Nondaily hormonal contraceptives: Establishing a fit between product characteristics and patient preferences

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Practice recommendations

■ Consider progestin-only DMPA-IM or L-IUS methods for women who want highly effective, nondaily, reversible contraception, and who regard amenorrhea as a desirable side effect; also suitable when estrogen therapy is contraindicated (SOR: **C**).

■ Consider the NE-patch or EE-ring, both containing estrogen and progestin, for women who are candidates for combined oral contraceptives, including those desiring shorter-term contraception and regular bleeding cycles (SOR: **C**).

■ To help women select the most appropriate and acceptable nondaily contraceptive option, review with patients each method's route and schedule of administration, perfect vs typical use efficacy, potential noncontraceptive health benefits, reversibility, side effects, and long-term safety profile (SOR: **C**).

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Oral contraceptives have made a major contribution to both women and society by substantially reducing the rate of unintended pregnancies. However, in actual clinical practice, contraceptive failures remain a problem. For example, the first-year pregnancy rate with oral contraceptives can be as high as 5% to 8%.[1] Experts agree that a leading reason for unintended pregnancy among oral contraceptive users is incorrect and inconsistent use. Women who do not use oral contraceptives consistently are nearly 3 times as likely to become pregnant as those who use them consistently.[2]

Today, women have alternatives to the daily regimen of oral contraceptives. Highly effective, convenient, nondaily contraceptive choices are available in injectable, intrauterine, intravaginal, and transdermal delivery systems, which may be administered weekly, monthly, every 3 months, or every 5 years, depending on a woman's family planning needs and preferences.

This article compares the efficacy, noncontraceptive health benefits, side-effect profiles, and long-term safety of the available nondaily hormonal contraceptive options. It also reviews other factors to consider when selecting the most appropriate and acceptable option for women who are seeking nondaily contraception.

■ OPTIONS FOR NONDAILY CONTRACEPTION

The first available nondaily contraceptive, *depot-medroxyprogesterone acetate* (DMPA-IM; Depo-Provera), is a progestin-only injectable introduced in 1963 that has been used by more than 30 million women worldwide.[3] Its efficacy, safety, and health benefits have been established through large-scale epidemiologic investigations, and it was approved for use in the United States in 1992.

In the past 2 years, other nondaily hormonal contraceptives with a variety of delivery systems have been introduced to the US market. The *levonorgestrel-releasing intrauterine system* (L-IUS; Mirena) is also a progestin-only method that has been in use worldwide for 10 years. Its health benefits and hormone-associated side-effect profile are similar to DMPA-IM (particularly bleeding patterns).

The *etonogestrel/ethinyl estradiol vaginal ring* (EE-ring; NuvaRing), and the *norelgestromin/ ethinyl estradiol transdermal system* (NE-patch; Ortho Evra) will likely offer improved efficacy to oral contraceptives with a similar long-term safety profile.

Nondaily contraception potentially more convenient and effective

Unlike oral contraceptives, which must be taken every day, nondaily contraceptives offer dosing options ranging from weekly to every 5 years (**Table 1**). These extended dosing intervals reduce the likelihood of missed doses and are more convenient for many women than daily dosing. These methods also provide greater privacy because there is no visible evidence of their use, with the exception of the patch, which can be worn on discreet locations under clothing.

Improved adherence associated with less frequent dosing of nondaily hormonal contraceptives appears to enhance contraceptive efficacy, an example of which is the similarity between first-year pregnancy rates during perfect and typical use of DMPA-IM (**Table 2**). The antiovulatory

concentrations of medroxyprogesterone acetate achieved within 24 hours of injection provide almost immediate protection against pregnancy and likely contribute to the high contraceptive efficacy seen with DMPA-IM.[4] The lowest reported pregnancy rates with perfect and typical use of L-IUS are comparable, and there is no need for backup contraception following insertion.[5] Furthermore, even with typical use, reported pregnancy rates for DMPA-IM and L-IUS (0.3% and 0.1%, respectively) are comparable to sterilization (0.5%).[1,5]

Pregnancy rates during perfect use of the NE-patch and EE-ring also are low, but it is not yet possible to accurately estimate the failure rates of these methods during typical use due to limited US postmarketing experience.[6,7] A backup method is recommended for the first 7 days of EE-ring use if the patient has not previously taken hormonal contraception or is switching from a progestin-only method,[7] and for the first 7 days of NE-patch use if the first patch is applied after Day 1 of menses.[6]

■ NONCONTRACEPTIVE HEALTH BENEFITS

Nondaily hormonal contraceptive options have documented non-contraceptive health benefits.

DMPA-IM. This drug reduces the risk of endometrial cancer by 80% after 1 year, a protective effect that appears to extend for at least 8 years after cessation of use.[8] DMPA-IM also decreases risk of iron deficiency anemia, pelvic inflammatory disease[9] and uterine leiomyomas,[10] and reduces pain crises among users with sickle cell disease.[11]

Clinical experience has shown that DMPA-IM may be an effective treatment option for a number of gynecologic conditions, including (though these are unapproved off-label uses) menorrhagia and dysmenorrhea, pain associated with endometriosis, ovulatory pain, and menopause-related vasomotor symptoms.[9,12] Many of the menstrual-cycle related benefits of DMPA-IM result from the high incidence of amenorrhea, which may be particularly appealing to women

TABLE 1

Nondaily hormonal contraceptives (currently available in the US), compared with oral contraceptives

Method, *Administration*	Mechanism of action	Dosing schedule	Pregnancy first year (%)	
			Perfect use	**Typical use**
DMPA-IM[1] (Medroxyprogesterone acetate; Depo-Provera) *Intramuscular injection, given by health provider*	Inhibits secretion of gonadotropins, which prevents follicular maturation and ovulation and results in endometrial thinning	Every 3 mo	0.3	0.3
L-IUS[5] (Levonorgestrel; Mirena) *Intrauterine system, placed by health provider*	Effects morphological changes in the endometrium, including stromal pseudodecidualization, glandular atrophy, and leukocytic infiltration; inhibition of ovulation is observed in some women	Every 5 y	0.1	0.1
EE-Ring[7] (Etonogestrel/ethinyl estradiol; NuvaRing) *Intravaginal ring, self-applied*	Suppression of gonadotropins inhibits ovulation; other alterations include changes in cervical mucus and endometrium	Monthly (1 ring-free wk/mo)	1.0–2.0	Unknown*
NE-Patch[6] (Norelgestromin/ ethinyl estradiol; Ortho Evra) *Transdermal patch, self-applied*	Suppression of gonadotropins inhibits ovulation; other alterations include changes in cervical mucus and endometrium	Weekly (1 patch-free wk/mo)	1.0	Unknown*
Oral contraceptives[1] Combined or progestin-only *Oral pills, self-administered*	Suppression of gonadotropins inhibits ovulation; other alterations include changes in cervical mucus and endometrium	Daily (1 hormone-free wk/mo)	Combined: 0.1 Progestin: 0.5	Combined: 5.0 Progestin: 5.0

*Due to limited US postmarketing experience, a precise estimate of failure rate during typical use is not yet available.

who have menstrual-cycle related disorders, such as mittelschmerz, and for women who have problems with menstrual hygiene.

Additional advantages of progestin-only DMPA-IM compared with estrogen-containing contraceptive options include efficacy that is not compromised by concomitant anticonvulsive therapy.[9] It also has no adverse effect on lactation, allowing use as early as the sixth week postpartum in breast-feeding women.[13]

L-IUS. This agent may also have several non-contraceptive benefits related primarily to the oligoamenorrhea experienced by many users. These include increased hemoglobin concentrations (thus possibly preventing iron deficiency anemia), off-label use as a treatment for menorrhagia or dysmenorrhea, an alternative to hysterectomy for heavy menstrual bleeding, and for progestin opposition in post-menopausal women on estrogen replacement therapy.[14] Small case-series reports

TABLE 2

Nondaily hormonal contraceptive side effects and long-term safety

Side effect	Combined oral contraceptives	Depo-Provera	Mirena	NuvaRing	Ortho Evra
Bleeding patterns					
Regular cycles	Yes	No	Variable	Yes	Yes
Intermenstrual bleeding/spotting		7.6%–27% at 1 year[17,18]	16% at 1 year[20]	3.8% at 1 year[32]	<10% at 1 year[22,38]
Menorrhagia		6.7% at 9 mo[16]	Rare[20]	None reported[32]	None reported[22]
Amenorrhea		70%–73% at 1 year[17,18]	20%–50% at 1 year[5,20]	None reported[32]	0.1%[22]
Discontinuation due to bleeding changes		20% at 1 year[16]	10.6% at 1 year[57]	<1% at 1 year[32]	<1% at 1 year[22]
Weight gain	Mean 1.3 kg at 1 year[29]	Mean 2.5–3.0 kg at 1 year[13,29]	<1.0 kg at 1 year[33]	<1.0 kg at 1 year[32]	<1.0 kg at 1 year[22]
Mood	Depression, 4.8%[40]	Depression, <2%[19]	Depression 5%[5]	Emotional lability 2.8%[32]	Emotional lability 1.5%[38]
Hormone delivery system–related side effects	Allergies to dyes in pills; efficacy may be compromised by gastrointestinal or hepatic metabolism	Minor injection site pain (<1%)[13]	Expulsion (6.6%)[20] Sepsis, PID, embedment/ perforation[5]	Vaginitis (5.6%) leukorrhea (4.8%) device-related events (4.4%)[32]	Patch application site reactions (20%)[22]
Breast and gynecologic cancers*			No studies	No studies	No studies
Breast	1.24 (1.15–1.33)[39†§] 1.01 (0.96–1.05)[58‡]	1.5 (1–2.2)[40†§] 1.1 (0.97–1.4)[40‡]			
Endometrial	0.55 (0.26–1.17)[41]	0.21 (0.06–0.79)[8]			
Ovarian	0.5 (0.3–0.6)[42]	1.07 (0.6–1.8)[43]			
Cervical	1.30 (0.5–3.3)[45] 1.53 (0.99–2.36)[44]	1.11 (0.96–1.29)[46]			
Relative risk of cardiovascular disease					
All stroke	1.41 (0.90–2.20)[49]	0.89 (0.53–1.49)[50]	No studies	No studies	No studies
Acute MI Smokers <35 y Smokers ≥35 y VTE	4.69 (2.02–10.9)[48§] 34.9[47] 396.2[47§] 4.32 (2.88–6.49)[47§]	0.66 (0.07–6.0)[50] 2.19 (0.66–7.26)[50]			
Effects on bone mineral density	Variable, but usually positive	Reversible reduction	No studies	No studies	No studies

*Relative risk (95% CI). †Current use; ‡Any use; §Likelihood was significantly different relative to control; §Confidence intervals not reported.

PID, pelvic inflammatory disease; CI, confidence interval; MI, myocardial infarction; VTE, venous thromboembolism.

> Counseling about menstrual changes can increase user satisfaction and continuation rates

also suggest that L-IUS may have a modulatory effect on endometrial hyperplasia associated with tamoxifen exposure in women with breast cancer.[15]

EE-ring, NE-patch. Due to the limited experience with these products, it is not known whether users will enjoy noncontraceptive health benefits, although it is reasonable to assume that since they are derived from combinations of well-studied estrogens and progestins, their benefits may be similar to those of combined oral contraceptives.

■ SIDE-EFFECT PROFILES

Hormone-related side effects—including changes in bleeding pattern, weight gain, mood changes, headaches, breast tenderness, and nausea—can be problematic for many women using hormonal contraceptives (both oral contraceptives and nondaily methods) and are common reasons for discontinuation.[2,16] Therefore, it is important to consider differences in side-effect profiles when helping women to select an appropriate method, and to adequately counsel women regarding the expected effects prior to starting therapy.

Bleeding patterns

Nondaily hormonal contraceptives differ considerably in their effects on bleeding patterns (**Table 2**).

DMPA-IM is characterized by amenorrhea, which develops in 70% to 73% of users after 1 year.[17,18] Intermenstrual bleeding and spotting has been reported in 7.6% to 27% of DMPA-IM users at 12 months.[17,18] However, among those who experience irregular bleeding, it generally consists of spotting or light bleeding rather than heavy intermenstrual flow.[19]

Amenorrhea has been reported in 20% to 50% of **L-IUS** users after 1 year.[5,20] Among L-IUS users who do not experience amenorrhea, cycles are variable,[5] with spotting observed in 25% of women at 6 months, decreasing to 11% at 2 years.[20]

Amenorrhea is rarely seen among women using the **EE-ring** or **NE-patch**; rather, similar to oral contraceptives, regular menstrual cycles are established within the first few cycles of use.[21,22] Rates of intermenstrual bleeding/spotting at 1 year are less than 10% for each of these methods, with bleeding changes rarely cited as a reason for drug discontinuation.[21,22]

Counseling before treatment improves adherence. Counseling about menstrual changes, especially the absence of menses associated with DMPA-IM and L-IUS, can significantly increase user satisfaction and continuation rates.[23,24] In a prospective study of new users of DMPA-IM, women who were told about the possibility of amenorrhea were 2.5 times more likely to continue use at 1 year than those who were not given this information.[23] In fact, surveys of women's preferences indicate that most women prefer the convenience, comfort, and freedom of less frequent or absent menses.[25] Because the decision whether or not to menstruate is a personal one, this is an important issue to discuss with a patient selecting a contraceptive method.

Weight gain

Concern about weight gain can be significant enough for some women to pose a barrier to hormonal contraceptive selection and compliance. Variable effects of **DMPA-IM** on body weight have been reported, ranging from nonsignificant changes[26,27] to gains of approximately 3 kg to 4 kg at 1 year.[28,29] However, the most pronounced weight changes occurred in women who were overweight at the initiation of use or who may have been inherently predisposed to gain weight.[28,29]

In a long-term study of Thai women using either DMPA-IM or a nonhormonal intrauterine device, weight gain in both groups was comparable after 10 years of use (10.9 and 11.2 kg, respectively).[30] Furthermore, in the only randomized, placebo-controlled trial to assess weight gain, normal-weight women observed during the first 2 menstrual cycles following the initial injection of DMPA-IM did not experience weight gain.[31]

Data from 1-year multicenter clinical trials with the **NE-patch, EE-ring,** and **L-IUS** indicate that users of these methods experience minimal (<1 kg) or no weight gain.[22,32,33] However, long-term follow-up of women using L-IUS for 12 years found an increase in body weight of 0.49 kg/year during the study period and a mean overall increase of 5.7 kg.[34]

Mood changes

Although mood changes are often cited by women as a reason for discontinuing hormonal contraception,[2] data from clinical trials indicate that **DMPA-IM** does not cause mood changes or worsen existing depressive symptoms. Fewer than 2% of 3857 US women who used DMPA-IM in a 1-year multicenter trial reported depression.[19] Other studies specifically assessing mood changes in an adolescent health clinic[35] and inner-city family planning clinics[36] failed to find any adverse impact of DMPA-IM on mood. Only 1 study of women enrolled in a health maintenance organization found an association between DMPA-IM and symptoms of depression, but a causal relationship could not be established.[37]

To date, no studies have specifically examined the effects of the other nondaily hormonal contraceptive options on mood. **L-IUS** product labeling states that depression has been reported in more than 5% of patients,[5] while 1-year clinical trials report emotional lability in 1.5% of **NE-patch** users and 2.8% of **EE-ring** users.[32,38] However, in a small comparative trial, there were no reports of depression among 121 EE-ring users, whereas it was reported by 4.8% of 126 women using a combined oral contraceptive containing 30 μg ethinyl estradiol and 150 μg levonorgestrel.[21]

Delivery system–related side effects

All nondaily options have specific side effects related to local effects or the delivery system. **DMPA-IM** may cause pain on injection, but this is reported as an adverse event by fewer than 1% of subjects.[13]

In a US clinical trial of the **NE-patch**, application-site reactions were reported by 20% of

> **Use of hormonal contraceptives is not associated with greater overall risk of breast cancer**

participants, leading to discontinuation by 2.6% of women in the patch group; 4.6% of patches were replaced for either complete (1.8%) or partial detachment (2.8%).[22]

In a 1-year multicenter study of the **EE-ring** in 2322 women, common complaints were vaginitis (5.6%), leukorrhea (4.8%), and device-related events (4.4%) consisting of foreign body sensation, coital problems, and expulsion. The latter problem can occur during removal of a tampon or during bowel or bladder emptying, necessitating immediate reinsertion of the ring or replacement with a new ring.[7,32]

Expulsion is also a problem with **L-IUS** and can result in unintended pregnancy. During the first 2 years following insertion, L-IUS was discontinued by 6.6% of 256 women as the result of expulsion, which occurred significantly more frequently among women with heavy menstrual bleeding than those with normal bleeding (13% vs 5%, P=.01).[20] Other potential device-related effects of L-IUS include pelvic inflammatory disease, embedment or perforation, and sepsis.[5]

■ LONG-TERM SAFETY PROFILES
Cancer risks

To date, cancer risks associated with long-term use have been investigated only for DMPA-IM and combined oral contraceptives in large epidemiological studies (**Table 2**). Because women's concerns regarding the risk of breast cancer may make them reluctant to use a hormonal method of contraception, it is particularly important for clinicians to emphasize the evidence showing that use of hormonal contraceptives is not associated with an increase in the overall risk of breast cancer. Though a large-scale reanalysis of 54 studies found a slight increase in breast cancer risk among current combined oral contraceptive users (relative risk [RR]=1.24; 95% confidence interval

[CI], 1.15–1.33), this risk decreased over time and was the same as that of combined oral contraceptive never-users 10 or more years after cessation of use (RR=1.01; 95% CI, 0.96–1.05).[39] Similarly, a pooled analysis of DMPA-IM data from the World Health Organization (WHO) and New Zealand trials, which were completed in the early 1990s, also found a slight increase in breast cancer risk among current users (RR=1.50; 95% CI, 1.0–2.2), but showed no increase in the overall risk of breast cancer among ever-users.[40]

Women can also be advised that neither DMPA-IM nor combined oral contraceptives appear to significantly increase their risk of gynecologic cancers (**Table 2**). In fact, as previously discussed, these contraceptives decrease the risk of endometrial cancer,[8,41] an effect that is particularly strong for DMPA-IM (an 80% reduction in risk for ever-users, which appeared to last for at least 8 years following cessation of use).[8] Combined oral contraceptives are also associated with an approximately 50% reduction in risk of ovarian cancer.[42] While there is no evidence that DMPA-IM reduces the risk of ovarian cancers, it does not appear to be associated with a significant increase in risk (RR=1.07; 95% CI, 0.6–1.8).[43]

Because of confounding factors such as smoking, risk factors for sexually transmitted disease, and screening detection bias, it has been difficult to firmly establish the relationship between contraceptive use and cervical cancer. However, several studies suggest the use of combined oral contraceptives, particularly for longer durations, slightly increases the risk of invasive cervical cancer.[44,45] In contrast, the risk of invasive cervical cancer does not appear to increase in users of DMPA-IM, and no consistent pattern of risk with either duration of use or other time-related factors has been observed.[46]

Cardiovascular risks
DMPA-IM. Only DMPA-IM and combined oral contraceptives have been the subject of large-scale epidemiological investigations to assess the risk of cardiovascular disease, also summarized in

Table 2. Increased risk for venous thromboembolism (VTE) is related to the dose of estrogen in combined oral contraceptives. While currently available low-dose combined oral contraceptives (<50 µg estrogen) confer less risk than the higher-dose preparations of the past, they still confer a 3- to 4-fold higher risk of VTE than that experienced by nonusers.[47] The risk of VTE conferred by DMPA-IM is less than half that of combined oral contraceptives.

Users of low-dose combined oral contraceptives are also at increased risk of acute myocardial infarction compared with nonusers, though this risk reflects the frequent coexistence of other cardiovascular risk factors.[48] In fact, acute myocardial infarction is very rare among younger women (<35 years) who use combined oral contraceptives but who do not smoke, with an estimated attributable risk of approximately 3 per million woman-years. However, this attributable risk rises steeply to nearly 400 per million woman-years in older women (≥35 years) who smoke.[48]

Risk of stroke is slightly increased among users of low-dose combined oral contraceptives, again primarily among women aged ≥35 years. Overall, the excess attributable risk estimate is approximately 2 per 100,000 woman-years, which decreases to 1 per 200,000 woman-years in women <35 years who use low-dose combined oral contraceptives.[49]

In light of these risks, combined oral contraceptives are contraindicated for smokers ≥35 years, women with an increased risk or history of thromboembolism, and women with cerebrovascular or coronary artery disease.

Epidemiologic data from the WHO found no association between DMPA-IM use and an increased risk of any type of stroke or myocardial infarction (MI) (**Table 2**).[50] Although there was a slight increase in the risk of VTE compared with nonusers, this was not considered statistically significant (odds ratio [OR]=2.19; 95% CI, 0.66–7.26).[50] In addition, compared with nonusers, DMPA-IM users did not exhibit increased combined cardiovascular disease risk

(eg, stroke, VTE, myocardial infarction) (OR=1.02; 95% CI, 0.68–1.54).[50]

L-IUS, NE-patch, and EE-ring. Long-term epidemiologic data for these products are unavailable due to the relatively short postmarket experience, which precludes assumptions of long-term cardiovascular safety. Likewise, no evidence is available regarding whether the safety profile for transdermal or vaginal administration differs from oral administration. Therefore, it is not known whether NE-patch or EE-ring confer different risks for venous thromboembolism than combined oral contraceptives. Warnings about thromboembolic disorders are similarly listed in the package inserts of these options.[6,7]

Norelgestromin has been reported to have minimal androgenic activity, suggesting a possible lower risk of myocardial infarction than reported for more androgenically active progestin formulation.[6] In contrast, etonogestrel, the biologically active metabolite of desogestrel, has been associated with a higher risk of venous thromboembolism than some second-generation combined oral contraceptives.[7] For women with these risk factors, progestin-only methods, such as DMPA-IM or L-IUS, should be considered.

Bone mineral density

Historically, data have shown that oral contraceptives most often effect bone mineral density (BMD) positively in premenopausal women; retrospective studies of menopausal cohorts have shown positive effects from oral contraceptive use on BMD.[51] However, a recent study of 524 premenopausal women found that women who used oral contraceptives, compared with those that did not, had significantly lower BMD values (adjusted differences of 2.4% at the femoral neck to 4.3% at the trochanter).[51]

Use of progestin-only DMPA-IM particularly raises concern regarding effects on BMD. However, no increased incidence of fractures has been noted in more than 30 years of DMPA-IM use worldwide.

In a recent meta-analysis that compared data from 10 cross-sectional and 7 longitudinal studies of

> **The loss of bone mineral density seen among users of DMPA-IM is reversible following cessation of use**

BMD in 1039 women exposed to DMPA-IM with that of 2086 controls,[52] average BMD was decreased in current users of DMPA-IM compared with nonusers, but was within 1 standard deviation of the mean in nonusers.[52] Reductions in BMD tended to be greater as the duration of use of DMPA-IM increased, but stabilized after 3 to 5 years of use.[52,53] Notably, the loss of BMD seen among current users of DMPA-IM is reversible following cessation of use.

Cross-sectional studies in both postmenopausal women[52,54] and reproductive-age women,[52,55] showed that BMD in former users of DMPA-IM was not significantly different from that of never-users at any site, and a recent prospective study also confirmed the reversibility of bone loss after cessation of DMPA-IM use.[56]

■ ESTABLISHING A GOOD CONTRACEPTIVE FIT

Overall, clinicians can prescribe nondaily hormonal contraceptives with confidence. Primary considerations in selecting a contraceptive method are its efficacy during typical use and its suitability for the medical needs and lifestyle preferences of the individual.

DMPA-IM and L-IUS. Consider the progestin-only nondaily methods DMPA-IM and L-IUS for women who want highly effective, nondaily, reversible contraception and who regard amenorrhea is a desirable side effect. These methods are also suitable when estrogen therapy is contraindicated.

L-IUS, unlike DMPA-IM, is not recommended for teens, nulliparous women, or those who are not in a stable, mutually monogamous relationship. L-IUS should also be avoided when there is a history of pelvic inflammatory disease or ectopic pregnancy.[5]

Because of its 5-year efficacy, L-IUS should be offered only to those desiring contraception for sev-

eral years. Likewise, DMPA-IM is not recommended for those who wish to become pregnant within 1 to 2 years, because suppression of ovulation may persist beyond the 3-month dosing interval.

NE-patch and EE-ring. These products containing both estrogen and progestin are effective alternatives for women who would be candidates for combined oral contraceptives, including those desiring shorter-term or more rapidly reversible contraception and regular bleeding cycles.

When discussing contraceptive choices with a patient, review each method's route and schedule of administration, efficacy in typical and nontypical use, potential noncontraceptive health benefits, reversibility, side effects, and long-term safety profile. The availability of a broader array of contraceptive choices should help women and their clinicians find a method that will fit individual medical needs as well as lifestyle preferences.

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