The FDA approved 3 new contraceptive methods this past year, but they are not new types of contraceptives. Do these products—a pill, a patch, and a vaginal gel—represent anything novel for patients? We review efficacy and safety data for all 3 methods to aid in physician counseling and selection of appropriate contraceptive methods based on clinical factors.

A new contraceptive method should ideally provide improved access or a higher quality and safety option. Although unintended pregnancy rates in the United States are decreasing, significant disparities across race and socioeconomic status remain, and these disparities actually doubled from 1994 to 2011 even though the overall unintended pregnancy rate decreased. Specific people of color, those with lower income, and people with lower education levels had higher rates of unintended pregnancies than did White people with higher education and income, suggesting disparate access to contraception services. Thus, as new contraceptive methods are introduced, we must assess if they have the potential to address this disparity as well as continue to provide higher quality and safer options.

In this Update, we critically review the phase 3 data on efficacy and safety for 3 new methods that were introduced to the US market over the past year to evaluate their impact on the current contraceptive landscape.

The first method, newly approved by the US Food and Drug Administration (FDA), is a combined oral contraceptive (OC) that contains a novel endogenous estrogen, etestrol, or E4 (Nextstellis). E4 is a natural estrogen produced in the fetal liver that has lower potency and a longer half-life than estradiol. Nextstellis is a monophasic 24/4 OC pill that contains E4 14.2 mg and drospirenone 3 mg in each of the 24 hormone-containing pills. Most combined hormonal contraceptives (CHCs) in the United States today contain synthetically made ethinyl estradiol (EE) due to its high potency and oral bioavailability. Outside of the reproductive system, EE upregulates the production of hepatic proteins and alters procoagulant and anticoagulant factors, which results in an overall increase in venous thromboembolic (VTE) risk among CHC users.

After widespread use of combined oral contraceptives (COCs) started in the 1960s, data emerged regarding increased VTE risk. Subsequent research discovered that the type of estrogen used in CHCs directly correlates with the thrombosis risk due to the hepatic upregulation with both first- and second-pass metabolism. Although this risk was reduced as the EE dose decreased below 50 µg and concurrent VTE risk factors were contraindicated, CHC users still faced a 2-fold increase in VTE risk compared with nonusers. EE in contraceptive formulations increases VTE risk, likely related to upregulation of procoagulant factors and decreasing anticoagulant proteins. By contrast, a phase 2 trial of Nextstellis demonstrated more neutral effects of
The authors critically review phase 3 data on efficacy and safety for 3 new contraceptive methods: Nextstellis, Twirla, and Phexxi.

New OC with the novel estrogen E4 demonstrates good safety profile for VTE


The COC E4/drospirenone was evaluated in 2 parallel multinational studies. Here, we review the North American data that are more relevant for the US population; the European-Russian data also are published.

Study examined 1 year’s use of E4/drospirenone
The US–Canadian trial conducted by Creinin and colleagues enrolled 1,864 participants aged 16 to 50 years to evaluate contraceptive
efficacy, bleeding patterns, and adverse events with 1-year use (13 cycles) of E4/drospirenone. The primary efficacy group included 1,524 women aged 16 to 35. This study enrolled healthy, heterosexually active participants with a BMI ≤35 kg/m² and regular menses from 70 sites in the United States and 7 sites in Canada. The dropout rate was 45%, comparable to that in other contraceptive studies. Participants used E4/drospirenone cyclically, taking 1 hormone-containing pill daily for 24 days followed by 4 days of placebo pills.

**WHAT THIS EVIDENCE MEANS FOR PRACTICE**

Nextstellis provides safe, effective contraception with a PI comparable to that of other available CHCs as well as a favorable bleeding profile in healthy users who are adherent to treatment. Importantly, contraceptive efficacy was maintained in obese users with a BMI up to 35 kg/m². In contrast to EE or estradiol, E4 demonstrates a lower impact on the hepatic system, and preliminary findings suggest a lower VTE risk compared with other CHCs on the market. The European phase 3 trial of 1,553 participants also demonstrated a low rate of VTE, with only 1 case diagnosed. By contrast, similar phase 3 trials of available CHCs demonstrated more frequent VTE events despite low-dose EE formulations (TABLE 1). In general, most US phase 3 trials have 3 to 4 VTE events in the studied population, and the Nextstellis North American trial, of which 92% of participants were from the United States, had 0. However, confirmation of any potential lower VTE risk requires further analysis from large, population-based postmarketing studies.

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**TABLE 1** Study characteristics and VTE events from single phase 3 studies of Nextstellis, Twirla, and other contemporary CHCs

<table>
<thead>
<tr>
<th></th>
<th>Nextstellis²⁷</th>
<th>Nextstellis²⁵</th>
<th>Twirla¹⁰</th>
<th>Lo Loestrin¹⁶</th>
<th>Anovlar¹⁸,¹⁹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Route</td>
<td>Oral</td>
<td>Oral</td>
<td>Transdermal</td>
<td>Oral</td>
<td>Vaginal ring</td>
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<tr>
<td>Estrogen type</td>
<td>Estetrol</td>
<td>Estetrol</td>
<td>EE</td>
<td>EE</td>
<td>EE</td>
</tr>
<tr>
<td>Progestin type</td>
<td>Drospirenone</td>
<td>Drospirenone</td>
<td>Levonorgestrel</td>
<td>Norethindrone acetate</td>
<td>Segesterone acetate</td>
</tr>
<tr>
<td>Country of study</td>
<td>United States, Canada</td>
<td>Europe, Russia</td>
<td>United States</td>
<td>United States</td>
<td>United States</td>
</tr>
<tr>
<td>Study population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants</td>
<td>1,864</td>
<td>1,553</td>
<td>2,031</td>
<td>1,683</td>
<td>1,143</td>
</tr>
<tr>
<td>% obesea, n (%)</td>
<td>432 (23%)</td>
<td>89 (5.7%)</td>
<td>717 (35%)</td>
<td>284 (18%)</td>
<td>Unknown (mean BMI, 24.4 kg/m²)</td>
</tr>
<tr>
<td>Participants with VTE</td>
<td>0</td>
<td>1 (0.06%)</td>
<td>4 (0.20%)</td>
<td>3 (0.18%)</td>
<td>4 (0.35%)</td>
</tr>
<tr>
<td>during treatment, n (%)</td>
<td></td>
<td></td>
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</table>

*Abbreviations: BMI, body mass index; CHC, combined hormonal contraceptive; EE, ethinyl estradiol; VTE, venous thromboembolism.
*aBMI ≥30 kg/m².*
In an embryo-fetal development study, oral administration of estetrol to pregnant rabbits during the period of organogenesis (Days 6 to 18 of gestation) resulted in abortion, fetal litter loss, or decreased number of live fetuses at a dose of 9 mg/kg/day (about 0.6 times the MRHD), at 40 mg daily, based on AUC. No treatment-related malformations were observed in surviving fetuses. No treatment-related effects were observed at 3 mg/kg/day (about 0.1 times the MRHD) or lower. The binding affinity of estetrol to rabbit GRh receptors is unknown.

In a similar embryo-fetal development study, oral administration of estetrol to pregnant rats during the period of organogenesis (Days 6 to 17 of gestation) did not affect pregnancy status or fetal endpoints at doses up to 1000 mg/kg/day (300 times the MRHD), a dose at which maternal toxicity (decreased body weight gain and food consumption) was observed. A no-observed-adverse-effect level (NOAEL) for maternal toxicity was 200 mg/kg/day (66 times the MRHD). In rats, the binding affinity of estetrol for GRh receptors is more than 1000-fold lower than that in humans, and this study represents an assessment of non-pharmacological targets of estetrol during pregnancy. No treatment-related malformations were observed up to 1000 mg/kg/day in a pre-and postnatal developmental study in pregnant and lactating rats, oral administration of estetrol to rats during late pregnancy and lactation (Day 6 of gestation to Day 20 of lactation) had no effects on pre- and postnatal development at doses up to 1000 mg/kg/day (300 times the MRHD), a dose in which maternal toxicity was observed (effects on body weight gain). A NOAEL for maternal toxicity was 100 mg/kg/day (34 times the MRHD).

8.2 Lactation

There are no data on the presence of estetrol or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Metabolism in the breast milk of women receiving estetrol plus progestin therapy can reduce milk production in breastfeeding women. This reduction can occur at any time but is less likely to occur once breast-feeding is well established.

The developmental and health benefits of breast-feeding should be considered along with the mother’s clinical need for MYFEMBREE and any potential adverse effects on the breastfed child from MYFEMBREE or from the underlying maternal condition.

Data

Animal Data

In lactating rats administered a single oral dose of 30 mg/kg radiolabeled estetrol on post-partum day 14, radiolabeled estetrol and/or its metabolites were present in milk at concentrations up to 10-fold higher than in plasma at 2 hours post-dose.

8.3 Females and Males of Reproductive Potential

Based on animal data and the mechanism of action, MYFEMBREE can cause early pregnancy loss if MYFEMBREE is administered to pregnant women.

8.4 Pediatric Use

Safety and effectiveness of MYFEMBREE in pediatric patients have not been established.

8.7 Hepatic Impairment

MYFEMBREE is contraindicated in women with hepatic impairment or disease. The use of E2 (a component of MYFEMBREE) in patients with hepatic impairment is expected to increase the exposure to E2 and increase the risk of E2-associated adverse reactions.

10. OVERDOSAGE

Overdosage of estrogen plus progestin may cause nausea, vomiting, breast tenderness, abdominal pain, diarrhea, fatigue, and withdrawal bleeding. Supportive care is recommended if an overdose occurs. The amount of estetrol, estradiol, or norethindrone removed by hemodialysis is unknown.

Please see full Prescribing Information for Patient Counseling Information

This Brief Summary is based on MYFEMBREE Prescribing Information dated May 2021, which can be found at MYFEMBREE.com.

Manufactured by Pfizer Inc., 2100 Syntex Court, Mississauga, Ontario L5N 7K8, Canada. Manufactured for Myovant Sciences, Inc., Brisbane, CA 94005

Approved: May 2021
21494-MS-000

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PP-US-RBL-CT-210014 06/21

Efficacy of a new EE/levonorgestrel transdermal patch may be lower in overweight, obese women

were no restrictions based on BMI. On average, the study population was overweight, with a mean BMI of 28.3 kg/m², and 35% of the population was considered obese (BMI ≥30 kg/m²).

**Study design**
A total of 2,032 participants enrolled in the study, with separate populations defined for specific analysis on safety, contraceptive efficacy, and cycle control. The primary efficacy group included 1,736 participants. Fifty-one percent discontinued the study, most commonly due to “women’s decision” (15%) and lost to follow-up (11%). Users received bleeding diaries and returned periodically throughout the study for evaluation for efficacy, adherence, and adverse events.

**Efficacy associated with BMI**
The study results demonstrated an overall PI of 5.8 pregnancies per 100 woman-years for users aged younger than 35. **TABLE 2** demonstrates the overall trend of efficacy in relation to BMI. 

Participants with a higher BMI were found to have a higher PI, revealing lower contraceptive efficacy in more overweight and obese patients. The overall cumulative pregnancy rate over 13 cycles was 5.3%.

Participants reported decreasing frequency of bleeding/spotting days over the treatment duration of 13 cycles, from a mean (SD) of 6.2 (4.5) days in cycle 1 to 4.9 (3.5) days in cycle 13. Unscheduled bleeding

**WHAT THIS EVIDENCE MEANS FOR PRACTICE**
Available data demonstrate that the EE/norelgestromin patch exposes users to higher serum levels compared with the pill or the ring. The higher estrogen exposure with the patch may explain higher estrogen-related adverse effects and may result in increased VTE risk. Initial pharmacokinetic data of the EE/levonorgestrel patch showed lower EE concentrations, similar to marketed COCs and lower than EE/norelgestromin. Despite this lower estrogen exposure, the phase 3 trial by Nelson and colleagues did not demonstrate a safer profile with respect to thromboembolic events.

Further, the high PI of 5.8 pregnancies per 100 woman-years calls into question the efficacy of this patch compared with already available CHC options. Indeed, the efficacy appears reasonable in normal-weight individuals, with a PI of 3.5 pregnancies per 100 woman-years; however, this is still higher than its contemporary counterpart, Nextstellis, which has a PI of 2.65 pregnancies per 100 woman-years and included users with a BMI of up to 35 kg/m² (Table 2). Given the evidence of decreased efficacy, clinicians may consider reserving this option for only normal-weight women who cannot use or prefer not to use another CHC method. Obese individuals (BMI ≥30 kg/m²) should not use this patch due to decreased efficacy and increased VTE risk. Lastly, although use in overweight individuals (BMI ≥25 kg/m²) is not absolutely contraindicated, clinicians should counsel the overweight patient on the possibility of decreased contraceptive efficacy due to weight, and they may choose to reserve use of this patch in overweight individuals only when no other comparable or more effective method is an option.

**TABLE 2  Efficacy data comparing Nextstellis and Twirla by BMI**

|                      | Nextstellis (United States) | Twirla | Previous study
<table>
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<tbody>
<tr>
<td></td>
<td>N</td>
<td>Pregnancies</td>
<td>PI (95% CI)</td>
</tr>
<tr>
<td>Efficacy overall</td>
<td>1,524</td>
<td>26</td>
<td>2.7 (1.7–3.9)</td>
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<tr>
<td>Efficacy by BMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI ≥30 kg/m²</td>
<td>337</td>
<td>6</td>
<td>2.9 (1.1–6.4)</td>
</tr>
<tr>
<td>BMI &lt;30 kg/m²</td>
<td>1,187</td>
<td>20</td>
<td>2.6 (1.6–4.0)</td>
</tr>
<tr>
<td>BMI &lt;25 kg/m²</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BMI 25–29.9 kg/m²</td>
<td>–</td>
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</table>

**Abbreviations:** BMI, body mass index; CI, confidence interval; PI, Pearl Index.

*a Enrolled BMI ≤35 kg/m².

*b No BMI restrictions for enrollment.

**Pregnancies per 100 woman-years in users aged 35 years or younger.**
**Novel vaginal pH buffering spermicide is a new Rx-only option**

In an open-label phase 3 study, Thomas and colleagues enrolled 1,384 participants aged 18 to 35 with regular cycles at 112 sites in the United States to assess the contraceptive efficacy, safety, and

**WHAT THIS EVIDENCE MEANS FOR PRACTICE**

Prior to the approval of Phexxi, all currently available vaginal contraceptive gels in the United States contained nonoxynol-9 as the active ingredient, which is a surfactant that is spermicidal by damaging cell membranes. Although Phexxi provides a novel mechanism of action as a spermicide, the contraceptive efficacy is about the same as available spermicides on the market (see **TABLE 3** online). The FDA calculated a 13-cycle PI to include in the label (27.5 pregnancies per 100 woman-years) based on the results of this study; however, no reliable statistical method exists to calculate a true PI from a 7-cycle study. Thus, we recommend that clinicians counsel patients appropriately based on the 6-month rate noted in the study, and that this rate is similar to that with currently available over-the-counter products. This point is important, as Phexxi is available only by prescription, which may impact patient cost and access.

Equally important is Phexxi’s potential for sexually transmitted infection (STI) prevention. In a US-based randomized controlled trial, Phexxi use demonstrated significant risk reduction in gonorrhea and chlamydia infections among participants aged 18 to 45 years. That study showed a relative risk reduction of 50% and 78% for chlamydia and gonorrhea, respectively. Future research is planned to evaluate this spermicide as a novel STI prevention method. Ultimately, Phexxi may provide an alternative spermicide for users interested in moderately effective contraception and unable to tolerate available nonoxynol-9 formulations. Interested users will have to rely on a prescription, possibly limiting access to this novel spermicide. Further data are required to determine its potential as an STI prevention agent.

**CONTINUED ON PAGE 34**
acceptableability of Phexxi vaginal gel (lactic acid, citric acid, and potassium bitartrate) over 7 cycles (6 months). Participants were required to have at least 3 episodes of heterosexual vaginal intercourse per cycle and return throughout the treatment duration for study visits. Fifty-three percent of participants did not complete the study, most frequently due to loss to follow-up (18.1%) and participant withdrawal (12.3%). Most participants were White (69%) and had an average (SD) age of 27.7 (4.5) years.

**Efficacy and AE rates**
The investigators reported a cumulative pregnancy rate of 13.7% over 7 cycles (6 months). In this study, 45.2% of women experienced 1 AE, and most were noted to be mild (23.9%) to moderate (18.7%). The most reported AE was vulvovaginal burning (20.0%), followed by vulvovaginal pruritus (11.2%), urinary tract infection (5.7%), and vulvovaginal pain (3.8%). Less than 2% of participants discontinued the study due to an AE. Burning and itching decreased with time and with decreased frequency of use. When used twice per day compared with once per day, burning rates decreased from 4.6% to 2.1%, and itching rates decreased from 1.0% to 0.7%. Serious AEs were uncommon, occurring in 1.3% of users; only 1, cystitis, was noted to be “probably” related to the treatment.

**References**
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<thead>
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<tbody>
<tr>
<td>Study duration</td>
<td>7 cycles</td>
<td>7 cycles</td>
<td>7 cycles</td>
</tr>
<tr>
<td></td>
<td>(6 months)</td>
<td>(6 months)</td>
<td>(6 months)</td>
</tr>
<tr>
<td>Total participants (n)</td>
<td>1,114</td>
<td>633</td>
<td>299</td>
</tr>
<tr>
<td>Acts of intercourse per cycle (median)</td>
<td>3.6 (per 28-day cycle)</td>
<td>NR</td>
<td>8.0 (per 30-day cycle)</td>
</tr>
<tr>
<td>Pregnancy failure, % (95% CI)</td>
<td>13.7% (10.0%–17.5%)</td>
<td>12.0% (8.7%–15.3%)</td>
<td>10.0% (5.5%–14.5%)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NR, not reported; supp, suppository.

* Sold at pharmacies as VCF.

** Sold at pharmacies as Gynol II or therapeutic equivalent.