Editorial

›› **Robert L. Barbieri, MD** Editor in Chief

Potential for better cycle control

In the news, now on the shelf: A novel estradiol-based OC

The first birth control pill was sold in the United States in 1960. Fifty years later, oral contraceptives continue to evolve—as Natazia demonstrates.

Innovation over 5 decades has added options to the medicine chest of contraceptives that we can offer to our patients. The US Food and Drug Administration recently approved Natazia (Bayer HealthCare), a novel four-phase, estrogen step-down, progestin step-up regimen that contains a new estrogen, **estradiol valerate,** and the novel progestin, **dienogest.** Here is how this OC is constituted and how it works.

Why estradiol valerate?

Almost all oral estrogen-progestin contraceptives contain the potent estrogen ethinyl estradiol. The ethinyl group at C17 prevents conversion of this highly active estrogen to the weak estrogen, estrone, thereby extending its estrogenic bioactivity.

High estrogenic activity, and limited degradation of oral ethinyl estradiol, may account for its pronounced effects on the production of proteins in the liver, including **1)** an increase in thrombotic proteins and **2)** a decrease in some antithrombotic proteins. It's been speculated that using the natural estrogen, estradiol, in an oral estrogen-progestin contraceptive would reduce the magnitude of the liver protein changes observed with ethinyl estradiol. This, in turn, would (again, this is speculation) reduce the risk of deep-vein thrombosis, which has been observed among women who use contraceptives that contain ethinyl estradiol.[1,2]

Early attempts to formulate a monophasic oral estrogen-progestin contraceptive that contains estradiol and estriol did yield OCs that inhibited ovulation, but those products were associated with a high rate of irregular bleeding patterns, including amenorrhea and spotting.[3]

Now, the newly approved estrogen-progestin contraceptive, Natazia, which contains estradiol valerate (**FIGURE 1**, page 10) appears to overcome those unwanted side effects.

When estradiol valerate is taken orally, the intestines absorb almost all of it. The valerate group is cleaved within the intestines or in the first pass through the liver—thus converting the compound to estradiol and valeric acid. A woman who takes Natazia has a circulating level of estradiol of approximately 50 pg/mL and a higher level of estrone (250 pg/mL); this difference reflects the robust conversion and rapid degradation of orally administered estradiol to estrone.

Dienogest: Novel progestin

This new 19-nortestosterone derivative has a unique C-17 cyanomethyl group instead of the usual C-17 ethinyl grouping (**FIGURE 2**, page 10). Dienogest binds most avidly to the progesterone receptor; it does not bind to estrogen, glucocorticoid, or mineralocorticoid receptors. It binds weakly to the androgen receptor, and reportedly has antiandrogenic activity.

When dienogest is taken orally, more than 90% of the dose is absorbed; half-life is approximately 11 hours. It appears to have unparalleled potency among oral progestins when tested in estrogen-primed rabbit endometrium (McPhail test).[4]

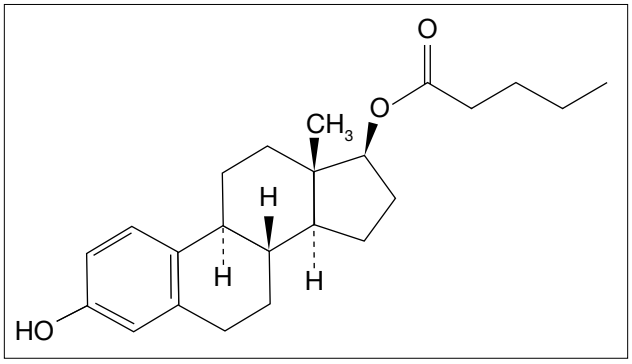
Dienogest is metabolized by the cytochrome P-450 CYP3A4 system. Concomitant administration of dienogest and CYP3A4 inducers—barbiturates, carbamazepine, phenytoin, primidone, rifampicin—may decrease the time needed to clear dienogest. Concurrent administration of dienogest and CYP3A4 *inhibitors*—antidepressants, azole antifungals, cimetidine, grapefruit juice, diltiazem, macrolides, verapamil—may increase the circulating concentration of dienogest.

CONTINUED ON PAGE 10

What do you know about the enzyme CYP3A4 and how it affects the work of some OCs?

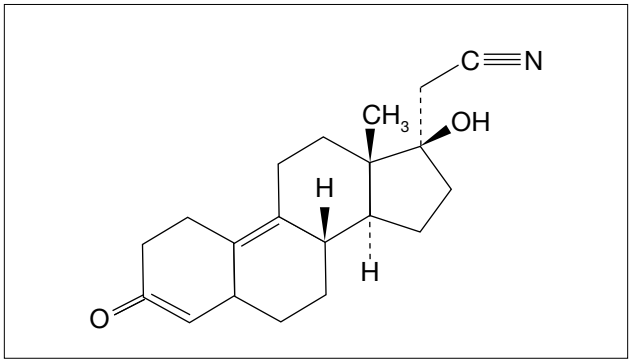
Take the **Instant Poll** on page 11

FIGURE 1 The structure of estradiol valerate



With absorption, estradiol valerate is metabolized to estradiol. Estradiol is metabolized to estrone and estrone sulfate.

FIGURE 2 The structure of dienogest



This new 19-nortestosterone derivative has a unique C-17 cyanomethyl group, not the usual C-17 ethinyl group.

Estrogen step-down, progestin step-up

Natazia is formulated as a four-phase estrogen step-down (from 3 mg to 1 mg), progestin step-up (from 2 mg to 3 mg) regimen (**TABLE**). A 28-day cycle has 26 pills containing hormones and two inert pills. Underlying this formulation are the theoretical concepts that:

- **estrogen step-down** ensures estrogen dominance in the first part of the cycle, thus stimulating endometrial proliferation and increasing endometrial production of progesterone receptors, which, in turn, sensitizes endometrium to the action of progestin
- **progestin step-up** ensures the stability of endometrial stroma and prevents endometrial hyperplasia.

Comparative study. The clinical effect of Natazia was explored in a randomized controlled trial in which it was compared with a monophasic estrogen–progestin combination of 20 µg ethinyl estradiol plus 0.1 mg levonorgestrel (EE-LNG) in a 21-7 cycle (a formulation found in the brand-name OCs Aviane, Alesse, and Lutera).[5] The findings of that trial?

- Both formulations were very effective: No pregnancies in women who took Natazia, one pregnancy in women who took EE-LNG
- In the first 90 days of the trial, women taking Natazia reported fewer days of bleeding or spotting than women taking EE-LNG (17 days and 22 days, respectively [$P < .0001$])
- Absence of withdrawal bleeding was observed more often in women taking Natazia than in women taking EE-LNG: With Natazia, about 19% of cycles were associated with an absence of withdrawal bleeding; with EE-LNG, 8% of cycles
- Approximately 80% of subjects in each of the two study groups were satisfied with the OC they were given.

Natazia for menorrhagia

As I noted, Natazia appears to be associated with **1)** fewer days of menstrual bleeding and **2)** more cycles without withdrawal bleeding than an EE-LNG contraceptive.[5] These findings suggest that Natazia may be especially useful for treating heavy menstrual bleeding.

Profile of four-phase Natazia

Day of cycle	Pill color	Pill count	Estradiol valerate content	Dienogest content
1, 2	Dark yellow	2	3 mg	None
3–7	Medium red	5	2 mg	2 mg
8–24	Light yellow	17	2 mg	3 mg
25, 26	Dark red	2	1 mg	None
27, 28	White	2	None	None

Two randomized clinical trials that were reported in abstracts at major professional meetings have tested this hypothesis[6,7]:

Trial #1. 190 women who had heavy menstrual bleeding were randomized to Natazia or placebo[6]:

- 44% of women who took Natazia experienced complete improvement in their heavy menstrual bleeding
- Only 4% of women in the placebo group experienced such improvement
- Natazia, but not placebo, was associated with an elevation in hematocrit, hemoglobin concentration, and ferritin level.

Trial #2. In a trial conducted to likewise test the efficacy of Natazia for heavy menstrual bleeding, the rate of complete improvement among women treated with Natazia was 41%; the rate was 2% in the placebo group.[7]

These studies show that Natazia may be especially useful for women who report heavy menses when they've taken other estrogen-progestin contraceptives.

More choices mean better tailoring

Effective counseling and consistent use of a contraceptive will reduce the high rate of unintended pregnancy in the United States. Having many contraceptive options available helps ensure that each woman can find the contraceptive that's best suited to her.

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Dr. Barbieri reports no financial relationships relevant to this article.

Instant Quiz

True or false? The enzyme CYP3A4 metabolizes many synthetic progestins and ethinyl estradiol.

Grapefruit juice increases the enzymatic activity of CYP3A4, thus increasing degradation and reducing the concentrations and effectiveness of progestins and ethinyl estradiol.

See page 50 for the answer.