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EXPERT REVIEW

The New Extended-Cycle Levonorgestrel-Ethinyl Estradiol Oral Contraceptives

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Abstract: Effective contraceptive counseling requires an understanding of a woman's preferences and medical history as well as the risks, benefits, side effects, and contraindications of each contraceptive method. Hormonal contraceptives using a variety of delivery methods are highly effective and this review highlights the new extended-cycle levonorgestrel-ethinyl estradiol contraceptives.
Extended-cycle OCPs are unique in offering fewer or no withdrawal bleeds over the course of one year but providers need to carefully counsel women regarding the initial increased breakthrough bleeding. Extended-cycle OCPs may be of particular benefit in women with medical comorbidities who would benefit from less withdrawal bleeds, those desiring to avoid monthly menses due to increased hormonal withdrawal symptoms, or simply women who don't desire a monthly period. The risks associated with all extended-cycle OCPs have been found to be similar to those of traditional OCPs therefore counseling on the risks and side effects is comparable to that of any combined hormonal contraceptives.
Newer extended-cycle regimens shorten or eliminate the hormone-free interval, decrease frequency of menses to four times per year or eliminate menses altogether. This can reduce the risk of common menstrual symptoms, endometriosis, or severe dysmenorrhea by offering potentially greater ovarian suppression and preventing endogenous estradiol production while still providing highly effective, rapidly reversible, and safe contraception.

Keywords: extended cycle, contraceptive, levonorgestrel

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Introduction

Primary care physicians need up to date knowledge on contraceptive counseling for women in order to provide the best match between patient and contraceptive method. Additionally, providers frequently need to supply contraceptives to women who have particular medical comorbidities that may be worsened by pregnancy or necessitate the use of potentially teratogenic medications. Newer oral contraceptive preparations are now available which differ from traditional oral contraceptives in their hormonal dosages, cycle length, and hormone-free intervals. Effective contraceptive counseling requires an understanding of a woman's preferences and medical history as well as the risks, benefits, side effects, and contraindications of each contraceptive method. The newer formulations and extended cycling regimens are attractive options to women for both their contraceptive and non-contraceptive benefits. In this review, we will focus specifically on providing an update on the extended-cycle levonorgestrel-ethinyl estradiol contraceptives.

Mechanism of Action

Oral contraceptive pills (OCPs) contain both an estrogen (ethinyl estradiol, mestranol, or estradiol valerate) and a progestin. Individual oral contraceptive packets differ in terms of their estrogen dosage, progestin type and dosage, cycle length, and hormone free interval. All combined-hormonal OCPs in the United States contain ethinyl estradiol (EE), usually at doses between 20–30 mcg, but many different progestins are available. Levonorgestrel (LNG) is a widely utilized contraceptive progestin which is found in many combined oral contraceptives but is also highly effective alone in progestin-only pills, long-acting subdermal implants, intrauterine devices, and in emergency contraception. Not all of these formulations are available in the US. The mechanism of action of LNG differs depending on its dose and delivery method (oral, intrauterine, transdermal). The oral bioavailability of LNG is approximately 90%–100% because it is not subject to first-pass metabolism.[1] When LNG (or another progestin) is used in combination with EE, the primary mechanism of action is prevention of the surge of luteinizing hormone thereby preventing ovulation; but progestins also thicken the cervical mucus and alter the endometrial lining to help prevent fertilization or implantation.

Traditional oral contraceptive pill regimens consist of a 21-day course of hormones followed by a 7-day hormone-free interval. This regimen was originally devised to mimic the natural menstrual cycle and help women feel comfortable in accepting the OCP. During the standard 7-day hormone-free interval that occurs with use of low-dose estrogen OCPs, the function of the hypothalamic-pituitary-ovarian axis recovers rapidly. This recovery can increase the risk of ovarian follicle development, unintended ovulation, and increased spotting due to endogenous estradiol production.[2–6] Fluctuating hormone levels also allow endometrial buildup and can exacerbate endometriosis and premenstrual symptoms (eg, headaches, tiredness, bloating, excessive bleeding, and menstrual pain) by creating hormone excess and withdrawal states.[3–6]

Newer extended-cycle regimens shorten or eliminate the hormone-free interval, decrease frequency of menses to four times per year or eliminate menses altogether. This can reduce the risk of common menstrual symptoms, endometriosis, or severe dysmenorrhea by offering potentiallygreater ovarian suppression and preventing endogenous estradiol production while still providing highly effective, rapidly reversible, and safe contraception.[7–13] Extended-cycle levonorgestrel-ethinyl estradiol pills (Seasonale, Seasonique, Lo-Seasonique) belong to this newer class of OCPs and offer women an 84/7 regimen with four withdrawal menses per year. Lybrel is a continuous-cycle pill with active hormones taken daily throughout the year with no hormone-free interval to induce a scheduled withdrawal bleed. These four FDA-approved formulations of extended-cycle (or continuous-cycle) levonorgestrel-ethinyl estradiol pills differ in their estrogen dosage, hormone-free intervals, and expected withdrawal bleeds (Table 1). Seasonale®, Seasonique®, and Lo-Seasonique® have varying doses of hormones and involve 3 months of continuous hormone treatment with 4 scheduled periods each year while women on Lybrel ultimately experience amenorrhea after initial unscheduled spotting.[14] Seasonique® and Lo-Seasonique® are unique amongst extended-cycle contraceptives in offering very low amounts of estrogen during the typical 7 day hormone free interval to minimize breakthrough bleeding and decrease incidence of premenstrual symptoms.[15] Lo-Seasonique® was designed to offer women a

Table 1. Extended-cycle levonorgestrel-ethinyl estradiol oral contraceptive summary.

Product	Formulation
Traditional OCP	21 tabs: progestin + 20 to 35 mcg EE 7 placebo pills
Seasonale®	84 tabs: 0.15 mg levonorgestrel + 30 mcg EE 7 placebo pills
Seasonique®	84 tabs: 0.15 mg levonorgestrel + 30 mcg EE 7 tabs: 10 mcg EE
Lo-Seasonique®	84 tabs: 0.10 mg levonorgestrel + 20 mcg EE 7 tabs: 10 mcg EE
Lybrel®	28 tabs: 0.09 mg levonorgestrel + 20 mcg EE 0 placebo pills

very low dose extended-cycle OCP with theoretical decrease in estrogen-related side effects and adverse effects (breast tenderness/nausea, VTE) though with potential for more unscheduled bleeding.[14]

Efficacy

While initial studies speculated that extended-cycle OCPs may have higher efficacy rates due to the decreased likelihood of escape ovulation due to greater ovarian suppression,[16,17] a systematic review of extended-cycle versus traditional 28-day cycle OCPs found similar efficacy and safety. Therefore, users of extended-cycle OCPs can expect failure rates which vary from 0.3% with perfect use to 8% with typical use.[18] As expected, users of extended-cycle OCPs had greater improvement of menstrual symptoms, but despite this, the systematic review found no difference in adherence or discontinuation rates.

Safety—Side Effects and Risks

LNG is particularly popular when combined with low-dose EE in OCPs because of its long track record of safety, especially when compared with third-generation progestins such as desogestrel and gestodene[19–21] and the newer progestin, drosperinone[22,23] which have all been associated with higher rates of venous thromboembolism (VTE) than LNG-containing OCPs. Breakthrough bleeding is often more frequent in the extended-cycle regimens, particularly early on, but compliance rates are similar to traditional OCPs. Breakthrough bleeding does decrease over time with a mean number of breakthrough bleeding days of 14 in cycle one but decreasing to 8 in cycle four.[15]

Extended-cycle OCPs, particularly Seasonique® and Lo-Seasonique®, may expose women to an increased cumulative amount of estrogen compared with a traditional 21/7 regimen thus making risk of VTE of particular concern to patients and providers. Current data does not demonstrate an increased risk of VTE for extended-cycle OCPs.[15] Additionally, there may be a concern that decreasing or eliminating withdrawal bleeding leads to endometrial hyperplasia, however studies have shown that most women have inactive or atrophic endometrium with no significant endometrial hyperplasia reported in women receiving extended- or continuous-cycle OCPs.[15]

The risks associated with all extended-cycle OCPs have been found to be similar to those of traditional OCPs in a well-done systematic review, therefore it is critical to counsel women who use extended-cycle OCPs on the risks and side effects associated with use of all combined hormonal contraceptives. Fortunately, combination hormonal contraception can be used safely in women with a range of medical conditions including well-controlled hypertension, uncomplicated diabetes, mild hyperlipidemia, depression, uncomplicated valvular heart disease, HIV infection, various connective tissue disorders, migraines without aura, systemic lupus erythematous without antiphospholipid antibodies, and uncomplicated liver disease.[24,25] Prescribing OCPs to healthy, non-smoking women older than 35 years old is also generally safe provided that other contraindications to combined hormonal contraception do not exist.[24,26] Indeed, data from US trials suggest that stroke and myocardial infarction (MI) risks for OCP users compared with nonusers are similar in younger and older non-smoking women.[27,28]

Despite the varying hormonal doses and delivery methods of various OCP formulations, the risks and benefits are generally felt to be similar and are grouped together by the World Health Organization (WHO). The majority of serious risks relate to the effects of estrogen on the cardiovascular system such as VTE and less commonly, myocardial infarction or stroke. These risks are accentuated in women older than 35 years who smoke. OCPs have been shown to elevate systolic and diastolic blood pressure by about 8 and 6 mm HG respectively,[29] and caution should be used

in starting OCPs in women who already have elevated blood pressures, especially women older than 35 years. Guidelines from both the WHO and American College of Obstetrics and Gynecology (ACOG) suggest that the risks of OCPs outweigh the benefits if blood pressure is uncontrolled.[24,25] ACOG recommends that the use of OCPs in women with diabetes should be limited to women less than 35 years who are nonsmoking, otherwise healthy, and show no evidence of hypertension, nephropathy, retinopathy, or other vascular disease.[24] While migraine with aura is a contraindication to the use of OCPs, use can be considered for women with migraines if they do not have focal neurological signs, do not smoke, are less than 35 years of age, and are otherwise healthy.[24–26,30] It is important to balance contraceptive risks with the risk of complications from an unintended pregnancy in women with obesity. The WHO considers the benefits of OCPs in obese women greater than the harms[25] while ACOG suggests that a progestin-only method may be safer.[24] The absolute risk of VTE in OCP-users is generally low, and is actually lower than the risk of VTE associated with pregnancy. However, the relative risk of VTE in OCP-users compared to non-users is about four times higher.[31] Most studies suggest that VTE risk is highest in the first year of use and diminishes with increasing duration of use. Although combination hormonal contraception can increase risk for VTE in all users, risk is especially high and is contraindicated in women with personal history of VTE or with antiphospholipid antibodies.[24] A complete list of contraindications for combination hormonal contraception can be seen in Table 2.

LNG is a more androgenic progestin which may cause some patients or providers to have concern about using extended-cycle contraceptives for those with acne or polycystic ovarian syndrome (PCOS), or possibly worsening these conditions. Though available data is limited, similar to other formulations of combination hormonal contraception, LNG decreases peripheral androgen levels.[32] Additionally, few differences have been seen between OCP types and effectiveness in treating acne and PCOS, keeping the LNG-containing extended-cycle OCPs as a possible choice for women with these issues.[33,34]

Table 2. WHO Medical Eligibility Criteria Contraindications (Category 3 or 4) to combined oral contraceptives, patch, and the vaginal ring.[26]

- History of DVT/PE
- Acute DVT/PE
- DVT/PE and established on anticoagulant therapy*
- Major surgery with prolonged immobilization
- SLE with positive (or unknown) antiphospholipid antibodies
- Acute viral hepatitis or flare*
- Severe decompensated cirrhosis
- Hepatocellular adenoma*
- Malignant hepatoma
- Antiretroviral therapy with Ritonavir-boosted protease inhibitors*
- Certain anticonvulsants (phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine)
- Lamotrigine*
- Rifampicin or rifabutin therapy*
- <21 days postpartum
- <6 months postpartum (primarily breastfeeding)
- Smoking >35 years old
- Multiple risk factors for CV disease (older age, smoking, diabetes and hypertension)
- Uncontrolled hypertension (>140/90)
- Vascular disease
- Known thrombogenic mutation
- Stroke
- Uncontrolled hyperlipidemia
- Complicated valvular heart disease(pulmonary hypertension, atrial fibrillation, history of endocarditis)
- Migraines in women >35
- Migraine with aura at any age
- Breast cancer (current or past)
- Diabetes with nephropathy, retinopathy or neuropathy
- Acute gallbladder disease
- CHC-related cholestasis

Note: *Indicates change from third edition to fourth edition.

Patient Preference

Many women still have the misconception that monthly menses remain the most natural process, therefore the newer formulations outlined above may require increased patient education on the part of providers.[35] The low doses of hormones utilized in OCPs do not result in buildup of the endometrium, thus no particular reason exists for a monthly withdrawal bleed beyond patient comfort. Because these bleeding patterns differ largely from traditional monthly withdrawal bleeds, it's important to discuss patient preferences for menstrual frequency and tolerance for scheduled and unscheduled bleeding when deciding which contraceptive will best fit the needs of patients. Nearly two-thirds of US women have demonstrated interest in menstruating less often with just over half expressing interest in menstruating every

3 months or not at all.[36] It is also important to note that despite the lengthened cycles, women can expect rapid resolution of fertility after stopping extended-cycle OCPs. Determining a patient's preference for an extended-cycle OCP will include a discussion of the symptoms surrounding her menses, her desire to avoid menses and her ability to tolerate potential unscheduled bleeding.

Place in Therapy

Extended-cycle levonorgestrel contraceptives may be particularly useful for women who desire less frequent withdrawal bleeding. Some studies have shown that extended-cycle OCPs may be useful for women during perimenopause, with endometriosis, menorrhagia, menstrual migraine or PMDD.[15] These women need to be counseled regarding the initial increased frequency of breakthrough bleeding and spotting in order to try to maximize long term compliance with their contraceptive method.

Conclusion

The use of levonorgestrel extended-cycle OCPs is safe and effective in healthy women. Though they have not been compared directly to each other, each hassimilar risks and side effects to the traditional 21/7 OCP regimen. Extended-cycle OCPs are unique in offering fewer or no withdrawal bleeds over the course of one year but providers need to carefully counsel women regarding the initial increased breakthrough bleeding. Extended-cycle OCPs may be of particular benefit in women with medical comorbidities who would benefit from less withdrawal bleeds, those desiring to avoid monthly menses due to increased hormonal withdrawal symptoms, or simply women who don't desire a monthly period.

Disclosures

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