Ultra-Low-Dose Oral Contraceptives: Are They Right for Your Patient?

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Introduction

Oral contraceptives (OCs) are currently the most popular reversible method of contraception in the United States. The pills first marketed in the United States 40 years ago contained 150 micrograms (mcg) of a synthetic estrogen, mestranol, that metabolizes to ethinyl estradiol (EE). By contrast, most OCs prescribed today contain 35 mcg or less of EE (Figure 1). This striking reduction in the EE dose was prompted primarily by efforts to reduce the incidence of adverse cardiovascular side effects.

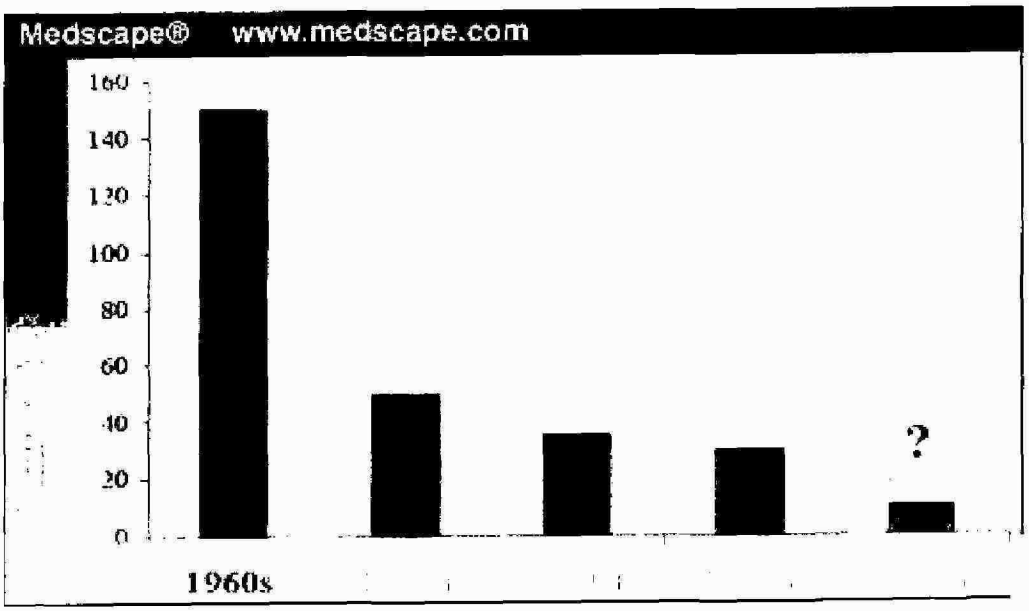

Figure 1. Declining hormone levels in OCs.

Studies have established that so-called "low-dose" pills (<= 35 mcg EE) provide the same level of contraceptive efficacy as their higher-dose forerunners but are associated with a lower risk of venous thromboembolism (VTE), stroke, and myocardial infarction (MI).[1-4] In keeping with the trend toward producing OCs with progressively lower doses of estrogen, the first OC containing 20 mcg EE was introduced in 1973 and promoted for women with a high risk of cardiovascular disease because of smoking or age.[5] Recently, other formulations containing 20-mcg EE have become available and are advocated for general use.

This review is designed to assist clinicians involved in prescribing contraceptive regimens by providing an overview of the risks and benefits of these "ultra-low-dose" 20-mcg EE OC preparations. As clinical practice shifts from reserving these pills for specific patient populations to using them as first-line therapy, clinicians should be familiar with the efficacy, menstrual cycle control, side-effect profile, and continuation rates associated with low-dose OCs. Table 1 lists the issues to be considered in determining whether 20-mcg EE OC preparations should be the new standard.

Contraceptive Efficacy

OCs prevent pregnancy through several mechanisms. They suppress ovulation by decreasing gonadotropin secretion, which results in diminished cycling concentrations of estradiol and progesterone. The progestin component causes the cervical mucus to become viscous and virtually impenetrable by spermatozoa. OCs also inhibit endometrial proliferation.

Contraceptive efficacy is measured by assessing the number of pregnancies that occur in women using OCs. Transvaginal ultrasonography can be used to examine follicle-like structures. Generally, ovulation occurs when the follicle is 18-20 mm in diameter.

For healthcare providers and consumers alike, contraceptive efficacy is of utmost concern when choosing an OC. The dramatic decline in steroid hormone doses has caused some concern regarding the ability of these combination OC preparations to prevent pregnancy. Numerous studies, however, have demonstrated that OCs containing 20 mcg of EE combined with gestodene, desogestrel, or levonorgestrel effectively inhibit ovulation and decrease cervical mucus scores.[5-11]

But is the contraceptive efficacy of these newer products equivalent to that provided by the numerous tried and true 30/35-mcg preparations available? Rosenberg and colleagues[12] shed light on this issue by comparing the efficacy of 2 20-mcg EE products (Alesse, Mircette) to a 35-mcg EE formulation (Ortho Tri-Cyclen) in a randomized trial of 463 women. Contraceptive efficacy did not differ between the treatment groups. In all, 4 pregnancies occurred: 3 in Tri-Cyclen users, 1 in an Alesse user, and none among Mircette users. Corresponding Pearl Index rates[13] were 4.4, 1.5, and 0.0 per 100 woman-years of use. (The Pearl Index is defined as the number of unintended pregnancies per hundred women per year -- that is, the number of pregnancies in 1200 observed months of use.)

Reisman and colleagues[14] similarly compared the effects of 2 20-mcg EE pills (Alesse, Levlite, or Loette) to that of 35-mcg EE (Ortho-Novum 7/7/7 or TriNovum) preparations in 167 women for 1 to 4 cycles. Their results also demonstrate that 20-mcg EE preparations provide equivalent contraceptive reliability to that obtained with an OC containing 35 mcg EE.

Archer and colleagues[10] recently evaluated the efficacy of a combination OC containing 100 mcg levonorgestrel and 20 mcg EE (Alesse) in 1708 women. Over the course of 26,554 menstrual cycles, 18 pregnancies occurred, giving a Pearl Index of 0.88. Similarly, an 18-month multicenter trial of 1143 women using Mircette found the Pearl Index for total pregnancies during treatment to be 1.02.[21] These and other comparative studies have found that the efficacy of 20-mcg preparations is similar to that provided by 30/35-mcg formulations of OCs.[15-21] Overall, the Pearl rates for women taking 20-mcg EE formulations range from 0.2 to 1.0.

Cycle Control

The ongoing trend of development of OCs with progressively lower doses of EE has raised the issue of whether pills containing 20 mcg of EE can produce normal menstruation-like bleeding patterns and breakthrough bleeding rates as low as the higher estrogen-containing products. Cycle control is extremely important, as it, along with the incidence of other side effects, is the strongest predictor of whether a woman will use OCs correctly and continue with their use.[22-24] In a study of 6676 women, Rosenberg and colleagues[24] demonstrated that intermenstrual bleeding was associated with an increased risk of missing pills (relative risk [RR] 1.3) and discontinuation (RR 1.9). Other side effects and reasons women discontinue OC use are listed in Tables 2 and 3.

Although estrogen dose is a major determinant, cycle control is also affected by patient characteristics, estrogen, and progestin dose and type. Cycle control is most frequently evaluated by the percentage of cycles with breakthrough bleeding, spotting, or both. Other indicators are the incidence of amenorrhea, duration of menses, mean intensity of menstrual bleeding, and cycle length.

Data comparing cycle control in women taking 20- and 35-mcg EE preparations are limited and inconsistent. The variation is due to the lack of true head-to-head comparisons of factors affecting tolerability and continuation rates in addition to the disparate definitions of abnormal bleeding. Products compared in some studies differ with regard to both estrogen dose and progestin component and phasing. However, when OC formulations with the same progestin component are compared, the lower the dose of estrogen, the more diminished is the cycle control.[15,16,25]

Rosenberg and colleagues[26] demonstrated the effect of progestins on cycle control by analyzing data from 2 clinical trials that included 15,421 cycles among 2767 women. One study compared 75 mcg gestodene + 30 mcg EE with 150 mcg desogestrel + 30 mcg EE, while the other compared the same gestodene preparation with 150 mcg desogestrel + 20 mcg EE. They found that the risk of intermenstrual bleeding or spotting is significantly lower in women taking preparations containing gestodene than in those containing desogestrel, regardless of whether the pills contained 20 mcg or

30 mcg of EE. Better cycle control with gestodene preparations has similarly been demonstrated in other studies examining combined OCs containing 20 mcg of EE.[27,28]

Pharmacokinetic differences between progestin types may also result in differences in cycle control between various 20- and 30/35-mcg of EE preparations. For example, levonorgestrel has a longer half-life than norethindrone,[29] a difference that may cause the longer latent period associated with levonorgestrel formulations.[14,18,30] In addition, oral bioavailability is greater for levonorgestrel,[31] whereas norethindrone undergoes first-pass metabolism, which results in wider variations in serum levels and biologic effects.[29]

Taken as a whole, the data on ultra-low dose pills and cycle control are ambiguous. Bounds and colleagues[32] studied 555 women in one of the earliest randomized trials that compared a pill containing 20 mcg EE and 1 mg norethisterone acetate with a formulation consisting of 30 mcg EE and 150 mcg levonorgestrel. They found that the rate of discontinuation as a result of abnormal bleeding was significantly higher for women taking the 20 mcg EE preparation (27%) than for those taking the 30 mcg EE pill (3.7%). A World Health Organization (WHO) Task Force on Oral Contraceptives[33] found similarly high discontinuation rates (23.2%) attributed to poor cycle control for women taking a 20-mcg EE preparation plus 400-mcg norethisterone acetate compared with other combination OCs. Other studies have demonstrated a lower frequency of intermenstrual bleeding associated with the use of 30- and 35-mcg EE products compared with 20-mcg EE formulations.[15-17]

A recent randomized trial by Reismann and colleagues,[14] however, contradicts these findings. They compared cycle control in 155 women who took 100-mcg levonorgestrel with 20 mcg EE to 167 women who took a triphasic preparation of 500, 750, and 1000 mcg norethindrone with 35 mcg EE. Overall cycle control was comparable between the 2 groups, with a similar percentage of normal cycles and cycles with intermenstrual and withdrawal bleeding. In the 20-mcg EE group, there was a statistically significantly longer latent period and a statistically significantly shorter withdrawal-bleeding episode.

Similarly, Chavez and colleagues[18] demonstrated that a 20-mcg EE preparation provided better cycle control than a product containing 35 mcg of EE. They compared cycle control in women taking 100 mcg levonorgestrel + 20 µg EE formulation to those using a triphasic 500, 750, and 1000µg norethindrone + 35-mcg EE preparation. By cycle 4, 69.9% of cycles were normal in women taking the 20-mcg EE formulation and only 54.4% of cycles were normal in those taking the 35-mcg EE preparation ($P < .05$) .

Variations in data on cycle control result from the disparate manner in which abnormal bleeding is defined and measured. Typically it is reported in terms of incidence of women bleeding during a specific interval. As such, there is no differentiation between women with prolonged bleeding and those with minor spotting, and any degree of spotting or bleeding carries the same weight.[34]

Overall, however, studies that have used the WHO criteria for intermenstrual bleeding[35] have demonstrated consistent rates of cycle control for 100 mcg levonorgestrel plus 20-mcg EE

preparations. The total proportion of women who had normal cycles when taking this formulation ranged from 64% to 82%.[18,20,30,36]

Estrogenic Side Effects

Although cycle control plays an important role, the frequency of bloating, breast tenderness, and nausea also predict satisfaction and compliance in OC users.[22-24] Estrogenic side effects are particularly common in new users. Their incidence contributes to the discontinuation rates in this population, which approach 50% during the first year of use.[37]

Many studies have suggested that 20-mcg EE formulations are associated with a lower frequency of estrogen-related side effects than their higher estrogen-dose counterparts. For example, results of a recent randomized trial demonstrate that bloating, breast tenderness, and nausea were approximately 50% more common in women using the 35-mcg EE as compared with the 20-mcg EE preparations.[12] Notably, however, discontinuation rates for women taking the 35-mcg EE formulation were not significantly higher. Other studies have demonstrated that tolerability profiles of ultra-low-dose preparations are better or comparable to those of the 30/35-mcg EE pills.[16,17]

Ultra-Low-Dose Pills and Cardiovascular Disease

Cardiovascular side effects are the most important potential adverse events associated with OC use. The incidence of thromboembolic events is directly related to the dose of estrogen. Meade and colleagues[38] demonstrated that reducing the EE dose from 50 to 30 mcg resulted in a 60% decrease in deaths from cardiovascular events. Many assumed that reducing the dose of EE to 20mcg would further diminish the rate of OC-related cardiovascular events. Currently, however, there is not enough data from large, long-term clinical trials to define the influence of 20-mcg EE OCs on cardiovascular disease and thromboembolic events.[39] A number of studies, however, have investigated the effect of these formulations on coagulation and lipid profiles. Changes in these parameters may predict the potential for increased risk of cardiovascular disease.

Lipids and Lipoproteins

A number of trials have demonstrated that 20-mcg EE OCs have a more favorable effect on lipids and lipoproteins than do higher-EE-dose OCs.[40-42]

For example, Young and colleagues[42] evaluated the effects of an OC containing 100 mcg of levonorgestrel and 20 mcg EE on serum lipid concentrations over a period of 2 years. Concentrations of triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoproteins A-1 and B were analyzed for 24 cycles in 28 women and compared with their baseline levels.

Although many significant changes in lipid measures were noted, they were smaller than those reported for OCs containing higher doses of EE.[40,41] Furthermore, all lipid values returned to

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