week out
- Same ring used for up to a full year

Anovera Prescribing Information, Archer et al. Lancet Global Health, 2019.

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SEGESTERONE ACETATE AND ETHINYL ESTRADIOL VAGINAL SYSTEM

Segesterone Acetate (Nestorone)

- 19-norprogesterone derivative
- Not orally absorbed
- Lacks androgenic and glucocorticoid activity

Archer et al. Lancet Global Health, 2019.

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SEGESTERONE ACETATE AND ETHINYL ESTRADIOL VAGINAL SYSTEM

Two, 13-cycle, open label, Phase 3 clinical trials

- 2265 women
- Mean age 26.7, Mean BMI 24
- Pearl index 2.98 (CI 2.13, 4.06)
- Not influenced by BMI

Anovera Prescribing Information, Archer et al. Lancet Global Health, 2019.

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SEGESTERONE ACETATE AND ETHINYL ESTRADIOL VAGINAL SYSTEM

- Adverse Reactions
 - Similar to other combined hormonal methods
 - 4 nonfatal VTEs occurred during clinical trials
 - 3 women had risk factors for VTE
 - 2 had BMI > 29
 - 1 had Factor V Leiden heterozygous

Adverse Reactions Reported by ≥5% of Subjects	% (n = 2268)
Headache, including migraine	38.2
Nausea/vomiting	28.0
Vagrovaginal mycotic infection/vaginal candidiasis	14.5
Abdominal pain/low/back	13.3
Dysmenorrhea	12.3
Vaginal discharge	11.4
UTI/vaginitis/candidiasis/genitourinary tract infection	10.0
Breast pain/tenderness/discomfort	9.5
Menorrhagia/abnormal disorder	7.5
Diarrhea	7.2
Genital pruritus	5.5

Adverse Reactions Leading to Discontinuation by ≥1% of Subjects	% (n = 2268)
Menorrhagia/amenorrhea	1.7
Headache, including migraine	1.3
Vaginal discharge/vagrovaginal mycotic infections	1.3
Nausea/vomiting	1.2

Genzall et al., Contraception 2019, Anovera Prescribing Information.

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SEGESTERONE ACETATE AND ETHINYL ESTRADIOL VAGINAL SYSTEM

Bleeding profile

- *98% documented scheduled bleeding/spotting
- *Unscheduled bleeding/spotting ranged from 13.2-21.7% of women per cycle
- *1.8% discontinued due to bleeding pattern

Number of Unscheduled Bleeding and Spotting Days per Cycle

Verio et al., Contraception 2019.

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SEGESTERONE ACETATE AND ETHINYL ESTRADIOL VAGINAL SYSTEM

- *89% if women reported satisfaction with method
- *Ease of removal, few side effects, not feeling ring while wearing it and no change in sexual pleasure/frequency were associated with higher odds of satisfaction
- *Satisfied patients had > 2x the odds of being adherent

Fig. 1. Final odds of NERSSE CVR acceptability.

Markatz et al., Contraception 2014.

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OTHER NEW METHODS

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PHEXXI VAGINAL GEL

- *Non-hormonal, prescription vaginal gel to prevent pregnancy
- *Only FDA approved contraceptive gel
- *Active ingredients: 90 mg lactic acid, 50 mg citric acid, 20 mg potassium bitartrate
- *5 grams per applicator

Thomas et al., Contraception 2020.

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PHEXXI VAGINAL GEL

Mechanism of Action

- *Maintain the acidic vaginal environment in the presence of alkaline sperm
- *Reduces sperm motility
- *Bioadhesive and viscosity retaining properties enabling gel to stay in vagina up to 8-10 hours
- *Avoid using with vaginal contraceptive rings!

Thomas et al., Contraception 2020.

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PHEXXI VAGINAL GEL

How to use

- *Insert applicator before vaginal sex
- *Must be inserted within 1 hour before vaginal sex
- *If more than 1 act of vaginal intercourse within one hour, an additional dose must be applied

8 Simple Steps

1. Wash your hands.
2. Remove the pre-filled applicator and plunger rod from the foil pouch.
3. Insert the plunger rod into the applicator, and push up the charger rod connected to the applicator. Use a new pre-filled applicator if gel gives into the pink cap.
4. Remove the pink cap.
5. PHEXXI™ IS NOW READY FOR USE!
6. In an appropriate position, insert the Phexxi™ pre-filled applicator into your vagina as far as will comfortably go while you continue to firmly hold it by the grooved area of the applicator.
7. Using your index finger, push the plunger rod until it stops to ensure you receive the entire dose of Phexxi™.
8. Remove the used Phexxi™ pre-filled applicator from your vagina. A small amount of gel may be left in the applicator. However, you will get the right dose.

There are 3 (three) left of the used Phexxi™ pre-filled applicator and cap.

Always use Phexxi™. If you or your partner is allergic to any of the ingredients in Phexxi™.

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REFERENCES

- Archer DF, Markkuz RB, Bohamondes L, et al. Efficacy of the 1-year (13-cycle) gestodene acetate and ethinyl estradiol contraceptive vaginal system: results of two multicentre, open-label, single-arm, phase 3 trials. *The Lancet Global Health*. 2019;7(8):e1054-e1064. doi:10.1016/S2214-109X(19)30265-7
- Crainin MD, Westhoff CL, Bouchard C, et al. Etonogestrel-drospirenone combination oral contraceptive: North American phase 3 efficacy and safety results. *Contraception*. 2021;104(3):222-228. doi:10.1016/j.contraception.2021.05.002
- DuJarsy LM, Heger-Mahler D, Drouot D, Collé E, Slouby S. Maintenance of ovulation inhibition with a new progestogen-only pill containing drospirenone after scheduled 24-h delays in pill intake. *Contraception*. 2016;93(4):303-309. doi:10.1016/j.contraception.2015.12.007
- Edelman AB, Koontz SL, Nichols MD, Jensen JT. Continuous Oral Contraceptives. *Obstet Gynecol*. 2006;107(3):9.
- Gallo MF, Lopes LM, Grimes DA, Carayon F, Schulz KF, Halperin FM. Combination contraceptives effects on weight. *Cochrane Fertility Regulation Group*, ed. *Cochrane Database of Systematic Reviews*. Published online January 29, 2014. doi:10.1002/14651858.CD003987.pub5
- Gemzell-Danielsson K, Strub-Worel R, Crainin MD, et al. Segestrono acetate/ethinyl estradiol 12-month contraceptive vaginal system safety evaluation. *Contraception*. 2019;99(6):323-328. doi:10.1016/j.contraception.2019.02.001
- Grandi G, Del Savio MC, Lopes da Silva-Filho A, Facchinetti F. Etonogestrel (E4): the new estrogenic component of combined oral contraceptives. *Expert Review of Clinical Pharmacology*. 2020;13(4):327-330. doi:10.1080/17512433.2020.1750365
- Grimes DA, Schulz KF. Nonspecific side effects of oral contraceptives: nausea or noise? *Contraception*. 2011;83(1):5-9. doi:10.1016/j.contraception.2010.06.010
- Hatcher RA, Nelson AL, Trussell J, Cribb C, Coon F, Polcar MS, Edelman A, Allan ABA, Morrazzo L, Kowal D, eds. *Contraceptive technology*. 21st ed. New York, NY: Ayer Company Publishers, Inc., 2018.

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REFERENCES

- Kimble T, Burke AE, Barnhart KT, Archer DF, Collé E, Westhoff CL. A 1-year prospective, open-label, single-arm, multicenter, phase 3 trial of the contraceptive efficacy and safety of the oral progestin-only pill drospirenone 4 mg using a 24/4-day regimen. *Contraception*. 2020;2100020. doi:10.1016/j.contraception.2020.100020
- Lowrie TA, Halperin FM, Maitra NK, Kular R, Bloemkamp K, Gilmanzo AM. Types of progestogens in combined oral contraception: effectiveness and side-effects. *Cochrane Fertility Regulation Group*, ed. *Cochrane Database of Systematic Reviews*. Published online May 11, 2011. doi:10.1002/14651858.CD004861.pub2
- Markkuz RB, Plogianos M, Haskin E, Cooney M, Hewett PC, Mensch BS. Acceptability of the nestorone®/ethinyl estradiol contraceptive vaginal ring: development of a model; implications for introduction. *Contraception*. 2014;90(5):514-521. doi:10.1016/j.contraception.2014.05.015
- O'Connell K, Davis AB, Kerns J. Oral contraceptives: side effects and depression in adolescent girls. *Contraception*. 2007;75(4):299-304. doi:10.1016/j.contraception.2006.09.008
- Phaxsi. Prescribing information. Evofem Biociences; 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/208352-0008b.pdf
- Speroff L, Darney PD. *A Clinical Guide for Contraception*. Wolters Kluwer Health | Lippincott Williams & Wilkins; 2020.
- Thomas MA, Chappell BJ, MacIntyre S, Linnell KB, Dani C, Howard B. A novel vaginal pH regulator: results from the phase 3 AMPPOWER contraceptive clinical trial. *Contraception*. 2020;2100031. doi:10.1016/j.contraception.2020.100031
- Vistra CS, Fraser IS, Plogianos MG, et al. Bleeding profile associated with 1-year use of the segestrono acetate/ethinyl estradiol contraceptive vaginal system: pooled analysis from Phase 3 trials. *Contraception*. 2019;100(6):438-444. doi:10.1016/j.contraception.2019.07.145
- Westhoff CL, Heartwell S, Edwards S, et al. Oral Contraceptive Discontinuation Do Side Effects matter? Published online 2008:14.

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SUMMARY

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