Editorial

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Big step forward and downward: An OC with 10 µg of estrogen

Lo Loestrin Fe delivers an ultra-low dose of ethinyl estradiol—a novel and noteworthy option when you're considering an estrogen-progestin contraceptive.

Let's be honest, OK? The original estrogen-progestin oral contraceptives (OCs) contained **far too much estrogen.** True, they were effective—yielding a reliable pattern of uterine withdrawal bleeding—but those high, high-dose estrogen formulations, such as Enovid, also carried an excessive rate of deep venous thrombosis (DVT) and pulmonary embolism (PE). In the 1960s, many women turned away from OCs because they had a justifiable fear of side effects.

We've come a long way from the 1960s, when OCs that delivered a daily dose of 150 µg of mestranol (mestranol is 3-methoxy ethinyl estradiol) or 50 µg of ethinyl estradiol were widely prescribed. Now, effective low-dose OCs routinely deliver a daily dose of 20 to 30 µg of ethinyl estradiol. With that decrease in the dosage of estrogen, we have clearly observed a decrease in serious side effects, such as DVT and PE.

Now, Lo Loestrin FE (Warner Chilcott), which delivers a daily dose of 10 µg of ethinyl estradiol, represents the next big step in the historic march to an ever-lower dose of estrogen (see "The ultra-low estrogen formulation," on this page). This is truly an extraordinary advance.

How does the estrogen-progestin contraceptive work?

The principal mechanism of estrogen-progestin OCs is **suppression of ovulation.** They also work by **altering endometrial development** and **reducing sperm transport** from the vagina into the upper reproductive tract.

Estrogen-progestin pills that contain 30 to 35 µg of ethinyl estradiol have an ovulation suppression rate of 98%; those that contain 15 to 20 µg of ethinyl estradiol have an ovulation suppression rate of 99%. In contrast, progestin-only OCs (i.e., no estrogen) have an ovulation suppression rate of only 67%.[1]

Estrogen-progestin OCs likely work to suppress ovulation by **decreasing hypothalamic kisspeptin activity.** That decrease reduces gonadotropin-releasing hormone (GnRH) secretion, in turn **1)** decreasing pituitary luteinizing hormone (LH) and follicle-stimulating hormone (FSH) and **2)** blocking development of a dominant ovarian follicle. In addition, estrogen-progestin contraceptives directly block LH and FSH release at the level of the pituitary.

In the absence of a dominant ovarian follicle, no LH surge occurs, and ovulation cannot occur.

The impact of 26 days of hormone-active pills

The standard estrogen-progestin OC has 21 active (containing hormone) tablets and 7 tablet days without hormonal treatment. The 7-day hormone-free interval is associated with increased LH and FSH secretion and increased ovarian follicle activity.

Adding estrogen-progestin pills or estrogen-only pills to the standard 7-day hormone-free interval (as Lo Loestrin Fe does) decreases both secretion of LH and FSH and ovarian follicle activity.[2,3] **By adding hormone treatment to the standard 7-day hormone-free interval, therefore, the daily dose of hormones can be decreased without reducing contraceptive efficacy.** Lo Loestrin Fe takes advantage of this phenomenon by having 26 days of hormone

The ultra-low estrogen formulation

Lo Loestrin Fe comprises 28 tablets in this order:

- 24 blue tablets, each containing 10 mg of ethinyl estradiol and 1 mg of norethindrone acetate
- 2 white tablets, each containing 10 mg of ethinyl estradiol but no norethindrone acetate
- 2 brown tablets, each containing 75 mg of ferrous fumarate only

ILLUSTRATION: LAEL HENDERSON/STOCK ILLUSTRATION SOURCE

treatment in every 28-day cycle. Instead of only 21 estrogen-progestin pills, Lo Loestrin Fe contains 24 estrogen-progestin pills and two estrogen-only pills.

20 µg or less of ethinyl estradiol: Benefits and side effects

In a clinical trial, women taking a higher dose (35 µg) of ethinyl estradiol (in a tricyclic preparation) were approximately 50% more likely to report bloating, breast tenderness, and nausea, compared with women taking a lower dose (20 µg) (in a monophasic formulation).[4] It's conceivable that an **ultra-low estrogen pill** will be associated with even fewer episodes of bloating, breast tenderness, and nausea than an OC containing a higher dose.

On the other hand, an ultra-low estrogen pill may be associated more often than a high-estrogen pill with abnormal patterns of bleeding. In a systematic review, contraceptives that contained 20 µg or less of ethinyl estradiol were associated with an increased risk of bleeding irregularities—including infrequent bleeding, prolonged or frequent bleeding, and unscheduled bleeding or spotting—than contraceptives that contained more than 20 µg of ethinyl estradiol.[5]

How potent a progestin is norethindrone acetate?

A widely used method of assessing the potency of a synthetic progestin in women is the so-called delay of menses test, based on the principle that surgical removal of a corpus luteum any time after ovulation results in uterine bleeding within 48 hours because of the withdrawal of progesterone support.

The potency of a specific dose of a progestin is tested by administering the compound daily, starting on Day 20 or Day 21 of the cycle, and continuing to do so for at least 21 days. To help improve the reliability of the test, 100 µg of mestranol is also given daily to stabilize estrogen levels during the testing interval. If menses do not occur until after the 21 days of progestin, that dose is considered adequate to support the endometrium.

Using this approach to assess the potency of progestin, **norethindrone acetate is about twice as potent as an equivalent amount of norethindrone.**[6,7]

Lo Loestrin Fe contains 24 pills with 1 mg of norethindrone acetate; each pill, therefore, is pharmacologically equivalent to a pill that contains 2 mg of norethindrone. Because norethindrone, at a daily dose of 0.35 mg, is an FDA-approved progestin-only contraceptive, it isn't surprising that a dose of norethindrone acetate equivalent to 2 mg of norethindrone, for 24 out of 28 days each cycle, would also be an effective contraceptive.

Circumstances in which a low-estrogen OC might be especially useful

Pelvic pain caused by endometriosis. Endometriosis is an estrogen-dependent disease process that responds well to interventions that reduce ovarian estrogen production, such as bilateral oophorectomy or hormone therapy with a GnRH analogue, progestin or danazol.[8] Although the notion is somewhat counterintuitive, an estrogen-progestin OC is also effective for treating the pelvic pain caused by endometriosis.[9,10]

The progestin dominance of the modern estrogen-progestin pill probably accounts for why it is an effective treatment for endometriosis. Given that endometriosis is an

estrogen-dependent disease process, it would be logical to use an estrogen-progestin OC with the lowest dose of estrogen, to avoid stimulating the growth of endometriosis lesions. The 10 µg of ethinyl estradiol in Lo Loestrin Fe makes it an interesting option for treatment of an estrogen-dependent disease.

After surgery for endometriosis, an estrogen-progestin OC may help prevent the return of pelvic pain, regrowth of endometriosis lesions, and recurrence of endometriosis ovarian cysts.[11,12] An ultra-low-dose estrogen-containing contraceptive may therefore deserve consideration for long-term treatment following surgery for endometriosis.

The perimenopausal woman. During the perimenopause, many women have cycles characterized by markedly abnormal hormone levels. For example, some cycles in perimenopausal women are characterized by excessively high estradiol secretion and very low progesterone secretion. Other cycles are characterized by low estradiol secretion for an extended length of time. These abnormal patterns of hormone secretion contribute to menstrual cycle length irregularity, menorrhagia, and vasomotor symptoms.

Treatment with a progestin-dominant OC is often a first-line option for these women. Because Lo Loestrin Fe contains an ultra-low dose of ethinyl estradiol, it might be a good option for perimenopausal women who suffer a menstrual disorder.

The young smoker. Approximately 27% of women between the ages of 18 to 44 years who smoke use an OC; 35% of nonsmoking women in the same age range use an oral contraceptive.[13] When I think about prescribing an OC to a smoker, I always vividly recall the black-box warning in the Food and Drug Administration's prescribing information for all estrogen-progestin contraceptives:

> Women over 35 years old who smoke should not use an estrogen-progestin contraceptive and cigarette smoking increases the risk of serious cardiovascular events from estrogen-progestin use.

I know that the progestin is likely not the cause of these associations, and that higher doses of estrogen are associated with an increased risk of cardiovascular events. Consequently, it seems prudent, when considering an estrogen-progestin OC for a young smoker, to prescribe the lowest dose of ethinyl estradiol available.

A basic principle of pharmacology applies

The lowest effective dose of a drug is, we know, typically a good choice because it's likely to minimize the risk of side effects. The history of the oral contraceptive is characterized by a continuous decrease in the daily dose of ethinyl estradiol—and that downward trend has prevented many cases of DVT and PE. Lo Loestrin Fe, delivering an ultra-low dose—10 µg daily—of ethinyl estradiol, is a novel option for women in whom you are considering an estrogen-progestin contraceptive.

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References

1. Milsom I, Korver T. Ovulation incidence with oral contraceptives: a literature review. J Fam Plann Reprod Health Care. 2008;34(4):237–246.
2. Schlaff WD, Lynch AM, Hughes HD, Cedars MI, Smith DL. Manipulation of the pill-free interval in oral contraceptive pill users: the effect on follicular suppression. Am J Obstet Gynecol. 2004;190(4):943–951.
3. Willis SA, Kuehl TJ, Spiekerman AM, Sulak PJ. Greater inhibition of the pituitary-ovarian axis in oral contraceptive regimens with a shortened hormone-free interval. Contraception. 2006;74(2):100–103.
4. Rosenberg MJ, Meyers A, Roy V. Efficacy, cycle control, and side effects of low- and lower-dose oral contraceptives; a randomized trial of 20 micrograms and 35 micrograms estrogen preparations. Contraception. 1999;60(6):321–329.
5. Gallo MF, Nanda K, Grimes DA, Lopez LM, Schulz KF. 20 µg versus >20 µg estrogen combined oral contraceptives for contraception. Cochrane Database Sys Rev. 2008;(1):CD003989.
6. Greenblatt RB. Progestational agents in clinical practice. Med Sci (Philadelphia). 1967;18:37–48.
7. Greenblatt RB. Delay of menses test. Pac Med Surg. 1966;74(3):127–130.
8. ACOG Committee on Practice Bulletins—Gynecology. Practice Bulletin No. 114: Medical management of endometriosis. Obstet Gynecol. 2010;116(1):223–236.
9. Harada T, Momoeda M, Tuketani Y, Hoshiai H, Terakawa N. Low-dose oral contraceptive pill for dysmenorrhea associated with endometriosis: a placebo-controlled, double-blind, randomized trial. Fertil Steril. 2008;90(5):1583–1588.
10. Vercellini P, Tresidi L, Colombo A, Vendola N, Marchini M, Crosignani PG. A gonadotropin-releasing hormone agonist versus a low-dose oral contraceptive for pelvic pain associated with endometriosis. Fertil Steril. 1993;60(1):75–79.
11. Seracchioli R, Mabrouk M, Manuzzi L, et al. Post-operative use of oral contraceptive pills for prevention of anatomical relapse or symptom-recurrence after conservative surgery for endometriosis. Hum Reprod. 2009;24(11):2729–2735.
12. Seracchioli R, Mabrouk M, Frasca C, Manuzzi L, Savelli L, Venturoli S. Long-term oral contraceptive pills and postoperative pain management after laparoscopic excision of ovarian endometrioma: a randomized controlled trial. Fertil Steril. 2010;94(2):464–471.
13. McClave AK, Hogue CJ, Brunner-Huber LR, Ehrlich AC. Cigarette smoking women of reproductive age who use oral contraceptives: results from the 2002 and 2004 behavioral risk factor surveillance systems. Women's Health Issues. 2010;20(6):380–385.

Correction: Drug dosage, Editorial, April 2011

The subcutaneous dosage of terbutaline given in the "Checklist" on page 8 is incorrect. The dosage of terbutaline should be given as 0.25 mg.

We regret this editing error. The corrected "Checklist" appears at http://www.obgmanagement.com/article_pages.asp?AID=9495&UID=

—The Editors