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Update on current contraceptive options: A case-based discussion of efficacy, eligibility, and use

ABSTRACT

With high rates of unintended pregnancy in the United States, it is crucial for clinicians to be well-informed about the full spectrum of contraceptive options to improve reproductive autonomy. We review new contraceptive options including a nonhormonal intravaginal gel, hormonal contraceptives in the form of new pills, patches, and vaginal rings, and combined hormonal contraceptives that contain new estrogens as alternatives to ethinyl estradiol. We review updated prescribing methods for several established hormonal contraceptives such as depot medroxyprogesterone acetate, which is now available for subcutaneous self-injection. Additional choices of available contraceptive methods have important clinical implications that may remove unnecessary barriers to contraceptive use.

KEY POINTS

Certain long-acting reversible contraceptive methods can prevent pregnancy beyond the approved duration of use. However, this does not allow for extending the duration of use for lowest-dose progestin intrauterine devices.

Intravaginal contraceptive gel offers a nonhormonal contraceptive alternative.

Contraceptives with longer approved durations of use or that do not require frequent access to healthcare professionals can improve adherence and outcomes.

DESPITE WIDELY AVAILABLE contraceptive methods, the percentage of unintended pregnancies in the United States remains stagnant at 45%, higher than in many industrialized nations, with many of these pregnancies in individuals of low socioeconomic status and subpar access to healthcare.¹ Several new contraceptive methods have become available in the last few years, and clinicians should be able to counsel on the full spectrum of options, as patient satisfaction with the method will improve adherence. Particularly now, with reproductive autonomy being discussed in many states, there is a need for action to ensure that every patient receives their preferred safe and effective contraceptive. In addition to preventing pregnancy, contraceptives often are used for symptom management in medical conditions including acne, hirsutism, dysmenorrhea, heavy menstrual bleeding, menstrual migraine, and perimenstrual mood disorders.

Herein, we discuss several new hormonal and nonhormonal contraceptive options. Please note that this article is focused on cisgender women who have sex with men. The term “she” in this paper refers to those assigned female sex at birth.

■ NONHORMONAL CONTRACEPTIVE INTRAVAGINAL GEL

A 47-year-old with latex allergy presents to the office. She is interested in contraception, but does not want anything that contains hormones.

Until recently, nonhormonal contracep-

tive options were limited to the copper intrauterine device (IUD), condoms (male and female), diaphragm, cervical cap, and spermicides.²⁻⁴ The use of a copper IUD requires a procedure and may lead to increased menstrual bleeding and cramping.^{5,6} Barrier methods are user-dependent, may impact spontaneity, have varying effectiveness, and variable unintended pregnancy rates per year of use (eg, 18% to 28% for spermicide).²⁻⁴ Most barrier methods require an office visit for optimal fitting and need to be used with spermicides, which may be associated with irritative vaginal or urinary symptoms.³

A new barrier method intravaginal gel (Phexxi; lactic acid 1.8%/citric acid 1%/potassium bitartrate 0.4%) is inserted within 1 hour prior to intercourse. The gel maintains the physiologically acidic pH of the vagina to inhibit sperm motility, and the viscosity offers a barrier to sperm over the cervix.⁴ A new applicator needs to be used with each act of intercourse.

The AMPOWER study was a multicenter, single-arm, open-label, phase 3 study of 1,384 women, of which 1,114 were included in the primary efficacy analysis.⁷ In this study, the intravaginal gel demonstrated 86.3% contraceptive efficacy with typical use (as opposed to preliminary studies submitted to the US Food and Drug Administration [FDA] that suggested 93% efficacy with perfect use over 7 cycles).⁷⁻⁹ When using contraceptive methods with lesser efficacy, an advanced prescription for an emergency contraceptive pill (such as ulipristal acetate) is recommended, especially if pregnancy prevention is an important goal for the patient.

The most common adverse events have been reported to be vaginal burning (18%) and itching (14.5%).⁹ Similar to other barrier methods, an association with cystitis, pyelonephritis, and urinary tract infections have been reported, perhaps due to the shift in pH of the genitourinary system.^{9,10}

Intravaginal gel is an option for patients desiring nonhormonal birth control (owing to preference or medical contraindication), wanting an on-demand option, or those who have allergies to other barrier methods such as latex condoms or spermicide. This method is particularly unique because it is on-demand and similar to condoms but not partner-dependent. It can also be used postpartum, post-miscarriage, or post-abortion. In addition, some women who are encouraged to use two methods of contraception (ie, when on a medication that will induce liver enzymes or has teratogenic potential) can use this method with a shorter-acting method such as birth control pills. This is a reasonable contraceptive option for women

in the late menopause transition, where the chance of unintended pregnancy is decreased (though still possible). Those who need a highly reliable method to prevent pregnancy should be counseled on the use of more effective methods.

■ INTRAVAGINAL RING

A 28-year-old shift-worker notes difficulties remembering her birth control pills. She is interested in an option that does not require daily use. You suggest an IUD or arm implant, but she wants to avoid a procedure. What method would you recommend?

Despite the variety of available contraceptive options, imperfect adherence remains an issue that decreases effectiveness. Nearly 48% of unintended pregnancies occur in women who use contraception.^{11,12} Most American women use short-acting hormonal contraceptives or combined oral contraceptives (COC), even though the chance of unintended pregnancy is significantly lower for an IUD and implant.^{5,6} Expanding the available non-oral formulations of short-acting hormonal contraceptives is crucial to ensure that women who do not desire a procedure or daily oral regimen have adequate efficacious options.

A new 13-cycle combined vaginal ring containing 150 µg segesterone acetate and 13 µg ethinyl estradiol provides one year of birth control using the same ring without being discarded (Annovera),¹³ unlike other vaginal contraceptive rings (eg, NuvaRing, EluRyng) that have a different type of progestin and are intended for only 1 month of use at a time. Similar to other vaginal rings, Annovera is placed inside the vagina for 21 days by the patient, then removed for 7 days to allow menses.¹³⁻¹⁵

The initial phase 3 trials included two multicenter, multinational studies of 3,052 women, with 999 completing 13 cycles of use with Annovera.¹⁶ Effectiveness in pregnancy prevention was noted to be 97.3% when used as recommended, comparable to perfect use of COCs.^{13,14}

Complete expulsions occurred in the studies in 7% of cycles, although these were mainly in the initial cycle.¹⁶ No backup contraception is needed if the intravaginal ring is reinserted within 2 hours of expulsion.¹⁷ This may not be an appropriate method for those with difficulty or pain using the vaginal ring, such as those with arthritis of the hands, pelvic floor dysfunction, vaginismus, preference to avoid intravaginal placement, or other limitations for correct use.

This method is a good choice for those who want longer-acting, reversible contraception that is not a pill, injection, or procedure, especially in patients struggling to adhere to a daily pill or with limited access to healthcare. The segesterone acetate and ethinyl estradiol ring has not been studied for continuous use (no placebo break), though it is used this way in clinical practice. A modeling study using pharmacokinetics data from 37 women suggested that serum levels of estrogen and progestin after 364 days of hypothetical continuous use would be appropriate for pregnancy prevention,¹⁵ but evidence from clinical trials to support continuous use is currently unavailable.

■ PROGESTIN-ONLY PILL

A 35-year-old needs contraception and would like to regulate her cycles. She has a history of lower extremity venous thromboembolism following intensive care unit hospitalization for viral pericarditis. She wants to avoid procedures or injections and prefers oral pills. She has tried a progestin-only pill in the past, does not recall its name, but does remember frequent breakthrough bleeding with that method.

Before 2019, the only progestin-only pill (POP) available in the US would have been 0.35-mg daily norethindrone, available in multiple generic names. Because it does not contain estrogen, a POP can be used in women with a history of arterial or venous thrombosis and those considered to be at high risk for these conditions (ie, uncontrolled hypertension, tobacco use, antiphospholipid syndrome, migraine with aura, etc.).^{5,6} Given that there are only a few contraindications to its use (such as active hormone-dependent breast cancer treatment), a POP can be offered as a “quick start” method to any woman who is sure that she is not pregnant and as a bridge for more effective methods requiring a procedure at a future time.

With traditional POPs, patients need to follow rigid daily timing as missed pills lessen effectiveness.¹⁸ Traditional POPs are different from estrogen-containing contraceptives in a variety of ways. They inhibit ovulation only in about 50% to 70% of user cycles.^{6,18} Thus, this method also prevents pregnancy with other mechanisms of action, such as impacting cervical mucus.^{18,19} Norethindrone-only pills also have a shorter half-life than COCs.¹⁸ Consequently, a POP user must adhere to a consistent pill schedule, with a maximum delay of 3 hours in dosing compared to 12 to 24 hours with a COC.^{18,19} Women who are more

than 3 hours late taking their norethindrone POP are encouraged to use additional backup contraception.¹⁸

The new 4-mg drospirenone POP, a derivative of spironolactone, acts as an antiminerocorticoid with antiandrogenic properties,^{18,19} with activity similar to 25-mg spironolactone. Therefore, it is likely to be beneficial in those with acne, hirsutism, or tendency toward fluid retention. Although it has not been directly compared to norethindrone POPs, the 4-mg dose for drospirenone was determined based on effective suppression of ovulation for up to 24 hours following a missed or delayed dose.¹⁸

Norethindrone POP is taken daily, without any placebo breaks. Thus, variable bleeding can occur, as can lighter regular bleeding, amenorrhea, or irregular spotting. Drospirenone is taken in a 24-active pill/4-placebo-pill formulation to induce a regularly scheduled withdrawal bleed as opposed to traditional POPs taken continuously.^{19,20}

As with all progestin-only methods, unscheduled or prolonged bleeding is common. It typically occurs in the first 6 months, between cycles 2 to 4, with declining frequency over time, and an eventually greater percentage of participants reporting lighter cycles or amenorrhea at a year or beyond.^{19,21,22} Based on a multicenter, noncomparative trial, the 4-mg drospirenone “24/4-day regimen” reduced unscheduled bleeding over time; participants reported 90% of bleeding days as light or moderate, with only 4.2% of participants stopping the study due to irregular bleeding.^{19,21,22} Prior to prescribing, appropriate counseling of expected bleeding patterns over the first year is likely to help with patient adherence and satisfaction with the method.

Similar to traditional POPs, drospirenone has a desirable safety profile.^{19,21,22,23} In a study of over 700 participants from 41 European sites, treated for one year, no one experienced cardiovascular events, thromboses, or hyperkalemia, despite participants having at least one cardiovascular risk factor.¹⁹ Drospirenone 3 mg is available in a COC together with ethinyl estradiol doses of 20 or 30 µg (with additional FDA approval to treat premenopausal dysphoric disorder).²³ Despite the higher dose of 4-mg drospirenone in the progestin-only formulation, plasma concentrations of drospirenone at a steady state have been shown to be higher after use of 3-mg drospirenone combined with ethinyl estradiol.²³ However, this difference is unlikely to have significant clinical implications for most individuals.

Given its effectiveness in ovulatory suppression, predictable bleeding pattern, and favorable side

effect profile, a 24/4-day regimen of 4-mg drospirenone would be an excellent option for women with contraindications to estrogen-containing hormonal contraceptives.

NEWER ESTROGEN OPTIONS

A frustrated 38-year-old visits the office for a birth control follow-up. She has tried multiple COCs with different progestin types, yet each caused her to develop a diffuse rash. She is adamant about not placing an intravaginal ring, arm implant, or intrauterine device. Are there any other options?

Most COCs contain ethinyl estradiol, a synthetic hormone with a long half-life, which helps with stability of dosing for effectiveness and bleeding control. Oral intake of ethinyl estradiol impacts the production of various liver proteins involved in coagulation, fibrinolysis, and hypertension, thus contributing to its commonly known thrombosis risk. Also, ethinyl estradiol is highly potent compared to more natural analogs of estradiol, which has led to a lowering of ethinyl estradiol doses over the years to improve the safety profile of hormonal contraceptives.²⁴ Although most women tolerate ethinyl estradiol-containing pills very well, for those who are intolerant, there were few alternative estrogen-containing contraceptive options until recently. In 2010, the FDA approved COCs containing estradiol valerate, followed by the recent approval of estetrol in 2021, expanding the number of options for those intolerant to the estrogen component of the pill.

Estradiol valerate is available in a quadriphasic formulation (US trade name Natazia), which decreases estrogen from 3 mg to 1 mg and increases the progestin (dienogest) from 1 mg to 4 mg, both over the course of the monthly regimen. Estradiol valerate is a synthetic prototype of natural 17 beta-estradiol, being rapidly metabolized to estradiol after oral intake.²⁵⁻²⁷ Two mg of estradiol valerate has the impact of 10 µg of ethinyl estradiol, qualifying this contraceptive as very low-dose.²⁷ Dienogest is a progestin with a 17-cyanomethyl group, causing its strongly progestogenic and weakly antiandrogenic activity.²⁵ Two inert (placebo) pills complete the pack for the last 2 days to allow for a shortened withdrawal bleed.²⁶⁻²⁸ Comparable to triphasic pills, the 26 active pills contain tapering doses of the active drugs in attempt to mimic the natural menstrual cycle.²⁶⁻²⁸ Although both estrogen and progestin components are newer to the US market, this particular progestin has been used in Europe since the 1990s.

Natazia was the first quadriphasic dosing regimen used to treat heavy menstrual bleeding.^{26,27} A multicenter, double-blind, randomized, placebo-controlled phase III study conducted in Europe and the Asia Pacific demonstrated the effectiveness of the estradiol valerate-dienogest combination in significantly reducing menstrual bleeding and improving productivity and daily activities in women's lives.²⁶ Though most COCs can treat heavy menstrual bleeding, this formulation has higher rates of amenorrhea compared with typical COCs, with amenorrhea occurring in 19% to 24% of women, making it potentially useful for those plagued with persistent breakthrough bleeding using other regimens.^{26,27} Also, estradiol valerate caused a significantly milder effect on metabolic parameters than ethinyl estradiol.²⁵⁻²⁹

Estetrol 14.2 mg is a novel estrogen combined with 3-mg drospirenone (US trade name Nextstellis, 2021). Estetrol is marketed as a "natural estrogen" because it is produced by the fetal liver during pregnancy and acts selectively in tissues (impacts alpha receptors), showing mixed estrogen agonist and antagonist activity.³⁰ Clinically, it has been shown to have minimal impact on the synthesis of coagulation factors, hepatic metabolism, triglycerides, and breast stimulation.^{24,30} Owing to these differences, estetrol cannot be translated into an equivalent dose of ethinyl estradiol that applies to all tissues. However, contraceptive efficacy of estetrol with drospirenone has been shown to be similar to other marketed ethinyl estradiol-estetrol with drospirenone containing COCs. Estetrol has been marketed as more environmentally friendly due to less accumulation of estrogen metabolites in the urine, with the hopes that it will be less likely to pollute water supplies.³¹ However, further study is needed to assess which of these factors, if any, will be of clinical significance.

Nextstellis is monophasic (all pills have consistent hormone dosing), available with 24 active pills and 4 days of placebo, leading to an optimum withdrawal bleeding pattern (typically, the fewer placebo days, the shorter the expected bleeding).^{24,30} Studies have suggested lower venous thromboembolism (VTE) incidence compared to traditional COCs,^{24,30} but there is need for more extensive studies (in real-world settings, in larger groups) to give a more accurate population estimate of VTE incidence. The additional absolute increase in the risk of venous thrombosis with the use of all estrogen-containing contraceptives (when compared to baseline population rates of VTE) is about 1 of 1,000 or less, in the rare category of risk, and well below the thrombosis risks of unintended

pregnancy.^{5,32} Thus, large populations need to be studied to assess thrombosis risk in otherwise healthy women during reproductive age.

The side effect profiles of these newer estrogens are similar to all other classes of combined hormonal contraceptives and may include mood changes, irregular bleeding, nausea, headache, and breast tenderness. Newer estrogen options might be beneficial in those with intolerance to multiple COCs, both in terms of symptoms and bleeding irregularities, and may be the desired option for those with cardiometabolic risk factors such as elevated triglycerides, pending further study. Estradiol valerate, in particular, could be a highly efficacious hormonal contraceptive for women with menorrhagia.

■ TRANSDERMAL OPTIONS

A 23-year-old needs birth control that will provide predictable cyclical bleeding and help her acne, but does not want to be required to remember pills. She has read that birth control patches increase the risks of blood clots more than other formulations and asks for your advice.

The delivery of hormonal contraceptives has evolved since the birth control pill was first introduced in the 1960s, now including oral, transdermal, subcutaneous implant, intrauterine, and intravaginal options. Transdermal delivery of hormones helps address poor adherence and fluctuation of hormones due to pharmacokinetic variations of serum hormonal levels associated with COCs.^{33–36}

Similar to a bandage, a small adhesive patch is placed on the lower abdomen, buttocks, upper arm, or upper torso (excluding the breast), worn continuously for 1 week, and is removed and replaced immediately by a new patch weekly for 3 weeks, followed by a patch-free week when the menstruation occurs. Alternatively, a new patch can be placed weekly without any breaks for continuous use. However, pharmacokinetic studies have suggested a gradual rise in serum ethinyl estradiol over time after 12 weeks of continuous use, thus long-term safety of patch use without placebo breaks is not clear.^{33–36} The patch is designed to stay in place while bathing, swimming, or exercising, but users should not apply lotion or oil near the patch site. Like all transdermal medications, allergic reactions to the adhesive are possible.

The first patch containing 35 µg ethinyl estradiol and the progestin norelgestromin was FDA approved in 2001 within the United States and internationally (initial trade name Ortho Evra, now Xulane). Once applied to the skin, a steady state is reached within

48 hours of application and maintained consistently until removal; like forms of hormonal contraceptives, the contraceptive effectiveness begins after 1 week of use.⁶ Several clinical trials indicate that the contraceptive patch is as effective as COCs and may lead to better adherence.^{34–50} However, this first generation of patches led to higher exposure of serum ethinyl estradiol, similar to a 50-µg COC,³⁶ leading to conflicting reports about whether rates of VTE were increased compared with COCs.³⁷ Some of these studies found no associated increase in VTE risk compared with low-dose comparators.^{38–40} While another found comparable VTE risks to levonorgestrel-containing pills (a progestin that typically shows lower relative risks of VTE among COCs) but could not exclude additional risk for older women.⁴¹ In contrast, several studies suggested that the norelgestromin-ethinyl estradiol patch magnifies relative risk for VTE compared with norelgestromin or levonorgestrel-containing pills by 2-fold.^{42–44} However, there were limitations to several of these studies, including that the 95% confidence intervals (CIs) crossed one in most analyses and had no adjustment for possible confounding variables.³⁶ Thus, the FDA Advisory Board concluded that though there may be an increased relative risk for VTE with the norelgestromin-ethinyl estradiol patch compared with some birth control pills, the absolute risk is still considered lower.⁴⁵

A new transdermal patch containing 30-µg ethinyl estradiol and 120-µg levonorgestrel daily dosing (Twirla; FDA-approved 2020) was designed to address the need for a lower-dose contraceptive patch and delivers daily hormone exposure compared with similarly dosed pills.³⁵ Twirla is well tolerated, with reported lower rates of detachment and site irritation than the norelgestromin-ethinyl estradiol patch.^{34,35} Based on evidence from five clinical trials, the norelgestromin-containing patch has a VTE frequency of 53 per 100,000 women (95% CI 1–294).³⁴ Though direct head-to-head studies are not available between the 2 patches, studies of the levonorgestrel-containing patch are estimated to have a VTE frequency of 32 per 100,000 women (95% CI 1–176).³⁴

Norelgestromin patch users typically had less breakthrough bleeding and spotting than COCs at cycle 13.⁴⁵ However, users of this patch were also more likely to report breast discomfort, dysmenorrhea, nausea, and vomiting.^{29,40,41} Users of the novel levonorgestrel patch were less likely to experience nausea and infrequently reported headaches and fatigue when compared to COC users.^{34,47,48} Again, it should be noted that studies directly comparing side

effects of the 2 patches are not available.

Based on limited evidence, there is concern of a higher risk for contraceptive failure in transdermal contraceptive users who have a body mass index (BMI) ≥ 30 kg/m².³⁵ Thus, relying on a hormonal contraceptive patch as the sole method to prevent pregnancy in women with a BMI ≥ 30 kg/m² is not recommended, especially when pregnancy prevention is a high priority.

Transdermal hormonal contraceptives are advantageous for individuals having difficulty with remembering a daily pill. Healthy women in their teens and 20s at low risk for VTE may still be candidates for norelgestromin patches, especially if higher doses are preferred for cycle control, improving acne (which tends to be treated best with higher estrogen-containing options), or combined with medications that may interact to decrease hormone levels. However, additional transdermal options with a lower estrogen dose will be useful in clinical practice.

■ SELF-ADMINISTERED DEPOT MEDROXYPROGESTERONE ACETATE

Depot medroxyprogesterone acetate (DMPA) users represented 2% of US women aged 15 to 49 between 2017 and 2019.⁵¹ DMPA-intramuscular 150-mg injections have historically required an office visit, which can pose additional barriers to staying consistent with a patient's preferred contraceptive method. Following their review, the Centers for Disease Control and Prevention and World Health Organization recommended self-administered 104-mg subcutaneous (SC) DMPA.⁵⁰ This formulation can be injected at home by the patient, which empowers self-care and removes barriers such as frequent in-person visits to a clinic. It is a user-controlled method with the potential to improve contraceptive access and reproductive autonomy.⁴⁹

Currently, the FDA label states DMPA-SC is only to be administered by clinicians. Nonetheless, following a shared decision between clinician and patient, an FDA-approved drug may be prescribed for off-label use, not excluding self-administration when medically needed. In clinical practice, many patients are encouraged to self-inject at home, and self-administered DMPA-SC has been shown to have a higher continuation rate than provider-administered DMPA.^{49,51} One study reported that 97% of patients found DMPA-SC easy to administer and reported an 87% satisfaction rate, which was higher than provider-administration at 12 months of follow-up.⁵¹ In a US study conducted during the COVID-19 pandemic,

37% of contacted DMPA-intramuscular patients were interested in self-administration of DMPA-SC, with 58% of those interested individuals transitioning to self-administration, reported to be similar to provider administration, and the safety profile was not different, though more injection site reactions have been reported in the self-administered group.⁵² Barriers to self-administration include a preference for an in-person visit, fear of needles, incorrect administration, and insurance coverage.⁴⁹

The recommendation for self-administered initiation, follow-up, and reinjection interval is the same as when provider administered. Repeat DMPA injections should be provided every 3 months and may be given up to 2 weeks late without requiring backup contraceptive protection.⁵³ Patients should receive instruction for self-administration and sharps disposal. These individuals should have access to follow-up care along with the opportunity to switch to provider-administration or another contraceptive method if desired.

■ USE OF LONG-ACTING CONTRACEPTIVE DEVICES BEYOND FDA-APPROVED DURATION OF USE

Long-acting reversible contraceptives (LARCs) have become an increasingly popular contraceptive choice because of their high degree of efficacy and safety profiles that include efficacy at preventing pregnancy, ability to be used for several years, limiting patient effort and thus user error, and offering rapid return to fertility. A prospective cohort study of over 9,000 women with normal weight and BMI > 30 kg/m² received the LARC of their choice (an IUD or arm implant) and observed a failure rate of less than 1 per 100-woman years without any difference according to BMI category.⁵³⁻⁵⁵

When long-term pregnancy prevention is priority, LARC may be the optimal contraceptive choice. Recently, research has shown that several commonly used LARC methods maintain efficacy 1 to 2 years after the FDA-approved duration of use (**Table 1**).^{5,6,53,56}

Subdermal implant

Nexplanon is a small polymer rod impregnated with the progestin etonogestrel. During a simple office procedure, this implant is placed subdermally in the non-dominant upper arm. While FDA-approved for only 3 years for contraception, emerging data have shown efficacy maintained for up to 5 years. An open-label, multicenter, randomized trial demonstrated that etonogestrel implants had a 5-year cumulative pregnancy rate of 0.6 per 100 women-years

TABLE 1
Comparison of commonly used LARCs, all with > 99% efficacy^a

Brand	LARC type	Progestogen, dose	Size, mm	FDA-approved duration of use	Data-supported duration of use	Bleeding patterns	Amenorrhea according to package insert	Other clinical pearls
Mirena	Levonorgestrel-IUD	52 mg	32 x 32	8 years	8 years	More likely to have significantly decreased menstrual bleeding and pain, especially after 1 year of use Progestin-only methods may be associated with irregular bleeding and spotting	1 year: 20% 5 years: 40%	Approved for treatment of heavy menstrual bleeding Can be used as emergency contraception ⁵⁶
Liletta	Levonorgestrel-IUD	52 mg	32 x 32	8 years	8 years		1 year: 19% 5 years: 40%	More affordable for patients with limited insurance coverage
Kyleena	Levonorgestrel-IUD	19.5 mg	28 x 30	5 years	5 years		1 year: 12% 5 years: 23%	Smaller size may be more suitable to nulliparous patients or those with anatomically smaller uterus
Skyla	Levonorgestrel-IUD	13.5 mg	28 x 30	3 years	3 years		1 year: 6% 3 years: 12%	
Paragard	Copper IUD	Hormone-free	32 x 36	10 years	12 years	Possible increased amount and duration of menstrual bleeding	No causal relationship established	Can be used as emergency contraception Best for highly effective contraception that is hormone free (ie, after breast cancer) When used during age of mid-late 30s, can provide contraception into menopause transition
Nexplanon	Subdermal etonogestrel implant	68 mg	2 x 40	3 years	5 years	Unpredictable bleeding pattern, though lightens over time for most	2 years: 20%	Does not require a pelvic examination Easy to learn procedure, training via drug company as opposed to clinician

^aAll the contraceptives are the most-effective contraceptive methods; safe in breastfeeding; no long-term effects on fertility, fertility is immediate following discontinuation; safe for women who cannot or prefer not to take estrogen.

FDA = US Food and Drug Administration; IUD = intrauterine device; LARC = long-acting reversible contraceptives

Based on data from references 5, 6, 53, and 56.

[n = 204; 95% CI, 0.2–1.8].⁵⁷ In contrast, the chance of unintended pregnancy at the end of 1 year is 6% to 9% with typical use of patient-controlled methods such as pills, rings, patches, and DMPA injections.⁶ Thus, even when used two years beyond the removal date, it is likely that contraceptive efficacy is considerably better than those of the short-term reversible methods.

In our experience, it is reasonable for a clinician to have a shared-decision-making conversation regarding the option to leave the device for 4 or 5 years or

replace it at year 3. Of note, there is insufficient data regarding the efficacy of the etonogestrel implant in extended use in patients with a BMI ≥ 30 kg/m², as obesity has been shown to decrease serum levels of progestin.^{5,6} Additionally, given that the progestin dosage decreases over time, some patients who opt for extended use may experience increased irregular bleeding. Before choosing this option, clinicians must discuss with patients to ensure a complete understanding of potential adverse effects.

Intrauterine devices

The highest dose (52 mg) levonorgestrel-releasing IUDs have the longest FDA-approved duration of use of the progestin IUDs available in the United States. Since 2022, both Mirena and Liletta are now FDA-approved for 8 years of use based on updated studies showing effectiveness beyond their originally approved duration of use (had been 5 years). The lower-dose hormonal IUDs (Skyla and Kyleena) should not be used beyond their FDA-approved duration of use due to lack of data.

Studies suggest that the nonhormonal copper IUD (Paragard) remains a highly effective contraceptive at least until 12 years of use.⁵⁸ In 1997, the World Health Organization and United Nations conducted a large, randomized, multicenter trial that determined the cumulative 12-year intrauterine pregnancy rate was 1.9 per 100 person-years (standard error, 0.6, $P < 0.001$), which is similar to all sterilization methods.⁵⁸

KEY MESSAGES

Now, more than any other time in recent US history, it is crucial for all clinicians to be well-informed about the full spectrum of contraceptive options. Shared

REFERENCES

- Finer LB, Zolna MR. Declines in unintended pregnancy in the United States, 2008–2011. *N Engl J Med* 2016; 374(9):843–852. doi:10.1056/NEJMsa1506575
- Grimes DA, Lopez LM, Raymond EG, Halpern V, Nanda K, Schulz KF. Spermicide used alone for contraception. *Cochrane Database Syst Rev* 2013; (12):CD005218. doi:10.1002/14651858.CD005218.pub4
- Cook L, Nanda K, Grimes D. The diaphragm with and without spermicide for contraception: a Cochrane review. *Hum Reprod* 2002; 17(4):867–869. doi:10.1093/humrep/17.4.867
- Chappell BT, Griffin BL, Howard B. Mechanisms of action of currently available woman-controlled, vaginally administered, non-hormonal contraceptive products. *Ther Adv Reprod Health* 2022; 16:26334941221107120. doi:10.1177/26334941221107120
- Shin R, Brant A, Batur P. Contraception. In: Falcone T, Hurd WW, eds. *Clinical Reproductive Medicine and Surgery*, 4th ed. Springer: Cham, Switzerland. 2022; 553–571
- Curtis KM, Tepper NK, Jatlaoui TC, et al. US medical eligibility criteria for contraceptive use, 2016. *MMWR Recomm Rep* 2016; 65(3):1–103. doi:10.15585/mmwr.rr6503a1
- Thomas MA, Chappell BT, Maximos B, Culwell KR, Dart C, Howard B. A novel vaginal pH regulator: results from the phase 3 AMPOWER contraception clinical trial. *Contracept X* 2020; 2:100031. doi:10.1016/j.conx.2020.100031
- Chappell BT, Culwell K, Dart C, Howard B. Perfect-use pregnancy rates with the vaginal pH regulator: efficacy results from AMPOWER [30]. *Obstet Gynecol* 2020; 135:995
- Evoform Inc. Phexxi. <https://hcp-phexxi.com/themes/custom/phexxi-HCP/dist/pdf/PhexxiUSPI.pdf#page=1>. Accessed February 13, 2023.
- Steinberg J, Lynch SE. Lactic acid, citric acid, and potassium bitartrate (phexxi) vaginal gel for contraception. *Am Fam Physician* 2021; 103(10):628–629. PMID:33982994
- Trussell J, Henry N, Hassan F, Prezioso A, Law A, Filonenko A. Burden of unintended pregnancy in the United States: potential savings with

decision-making between each patient and clinician is recommended to choose the best option, recognizing that the risks of any contraceptive are always less than the risks of unintended pregnancy. Though a growing body of evidence supports the safety of expanding the duration of LARC use, individuals should never be coerced into keeping the device longer than what they prefer. The bleeding profiles and contraceptive efficacy may be impacted negatively with a greater duration of use, and for some women, their highest priority may be the best possible protection from unintended pregnancy. Although increasing nonprocedural options with new pills, patches, and rings are important for patient choice, financial barriers to using these newer (and often more expensive) products remain a real challenge. We urge clinicians to advocate on behalf of their patients for various contraceptive options to be made available and affordable to all women who need them. ■

DISCLOSURES

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- increased use of long-acting reversible contraception. *Contraception* 2013; 87(2):154–161. doi:10.1016/j.contraception.2012.07.016
- Finer LB, Henshaw SK. Disparities in rates of unintended pregnancy in the United States, 1994 and 2001. *Perspect Sex Reprod Health* 2006; 38:90–96. doi:10.1363/psrh.38.090.06
- Archer DF, Merkatz RB, Bahamondes L, et al. Efficacy of the 1-year (13-cycle) segesterone acetate and ethinylestradiol contraceptive vaginal system: results of two multicenter, open-label, single-arm, phase 3 trials. *Lancet Glob Health* 2019; 7(8):e1054–e1064. doi:10.1016/S2214-109X(19)30265-7
- Teal S, Edelman A. Contraception selection, effectiveness, and adverse effects: a review. *JAMA* 2021; 326(24):2507–2518. doi:10.1001/jama.2021.21392
- Liu JH, Plagianos M, Archer DF, et al. Segesterone acetate serum levels with a regression model of continuous use of the segesterone acetate/ethinyl estradiol contraceptive vaginal system. *Contraception* 2021; 104(3):229–234. doi:10.1016/j.contraception.2021.03.024
- Gemzell-Danielsson K, Sitruk-Ware R, Creinin MD, et al. Segesterone acetate/ethinyl estradiol 12-month contraceptive vaginal system safety evaluation. *Contraception* 2019; 99(6):323–328. doi:10.1016/j.contraception.2019.02.001
- Virro JJ, Besinque K, Carney CE, Gross D, Bernick B, Mirkin S. Long-lasting, patient-controlled, procedure-free contraception: a review of annovera with a pharmacist perspective. *Pharmacy (Basel)* 2020; 8(3):156. doi:10.3390/pharmacy8030156
- Duijkers JM, Heger-Mahn D, Drouin D, Colli E, Skouby 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
- Archer DF, Ahrendt HJ, Drouin D. Drospirenone-only oral contraceptive: results from a multicenter noncomparative trial of efficacy, safety and tolerability. *Contraception* 2015; 92(5):439–444. doi:10.1016/j.contraception.2015.07.014
- Regidor PA, Colli E, Georgiev D, Koytchev R, Richter W. Safety, influence on the endometrium, sonographic changes and bleeding

- profile after 13 cycles with the new drospirenone only pill (DOP) for contraception. *Horm Mol Biol Clin Investig* 2020; 42(2):123–131. doi:10.1515/hmbci-2019-0061
21. **Palacios S, Colli E, Regidor PA.** Multicenter, phase III trials on the contraceptive efficacy, tolerability and safety of a new drospirenone-only pill. *Acta Obstet Gynecol Scand* 2019; 98(12):1549–1557. doi:10.1111/aogs.13688
 22. **Kimble T, Burke AE, Barnhart KT, Archer DF, Colli 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. *Contracept X* 2020; 2:100020. doi:10.1016/j.conx.2020.100020
 23. **Richter WH, Koytchev R, Kirkov V, Merki G, Colli E, Regidor PA.** Comparative pharmacokinetic estimates of drospirenone alone and in combination with ethinyl estradiol after single and repeated oral administration in healthy females. *Contraception* 2020; 101(2):137–143. doi:10.1016/j.contraception.2019.10.005
 24. **Duijkers I, Klipping C, Kinet V, Jost M, Bastidas A, Foidart JM.** Effects of an oral contraceptive containing estetrol and drospirenone on ovarian function. *Contraception* 2021; 103(6):386–393. doi:10.1016/j.contraception.2021.03.003
 25. **Whalen KL, Rose R.** Estradiol valerate/dienogest: a novel oral contraceptive. *Ann Pharmacother* 2011; 45(10):1256–1261. doi:10.1345/aph.1Q216
 26. **Yu Q, Zhou Y, Suturina L, Jaisamrarn U, Lu D, Parke S.** Efficacy and safety of estradiol valerate/dienogest for the management of heavy menstrual bleeding: a multicenter, double-blind, randomized, placebo-controlled, phase III clinical trial. *J Womens Health (Larchmt)* 2018; 27(10):1225–1232. doi:10.1089/jwh.2017.6522
 27. **Micks E, Jensen JT.** Estradiol valerate and dienogest: a novel four-phasic oral contraceptive pill effective for pregnancy prevention and treatment of heavy menstrual bleeding. *Womens Health (Lond)* 2011; 7(5):513–524. doi:10.2217/whe.11.49
 28. **Kangasniemi MH, Haverinen A, Luiro K, et al.** Estradiol valerate in COC has more favorable inflammatory profile than synthetic ethinyl estradiol: a randomized trial. *J Clin Endocrinol Metab* 2020; 105(7):dgaa186. doi:10.1210/clinem/dgaa186
 29. **Wiegatz I, Lee JH, Kutschera E, et al.** Effect of dienogest-containing oral contraceptives on lipid metabolism. *Contraception* 2002; 65(3):223–229. doi:10.1016/s0010-7824(01)00310-9
 30. **Gemzell-Danielsson K, Apter D, Zatik J, et al.** Estetrol-drospirenone combination oral contraceptive: a clinical study of contraceptive efficacy, bleeding pattern and safety in Europe and Russia *BJOG* 2022; 129(1):63–71. doi:10.1111/1471-0528.16840
 31. **GlobeNewswire.** Mitra Pharmaceuticals. E4 paves the road towards a revolutionary era of environmental friendly medicines. <https://www.globenewswire.com/news-release/2020/01/10/1968775/0/en/E4-Paves-the-Road-Towards-a-Revolutionary-Era-of-Environmental-Friendly-Medicines.html>. Accessed February 13, 2023.
 32. **Committee on Gynecologic Practice.** ACOG Committee Opinion Number 540: Risk of venous thromboembolism among users of drospirenone-containing oral contraceptive pills. *Obstet Gynecol* 2012; 120(5):1239–1242. doi:10.1097/aog.0b013e318277c93b
 33. **Zieman M, Guillebaud J, Weisberg E, Shangold GA, Fisher AC, Creasy GW.** Contraceptive efficacy and cycle control with the Ortho Evra/Evra transdermal system: the analysis of pooled data. *Fertil Steril* 2002; 77(2 suppl 2):S13–S18. doi:10.1016/s0015-0282(01)03275-7
 34. **Lopez LM, Grimes DA, Gallo MF, Stockton LL, Schulz KF.** Skin patch and vaginal ring versus combined oral contraceptives for contraception. *Cochrane Database Syst Rev* 2013; 2013(4):CD003552. doi:10.1002/14651858.CD003552.pub4
 35. **Nelson AL, Kaunitz AM, Kroll R, et al.** Efficacy, safety, and tolerability of a levonorgestrel/ethinyl estradiol transdermal delivery system: phase 3 clinical trial results. *Contraception* 2021; 103(3):137–143. doi:10.1016/j.contraception.2020.11.011
 36. **Nelson AL.** Transdermal contraception methods: today's patches and new options on the horizon. *Expert Opin Pharmacother* 2015; 16(6):863–873. doi:10.1517/14656566.2015.1022531
 37. **Bitzer J, Gemzell-Danielsson K, Roumen F, Marintcheva-Petrova M, van Bakel B, Oddens BJ.** The CHOICE study: effect of counselling on the selection of combined hormonal contraceptive methods in 11 countries. *Eur J Contracept Reprod Health Care* 2012; 17(1):65–78. doi:10.3109/13625187.2011.637586
 38. **Egarter C, Frey Tirri B, Bitzer J, et al.** Women's perceptions and reasons for choosing the pill, patch, or ring in the CHOICE study: a cross-sectional survey of contraceptive method selection after counseling. *BMC Womens Health* 2013; 13:9. doi:10.1186/1472-6874-13-9
 39. **Jick SS, Hagberg KW, Kaye JA.** Ortho Evra and venous thromboembolism: an update. *Contraception* 2010; 81(5):452–453. doi:10.1016/j.contraception.2009.12.016
 40. **Jick SS, Hagberg KW, Hernandez RK, Kaye JA.** Postmarketing study of Ortho Evra and levonorgestrel oral contraceptives containing hormonal contraceptives with 30 mcg of ethinyl estradiol in relation to nonfatal venous thromboembolism. *Contraception* 2010; 81(1):16–21. doi:10.1016/j.contraception.2009.07.004
 41. **Cole JA, Norman H, Doherty M, Walker AM.** Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users [published correction appears in *Obstet Gynecol* 2008; 111(6):1449]. *Obstet Gynecol* 2007; 109(2 Pt 1):339–346. doi:10.1097/01.AOG.0000250968.82370.04
 42. **Dore DD, Norman H, Loughlin J, Seeger JD.** Extended case-control study results on thromboembolic outcomes among transdermal contraceptive users. *Contraception* 2010; 81(5):408–413. doi:10.1016/j.contraception.2009.12.009
 43. **Lidegaard O, Nielsen LH, Skovlund CW, Løkkegaard E.** Venous thrombosis in users of non-oral hormonal contraception: follow-up study, Denmark 2001–10. *BMJ* 2012; 344:e2990. doi:10.1136/bmj.e2990
 44. **Galzote RM, Raffie S, Teal R, Mody SK.** Transdermal delivery of combined hormonal contraception: a review of the current literature. *Int J Womens Health* 2017; 9:315–321. doi:10.2147/IJWH.S102306
 45. **Heit JA, Kobbervig CE, James AH, Petterson TM, Bailey KR, Melton LJ 3rd.** Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30-year population-based study. *Ann Intern Med* 2005; 143(10):697–706. doi:10.7326/0003-4819-143-10-200511150-00006
 46. **Urdl W, Apter D, Alperstein A, et al.** Contraceptive efficacy, compliance and beyond: factors related to satisfaction with once-weekly transdermal compared with oral contraception. *Eur J Obstet Gynecol Reprod Biol* 2005; 121(2):202–210. doi:10.1016/j.ejogrb.2005.01.021
 47. **Kaunitz A, Foegh M, Mishell D.** Increased compliance independent of patient demographics with a low-dose combination contraceptive patch (AG200-15) compared with a low-dose combination oral contraceptive in a Phase 3 clinical trial (abstract). *Contraception* 2012; 86(3):314.
 48. **Simmons KB, Edelman AB.** Hormonal contraception and obesity. *Fertil Steril* 2016; 106(6):1282–1288. doi:10.1016/j.fertnstert.2016.07.1094
 49. **Kennedy CE, Yeh PT, Gaffield ML, Brady M, Narasimhan M.** Self-administration of injectable contraception: a systematic review and meta-analysis. *BMJ Glob Health* 2019; 4(2):e001350. doi:10.1136/bmjgh-2018-001350
 50. **Curtis KM, Nguyen A, Reeves JA, Clark EA, Folger SG, Whiteman MK.** Update to US selected practice recommendations for contraceptive use: self-administration of subcutaneous depot medroxyprogesterone acetate. *MMWR Morb Mortal Wkly Rep* 2021; 70(20):739–743. doi:10.15585/mmwr.mm7020a2
 51. **Kohn JE, Simons HR, Della Badia L, et al.** Increased 1-year continuation of DMPA among women randomized to self-administration: results from a randomized controlled trial at Planned Parenthood. *Contraception* 2018; 97(3):198–204. doi:10.1016/j.contraception.2017.11.009
 52. **Katz M, Newmark RL, Aronstam A, et al.** An implementation project to expand access to self-administered depot medroxyprogesterone acetate (DMPA). *Contraception* 2020; 102(6):392–395. doi:10.1016/j.contraception.2020.09.001

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53. Curtis KM, Jatlaoui TC, Tepper NK, et al. US selected practice recommendations for contraceptive use, 2016. *MMWR Recomm Rep* 2016; 65(4):1–66. doi:10.15585/mmwr.rr6504a1
54. Secura GM, Madden T, McNicholas C, et al. Provision of no-cost, long-acting contraception and teenage pregnancy. *N Engl J Med* 2014; 371:1316–1323. doi:10.1056/NEJMoa1400506
55. Peipert JF, Madden T, Allsworth JE, Secura GM. Preventing unintended pregnancies by providing no-cost contraception. *Obstet Gynecol.* 2012;120(6):1291–7. doi:10.1097/aog.0b013e318273eb56
56. Turok DK, Gero A, Simmons RG, et al. Levonorgestrel vs copper intrauterine devices for emergency contraception. *N Engl J Med* 2021; 384:335–344. DOI: 10.1056/NEJMoa2022141
57. Ali M, Akin A, Bahamondes L, et al. Extended use up to 5 years of the etonogestrel-releasing subdermal contraceptive implant: comparison to levonorgestrel-releasing subdermal implant. *Hum Reprod* 2016; 31(11):2491–2498. doi:10.1093/humrep/dew222
58. **United Nations Development Programme and World Health Organization.** Long-term reversible contraception. Twelve years of experience with the TCu380A and TCu220C. *Contraception* 1997; 56(6):341–352. PMID: 9494767
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