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REVIEW

The lowest-dose, extended-cycle combined oral contraceptive pill with continuous ethinyl estradiol in the United States: a review of the literature on ethinyl estradiol 20 μg/levonorgestrel 100 μg + ethinyl estradiol 10 μg

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Abstract: Extended-cycle oral contraceptives (OCs) are increasing in popularity in the United States. A new extended-cycle OC that contains the lowest doses of ethinyl estradiol (EE) and levonorgestrel (LNG) + continuous EE throughout the cycle is now available. It provides 84 days of a low-dose, combined active pill containing levonorgestrel 100 μg and ethinyl estradiol 20 μg. Instead of 7 days of placebo following the active pills, the regimen delivers 7 days of ethinyl estradiol 10 μg. Existing studies reveal a similar efficacy and adverse effect profile compared with other extended-regimen OCs. Specifically, the unscheduled bleeding profile is similar to other extended-cycle OCs and improves with the increase in the duration of use. Although lower daily doses of hormonal exposure have potential benefit, to our knowledge, there are no published studies indicating that this specific regimen offers a lower incidence of hormone-related side effects or adverse events. In summary, this new extended-cycle OC provides patients a low-dose, extended-regimen OC option without sacrificing efficacy or tolerability.

Keywords: continuous regimen, ethinyl estradiol, extended cycle, oral contraceptive

Background

In 1960, the US Food and Drug Administration (FDA) approved the first oral contraceptive (OC) Enovid®, which contained norethynodrel 10 mg and mestranol 150 μg.[1] Since the introduction of the earliest products, the US market has witnessed a continual evolution of the hormonal content and cycle regimen of OCs. The first major change in the OC dose occurred in the 1970s, when the ethinyl estradiol (EE) content has been decreased from 50 μg to 30–35 μg.[2,3] After this decrease in the EE content, the incidence of venous thrombosis events decreased significantly among OC users.[4] Subsequently, formulations containing EE 20 μg were developed, which did not further decrease major adverse events, but at least theoretically offered fewer estrogen-related side effects.[5,6] Most of the currently prescribed OCs contain 20–35 μg EE.[6]

A second major change in OCs was the alteration of the cycle regimen. Traditional dosing regimens emulated a 28-day menstrual cycle with 21 days of combined EE + progestin active pills and 7 days of placebo pills or a pill-free week. Monthly bleeding is not necessary for contraceptive efficacy or safety reasons. Since there is no biological basis for this original cycle regimen, several changes to the regimen were developed,

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offering women the option of experiencing fewer menses or improved side effects.[7]

One such change reduces the length of the active-pill-free interval. In an attempt to decrease estrogen-related withdrawal symptoms associated with the traditional 7-day hormone-free interval, some newer OC regimens adapted a 24/4 dosing regimen, which provided 24 active pills and 4 days of placebo pills, instead of the traditional 21 active pills followed by 7 days of placebo pills. Additionally, some evidence suggests that shortening the hormone-free interval results in greater ovarian suppression.[8,9]

Another recent major change in the cycle regimen is the introduction of extended-cycle OCs. The first dedicated products provide 84 days of active pills with a 7-day combined active-pill-free interval (placebo or EE alone). The major rationale for the use of extended-cycle OCs is potentially greater ovulation suppression. By reducing the frequency of withdrawal bleeding episodes, the extended-cycle OCs have been reported to treat menstrual-related symptoms, endometriosis, and dysmenorrhea.[10] Extended-cycle OCs also offer the option of fewer overall withdrawal bleeding episodes, a benefit preferred by many women.[11]

Several extended-cycle OCs are currently available (Table 1). In September 2003, the FDA approved an extended-cycle OC in an 84/7 dosing regimen, EE 30 μg/levonorgestrel (LNG) 150 μg (Seasonale®; Duramed Pharmaceuticals, Cincinnati, Ohio). A patient takes 84 days of the combined active pill followed by 7 days of placebo pills. This regimen establishes 4 scheduled withdrawal bleeding episodes per year.[12] Subsequently, in May 2006, the FDA approved a variation of this product (Seasonique®; Duramed Pharmaceuticals), with the same combined active pill containing LNG 150 μg and EE 30 μg, followed by 7 days of 10 μg EE pills, instead of placebo (EE 30 μg/LNG 150 μg + EE 10 μg). The rationale for the evolution of EE 30 μg/LNG 150 μg to EE 30 μg/LNG 150 μg + EE 10 mcg is that replacing the hormone-free interval with 7 days of EE provides the potential for greater ovulation suppression, possibly leading to greater effectiveness. In addition, patients may experience less breakthrough bleeding and fewer estrogen withdrawal symptoms, possibly improving compliance.[13] The FDA later approved EE 20 μg/LNG 90 μg (Lybrel®; Wyeth Pharmaceuticals, Philadelphia, Pennsylvania) in 2007, which is administered as a combined active pill containing LNG 90 μg and EE 20 μg in a continuous fashion, 365 days per year.[14,15]

Table 1 Extended-cycle oral contraceptives

Formulation	Pill regimen
EE 30 μg/LNG 150 μg	84 days combined active pill, 7 days placebo pill
EE 30 μg/LNG 150 μg + EE 10 μg	84 days combined active pill 7 days EE 10 μg
EE 20 μg/LNG 100 μg + EE 10 μg	84 days combined active pill, 7 days EE 10 μg
EE 20 μg/LNG 90 μg	Daily combined active pill, 1 withdrawal bleeding episode per year

Abbreviations: EE, ethinyl estradiol; LNG, levonorgestrel.

An OC formulation providing low-dose continuous EE received FDA approval in October 2008 (LoSeasonique®; Duramed Pharmaceuticals). This product delivers 84 days of EE 20 μg and LNG 100 μg, followed by 7 days of EE 10 μg (EE 20 μg/LNG 100 μg + EE 10 μg). The reason for the development of this product was to offer patients a very low dose extended-cycle OC. The novel formulation provides the lowest dose of EE available in extended-cycle regimens thus far, combined with EE during the placebo week. The lowest dose of EE in OCs currently available in the United States is 20 μg, which is likely near the lowest dose required to produce contraceptive efficacy.[16] Decreased estrogen exposure may result in fewer estrogen-related side effects, such as breast tenderness and nausea.[5,17] A speculated disadvantage of the new formulation of EE 20 μg/LNG 100 μg + EE 10 μg compared to EE 30 μg/LNG 150 μg + EE 10 μg is that decreasing the dosage of EE from 30 μg to 20 μg could predispose to more unscheduled bleeding and spotting. With the introduction of EE 20 μg/LNG 100 μg + EE 10 μg, a very low-dose extended-cycle OC containing continuous EE, it is important to understand how this new product compares to the existing extended-cycle OCs with regard to pharmacology, efficacy, safety, tolerability, and patient satisfaction.

Pharmacology and pharmacodynamics

EE 20 μg/LNG 100 μg + EE 10 μg contains the well-characterized progestin levonorgestrel [18,19-dinorpregn-4-en-20-yn-3-one-13-ethyl-17-hydroxy-,(17α)-,(-)-], a second-generation progestin derived from 19-nortestosterone. The oral bioavailability of LNG is approximately 90%–100% because the drug is not subject to first-pass metabolism. The volume of distribution of LNG is 1.8 L/kg. LNG is 97.5%–99% bound to sex hormone–binding protein and serum albumin.[18]

EE 20 μg/LNG 100 μg + EE 10 μg also contains EE 19-norpregna-1,3,5 (10)-trien-20-yne-3, 17-diol,(17α). EE is the orally active and the most common estrogen in current

OCs. The bioavailability of EE is only approximately 43% because it is subject to first-pass metabolism. The volume of distribution of EE is 4.3 L/kg. EE is 95%–97% bound to serum albumin.[18]

The mechanism of action of the combination of LNG and EE involves (1) ovulation suppression by inhibiting follicle stimulating hormone (FSH) and luteinizing hormone (LH); (2) cervical mucus changes that inhibit sperm penetration; and (3) endometrial changes that reduce the chances of successful implantation.[16] Since EE specifically causes the suppression of FSH, the additional 7 days of EE potentially results in greater ovulation suppression. EE also helps stabilize the endometrium and may potentially decrease intermenstrual bleeding.

Efficacy

A key question with the introduction of a new OC product is whether it confers similar efficacy to other OCs in preventing pregnancy. To evaluate the contraceptive efficacy of EE 20 μg/LNG 100 μg + EE 10 μg, Kroll et al[19] conducted a multicenter, open-label clinical trial at 56 sites throughout the United States. Of the 2,185 women aged 18–40 years recruited to participate, 1,249 participants completed the 12-month study. The Pearl index among all participants was 2.74 (95% CI, 1.92–3.78), based on 36 pregnancies that occurred after the onset of treatment and within 14 days of last combined active pill in women aged 18–35 years. The Pearl index among compliant participants was 1.73; 22 pregnancies occurred during the treatment among women aged 18–35 years. The Pearl index of EE 20 μg/LNG 100 μg + EE 10 μg was slightly higher but similar to EE 30 μg/LNG 150 μg (0.60), EE 30 μg/LNG 150 μg +EE 10 μg (1.2), and continuous EE 20 μg/LNG 90 μg (1.19).[13,17,20] Overall, the efficacy of EE 20 μg/LNG 100 μg + EE 10 μg compared with the extended-cycle and cyclic OCs is similar.[21]

Safety

In their study, Kroll et al[19] characterized the safety profile of EE 20 μg/LNG 100 μg + EE 10 μg in 1,249 participants. The most frequent adverse events were headaches (33%), nasopharyngitis (16%), and dysmenorrhea (11%). No venous thromboembolic events were reported during the study. The study population experienced increases in the levels of cholesterol, low-density lipoprotein, and triglycerides, but these increases were not clinically significant. Similar adverse events were reported in a safety and efficacy study of EE 30 μg/LNG 150 μg + EE 10 μg: intermenstrual bleeding (11.5%), nasopharyngitis (7.2%), sinusitis (6.5%), and menorrhagia (5.8%).[13] EE 20 μg/LNG 100 μg + EE 10 μg carries a similar adverse event profile compared with other extended-cycle and cyclic OCs.[21]

Tolerability

The major tolerability concern in prescribing extended-cycle OCs is unscheduled bleeding. Comparison of unscheduled bleeding between EE 30 μg/LNG 150 μg + EE 10 μg and EE 30 μg/LNG 150 μg is important, since one rationale for replacing the placebo week with EE was to potentially reduce the rate of unscheduled bleeding. In a retrospective cross-study analysis, Kaunitz et al[22] found that unscheduled bleeding decreased more quickly with EE 30 μg/LNG 150 μg + EE 10 μg compared with EE 30 μg/LNG 150 μg. Significant differences in scheduled bleeding were noted at each measured interval, with less bleeding experienced in EE 30 μg/LNG 150 μg + EE 10 μg users.

The unscheduled bleeding profile with EE 20 μg/LNG 100 μg + EE 10 μg approximates that of other extended-cycle OCs. In a multicenter, open-label study, Kroll et al[19] specifically studied unscheduled bleeding. Different types of bleeding were defined as follows: (1) bleeding was defined as vaginal bleeding that required use of sanitary pads, tampons, or both; (2) spotting was defined as vaginal bleeding that did not require use of sanitary pads, tampons, or both; (3) unscheduled bleeding was defined as spotting that occurred during the 84 days of active combination pills; (4) unscheduled bleeding/withdrawal bleeding was that occurring during the 7 days of EE-only pills. Intermenstrual bleeding or spotting decreased with time with both EE 20 μg/LNG 100 μg + EE 10 μg and EE 30 μg/LNG 150 μg + EE 10 μg, as shown in Table 2. The percentage of women who experienced intermenstrual bleeding or spotting decreased from the first 91-day treatment cycle to the fourth 91-day treatment cycle. In addition, the percentage of women who experienced a more than 20 days of intermenstrual bleeding or spotting declined between the first and the fourth treatment cycles.

The percentage of women who experienced intermenstrual bleeding with EE 20 μg/LNG 100 μg + EE 10 μg compared with EE 30 μg/LNG 150 μg + EE 10 μg is also shown in Table 2. In a multicenter, open-label clinical study by Anderson et al,[13] 1,006 women who were taking EE 30 μg/LNG 150 μg + EE 10 μg over 12 months kept daily electronic diaries of compliance and bleeding. The percentage of women experiencing intermenstrual bleeding is slightly higher for EE 20 μg/LNG 100 μg + EE 10 μg compared with EE 30 μg/LNG 150 μg + EE 10 μg, and there was a similar decrease in the percentage of women experiencing intermenstrual bleeding between cycle 1 and cycle 4.

Table 2 Percentage of women reporting unscheduled bleeding[a] with extended-cycle regimens with continuous ethinyl estradiol[b,c]

	Cycle 1 (days 1–91)		Cycle 2 (days 92–182)		Cycle 3 (days 183–273)		Cycle 4 (days 274–364)	
	EE 20 µg/LNG 100 µg + EE 10 µg	EE 30 µg/LNG 150 µg + EE 10 µg	EE 20 µg/LNG 100 µg + EE 10 µg	EE 30 µg/LNG 150 µg + EE 10 µg	EE 20 µg/LNG 100 µg + EE 10 µg	EE 30 µg/LNG 150 µg + EE 10 µg	EE 20 µg/LNG 100 µg + EE 10 µg	EE 30 µg/LNG 150 µg + EE 10 µg
More than 7 days	76	64	62	46	53	36	49	39
More than 20 days	44	29	28	16	21	10	18	11

[a]Intermenstrual bleeding and/or spotting; [b]LoSeasonique (levonorgestrel/ethinyl estradiol tablets and ethinyl estradiol tablets). Current US Prescribing Information. Duramed Pharmaceuticals.[c]Seasonique (levonorgestrel/ethinyl estradiol tablets and ethinyl estradiol tablets). Current US Prescribing Information. Duramed Pharmaceuticals.

Comparing the incidence of unscheduled bleeding for EE 20 µg/LNG 100 µg + EE 10 µg with EE 20 µg/LNG 90 µg is difficult, given the difference in cycle regimen. To date, there is no published study comparing unscheduled EE 20 µg/LNG 100 µg + EE 10 µg with EE 20 µg/LNG 90 µg. Unscheduled bleeding for EE 20 µg/LNG 90 µg has been studied independently. Teichmann et al[17] conducted a randomized, open-label trial comparing EE 20 µg/LNG 90 µg (n = 331) with a 21-day cyclic EE 20 µg/LNG 100 µg (n = 318). During the third month, 69.0% (n = 194) of EE 20 µg/LNG 90 µg users reported spotting, bleeding, or both. During the 12th month, 47.1% (n = 99) patients reported spotting, bleeding, or both. Overall, the incidence of unscheduled bleeding at the end of 1 year's use was similar but higher for EE 20 µg/LNG 90 µg (21%) compared with the 21-day cyclic EE 20 µg/LNG 100 µg (12%). These findings on bleeding patterns are similar to the data on EE 20 µg/LNG 100 µg + EE 10 µg because the percentage of women who experience unscheduled bleeding decreases with time. A study comparing the incidence of unscheduled bleeding of EE 20 µg/LNG 100 µg + EE 10 µg with a 21-day cyclic regimen has not been published.

Patient satisfaction

The extended-cycle OCs have similar compliance rates compared with 28-day cyclic OCs.[21] The discontinuation rate for EE 20 µg/LNG 100 µg + EE 10 due to an adverse event was 11.6%. The discontinuation rate partly attributed to the unscheduled bleeding was 9.6%.[19] In comparison, the discontinuation rate for EE 30 µg/LNG 150 µg + EE 10 µg due to an adverse event was 16%, including intermenstrual bleeding, menorrhagia, increased weight, and mood swings.[13] The discontinuation rates for other OCs are similar between 28-day and extended-cycle regimens. In addition, the discontinuation rates for other OC agents, specifically for bleeding problems, are comparable between these regimens.[21]

Conclusion

The major potential benefit of EE 20 µg/LNG 100 µg + EE 10 µg compared with the other available extended-cycle OCs is the lower hormonal exposure, which may result in fewer adverse effects, such as breast tenderness or nausea. However, no published study has specifically compared the estrogen adverse effect profile of EE 20 µg/LNG 100 µg + EE 10 µg extended-cycle OCs containing 30 µg EE. The lower hormonal exposure could theoretically confer a lower risk of major adverse events, such as venous thromboembolism, but no study documents such a decrease of adverse events.[21]

Furthermore, it is critically important to understand that the absolute risk of major adverse events with all low-dose OCs is exceedingly low, so using the lowest 20 µg dose of EE does not offer a clinical advantage for this purpose. It is similarly unclear whether lowering the LNG dosage is beneficial; no study has specifically investigated any short- or long-term benefit of LNG 100 µg when compared with higher doses, such as 150 µg.

Although more long-term studies should investigate the effects of lower hormonal exposure with EE 20 µg/LNG 100 µg + EE 10 µg and compare this drug with other extended-cycle OCs, sufficient information is available to recommend EE 20 µg/LNG 100 µg + EE 10 µg to patients as an option for an extended-cycle OC. EE 20 µg/LNG 100 µg + EE 10 µg provides similar efficacy compared with other extended-cycle OCs. The unscheduled bleeding or spotting per cycle for EE 20 µg/LNG 100 µg + EE 10 µg is similar to EE 30 µg/LNG 150 µg + EE 10 µg, which uses higher daily doses of estrogen and progestin. The unscheduled bleeding or spotting with EE 20 µg/LNG 100 µg + EE 10 µg decreases with the increase of number of cycles, similar to EE 30 µg/LNG 150 µg + EE 10 µg. Discontinuation rates are similar to those of other extended-cycle OCs. With regard to usage, women may choose EE 20 µg/LNG 100 µg + EE 10 µg because it offers both an extended-cycle regimen and less hormonal exposure, even though the clinical benefits of this lowered exposure are not clearly established. Overall, EE 20 µg/LNG 100 µg + EE 10 µg offers an option for safe, effective extended-cycle OC use.

Disclosure

The authors report no conflicts of interest in this work.

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