ORIGINAL RESEARCH ARTICLE

Oral Contraceptive Estrogen Dose Considerations

Andrew M. Kaunitz

Although the trend with oral contraceptive (OC) prescribing has been to reduce the steroid dose, the potential risks and benefits of further dose reduction should be considered before established prescribing patterns are changed. It is possible that the frequency of some of the advantages associated with the 30- to 35-μg ethinyl estradiol (EE) formulations—good cycle control and many noncontraceptive benefits—may be reduced with the use of 20-μg estrogen dose formulations. Clinicians should weigh these factors in the context of each patient's history and clinical profile when selecting the estrogen dose of an OC formulation.

Safety

Cardiovascular Events

Some clinicians have recommended that 20-μg formulations be used exclusively by OC users under age 35 who smoke. This recommendation is based on theory and is not supported by epidemiologic evidence. Women under age 35 who smoke and take OCs do not have an increased risk of venous thromboembolism (VTE) compared with nonsmokers. Their risk of myocardial infarction (MI) and stroke is low, and there are no data indicating that the risk is reduced with the use of 20-μg compared with 30- to 35-μg OC formulations.[1] Among normotensive, nonsmoking women without other risk factors for cardiovascular disease (CVD), use of 30- to 35-μg formulations has been shown to have eliminated excess risk of MI and stroke.[1]

The risk of VTE has been reduced, but not eliminated, by the use of 30- to 35-μg EE formulations. It might be expected that VTE risk could be further reduced by 20-μg pills. However, as described in the article by Ory in this supplement, "Cardiovascular Safety of Oral Contraceptives," epidemiologic data provide no indication that this occurs.[2–6] Therefore, from the perspective of cardiovascular safety, OC candidates may appropriately use any OC formulation with <50 μg EE, whether or not they smoke.[1]

Breast Cancer Risk

The Collaborative Group on Hormonal Factors in Breast Cancer[7] recently re-evaluated the relationship between breast cancer and oral contraception. Investigators incorporated epidemiologic information from 25 nations in their database, including data from 53,297 women with breast cancer and 100,239 women without. Overall, this reanalysis encompassed 90% of the epidemiologic data published to date on this subject. The results were highly reassuring, with the overall risk of breast cancer diagnosis not increased by OC use among women who had stopped using OCs 10 to 20 years earlier.

Current users and women who had used OCs in the previous 1 to 4 years appeared to be at a slightly increased risk of breast cancer diagnosis, with relative risks of 1.24 (95% confidence interval, 1.15 to 1.33) and 1.16 (1.08 to 1.23), respectively. As Figure 1 shows, women who ceased use between 5 and 9 years earlier showed only a marginal increase in relative risk, 1.07 (95% confidence interval, 1.02 to 1.13). Breast cancers diagnosed in women who were using or previously had used OCs were less clinically advanced than those presenting in age-matched never-users: OC users had a significantly reduced relative risk for diagnosis of cancers that had spread beyond the breast compared with nonusers—the relative risk was 0.88 (95% confidence interval, 0.81 to 0.95; $p = 0.002$).[7] These findings suggest that breast cancer is detected earlier in current or former OC users than in age-matched nonusers. Women who use OCs may be more consistent in performing breast self-examinations, and they may undergo more regular clinical examinations and mammographic studies than nonusers. The slightly increased risk of diagnosis of breast cancer in current or recent-past OC users compared to nonusers may be partially due to detection bias.

Breast cancer risk was not found to vary by OC estrogen dose. Overall, this massive reanalysis provides strong evidence that in the older age group,

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ISSN 0010-7824/98/$19.00
PII S0010-7824(98)00078-X

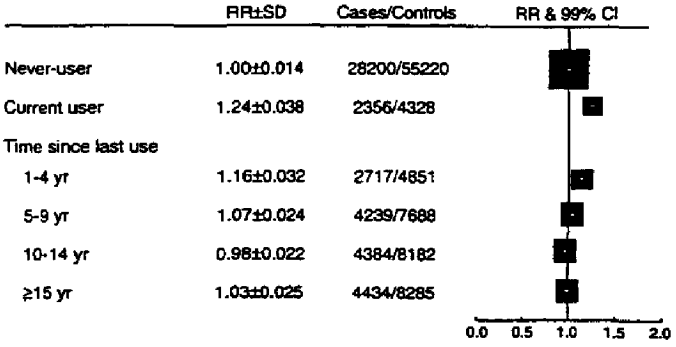

Figure 1. Relative risk of breast cancer by time since last use of combined oral contraceptives. Test for heterogeneity within users: χ^2 (4 df) = 41.5; $p < 0.00001$. Test for trend within users: χ^2 (1 df) = 31.7; $p < 0.00001$. Adapted with permission from Collaborative Group on Hormonal Factors in Breast Cancer. Collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. Lancet 1996;347:1713–27.[7] ©1996 The Lancet Ltd.

when breast cancer is most common, prior OC use does not affect breast cancer risk.

As indicated in the preceding sections, current epidemiologic data provide evidence for the *safety* of OCs formulated with <50 μg EE. The principal challenge facing contemporary OC users and their health care providers, therefore, relates to achieving high OC *efficacy*. Accordingly, maximizing OC compliance and continuation assumes a high priority as clinicians help their patients to select which OC formulation to use.

Cycle Control

With the safety issues involving OC use largely resolved, clinicians can now concentrate more on improving compliance and continuation rates.

Breakthrough (unscheduled) bleeding (BTB) is annoying and inconvenient. This side effect is the primary reason reported for brand/strength switching, as cited by nearly one-quarter of the respondents in a recent survey,[8] and women who experience BTB are substantially more likely to discontinue OCs than women without these problems.[9] Women who discontinue OCs frequently fail to adopt use of another reliable contraceptive, and they are, in consequence, at higher risk for unintended pregnancy.[10]

By providing endometrial support, the estrogen component of OCs prevents breakthrough bleeding. As OC estrogen doses decline, therefore, cycle control also declines. Accordingly, 20-μg EE OCs have been found to have higher rates of breakthrough bleeding and spotting than 30- to 35-μg EE formulations, an observation noted with norethindrone acetate[11] as well as with desogestrel formulations.[12]

In a single-blind, randomized, comparative study, Appel and colleagues[13] examined the efficacy and side effects associated with the use of OCs containing 1.0 or 1.5 μg norethindrone acetate and either 20, 30, or 50 μg ethinyl estradiol in 426 women between 18 and 36 years of age. As shown in Table 1, these investigators found that the incidence of BTB or spotting decreased as the amount of estrogen in the formulation increased: with the 20-μg pill, 44% had BTB or spotting; with the 30-μg pill, 27% experienced these side effects; and 23% had BTB or spotting with the 50-μg pill.

Åkerlund and colleagues[12] conducted a double-blind, randomized study comparing reliability, cycle control, and side effects of two OC formulations containing 150 μg desogestrel and either 30 or 20 μg EE. One thousand women aged 18 to 40 were enrolled in the year-long study. Both pills had high contraceptive reliability and were well tolerated, but, as shown in Figure 2, cycle control was less effective with the

Table 1. Number (percent) of patients with breakthrough bleeding, spotting, or both during treatment

Formulation	Total subjects/cycles	Breakthrough bleeding	Breakthrough spotting	Both
1.0 mg norethindrone acetate and 20 μg ethinyl estradiol	102/459	110 (24.0)	93 (20.3)	203 (44.2)
1.5 mg norethindrone acetate and 30 μg ethinyl estradiol	117/494	43 (8.7)	91 (18.4)	134 (27.1)
1.0 mg norethindrone acetate and 50 μg ethinyl estradiol	100/441	43 (9.8)	60 (13.6)	103 (23.4)

Reprinted with permission from Elsevier Science Inc. from Appel et al. A comparison of a new graduated estrogen formulation with three constant-dosed oral contraceptives. Contraception 1987;35:523–32.[13]

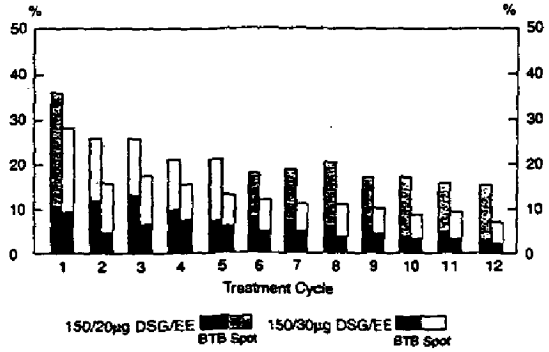

Figure 2. Irregular bleeding (BTB or spotting) in percentage of women per treatment cycle. DSG, desogestrel; EE, ethinyl estradiol. Adapted with permission of Blackwell Science Ltd. from Åkerlund et al. Comparative profiles of reliability, cycle control and side effects of two oral contraceptive formulations containing 150 µg desogestrel and either 30 µg or 20 µg ethinyl oestradiol. Br J Obstet Gynaecol 1993;100:832–8.12

150/20 combination than with the 150/30 formulation. Irregular bleeding (breakthrough bleeding or spotting) occurred more frequently with the 150/20 combination in all cycles, and the incidence was significantly higher in about two-thirds of the cycles randomly distributed over the duration of the study. Bleeding problems were reported by at least 15% of women using the 150/20 combination in all 12 cycles compared with at least 8% of women using the 150/30 formulation. Because of side effects (primarily bleeding problems), more women using the 150/20 combination discontinued the study, and women using this pill were also less willing to consider continuing the study drug at the end of the trial. These findings are consistent with other observations that bleeding problems are a major obstacle to compliance.[9]

Data on efficacy and safety of a 21-day OCs containing 20-µg EE and 100 µg levonorgestrel were recently published.[14] Interim results of the multicenter, open-label, noncomparative trial suggest that bleeding irregularities associated with this formulation are common and can be persistent. Breakthrough bleeding, spotting, or both were reported by 25.3% and 18.2% of women during cycles 6 and 12, respectively.[14]

The negative effect of 20-µg EE formulations on cycle control may be especially problematic for particular subgroups of women, such as adolescents and perimenopausal women who are using OC in order to establish or restore cycle control. As discussed below, the issue is also particularly relevant for women who smoke cigarettes.

A recent study showed that cigarette smoking adversely affects cycle control in users of OCs.[15] Three open-label, randomized clinical trials studied 2956 OC users for 16,506 cycles. The proportion of smokers who used OC and reported spotting or bleeding varied from 59% in the first cycle to 14% in the sixth cycle, averaging 23% per cycle. In contrast, the proportion of nonsmokers who reported bleeding ranged from 52% in the first cycle to 9% in the sixth cycle, averaging 19% per cycle for all six cycles. Among OC users who smoked compared to nonsmokers, the relative risk for breakthrough bleeding was elevated for every cycle, with the difference being statistically significant in five of six cycles. Adjusting for recency and consistency of OC use and the progestin component, smokers were 47% more likely to have spotting or bleeding than nonsmokers during six cycles of OC use.

Consistent with the findings of other studies,[12,13] the risk of spotting or bleeding also was found to be higher in each cycle among women using 20-µg formulations than among those using 30-µg formulations, but the authors did not report the statistical significance of this finding.[15] These results strongly suggest that smoking impairs cycle control and that this effect is also related to the estrogen dose. A causal mechanism might be the increased hepatic catabolism of estrogen known to occur in smokers.[15]

Noncontraceptive Benefits of OCs

Although the risks of OC use have been highly publicized, women remain largely unaware of the health benefits associated with their use.[16] Important health benefits have been clearly and consistently documented in epidemiologic studies. OCs protect women against endometrial cancer,[17–20] ovarian cancer,[17,21–25] ectopic pregnancy,[26] pelvic inflammatory disease,[27] benign breast disease,[28–30] loss of bone density,[31] ovarian cysts,[32,33] dysmenorrhea,[34,35] and menorrhagia.[36] One formulation, the triphasic OC containing norgestimate and ethinyl estradiol, has been shown in a randomized, placebo-controlled trial to reduce the amount of acne[37] and has recently received US regulatory approval as a treatment for acne.[37] In all of the studies that demonstrated noncontraceptive benefits of OCs, the formulations used contained 30 µg or more of EE. Therefore, it is uncertain whether each of these benefits will be maintained and achieve the same magnitude of benefits with OCs formulated with lower estrogen doses.

Between 35% and 50% of cortical and trabecular bone mass is lost over a woman's lifetime, and

Table 2. Distribution of women by bone mineral density (BMD) interval and history of oral contraceptive use

Oral contraceptive use	BMD interval category, No. (%)				
	1 (Low)	2	3	4 (High)	Total
Yes	28 (14.0)	153 (22.5)	373 (33.9)	127 (46.0)	681 (30.2)
No	172 (86.0)	527 (77.5)	726 (66.1)	149 (54.0)	1574 (69.8)
Total	200	680	1099	276	2255

Armitage χ^2 test for trend = 82.5, $p = 5.3 \times 10^{-20}$.
Adapted from Kleerekoper et al. Oral contraceptive use may protect against low bone mass. Arch Intern Med 1991;151:197–6.[40]

postmenopausal osteoporosis affects about 20 million women in the United States, accounting for more than one million fractures annually.[31] Cigarette smoking exacerbates the process of bone loss, having a negative impact on bone mineral density (BMD) that is sufficient to place both men and women at increased risk for fracture.[38,39]

Evidence from several studies suggests that use of OCs in reproductive age women may stabilize or even increase bone mass.[31] Eight of 12 published studies have shown that women using OCs have greater bone mass than nonusers,[31] with the greatest BMD benefit noted in women who have used OCs for at least 10 years.[40]

Kleerekoper and colleagues[40] conducted a cross-sectional retrospective epidemiologic study to investigate risk factors for low BMD in a group of women, 76% of whom were postmenopausal. Reproductive information, including history of OC use, BMD measurements, and other data were available from 2297 women screened for osteoporosis at 12 centers in 1986 and 1987. The investigators divided the BMD distribution within each center into quartiles.

A history of OC use was found to be protective against low BMD (odds ratio, 0.35; 95% confidence interval, 0.23 to 0.53). As shown in Table 2, although OC users comprised only 14% of the women in the lowest BMD quartile, nearly half of the women in the highest BMD quartile were OC users. Multivariate analysis confirmed these results and suggested that the degree of protection from lower BMD is related to duration of OC exposure.[40]

Because OCs have only been in use since the 1960s, epidemiologic data regarding the possible effect of OC use for preventing osteoporotic fractures among postmenopausal women is limited. However, it is thought that the possible enhanced bone density provided by OC use[31,40] may reduce the incidence of vertebral and hip fractures in later life.

The optimal OC estrogen dose for stabilizing BMD has not been determined.[41] However, the bone-sparing effects of estrogen are known to be dose-related.[31] Horsman and colleagues[42] reported that in postmenopausal women receiving estrogen therapy, changes in cortical bone mass correlated with the dose of ethinyl estradiol. Although a net loss of bone occurred at doses of EE < 15 μg, a net gain was observed at doses > 25 μg. At doses between 15 and 25 μg daily, bone was neither gained nor lost.

Prevention of Functional Ovarian Cysts

Functional ovarian cysts usually disappear spontaneously and require only expectant management unless they cause substantial pain or are large enough to rupture (with consequent intra-abdominal bleeding) or to cause torsion. Nonetheless, functional ovarian cysts represent the fourth most common gynecologic cause for hospitalization, and most hospitalizations result in surgery.[43] The incidence is highest in women aged 15 to 35,[43] a population well-suited for OC use. All currently available monophasic OCs reduce the incidence of functional ovarian cysts, although the degree of suppression is somewhat attenuated in formulations containing <50 μg EE compared with the 50-μg formulation.[33] There are no published data assessing the effectiveness of formulations with 20 μg EE for reducing the incidence of ovarian cysts.

Endometrial Cancer

Approximately 34,000 new cases of endometrial cancer are diagnosed each year in the United States, resulting in approximately 6000 deaths.[44] OCs have been well-documented as providing strong duration-dependent protection against endometrial cancer.[25]

As shown in Figure 3, endometrial cancer risk declines with duration of OC use. The 22 risk estimates plotted in this figure by Schlesselman[17] are based on 10 epidemiologic studies published between 1980 and 1994. OC use reduces the risk of endometrial cancer by approximately 50% within 4 years of use,[17–19] and the risk may be reduced by 72% after 12 years of use.[17] For every 100,000 women aged 20 to 54 in the United States who never use OCs, approximately 438 will develop cancer of the endometrium. For every 100,000 women using OCs for 8 years, 197 fewer cases would be expected. Because this protec-

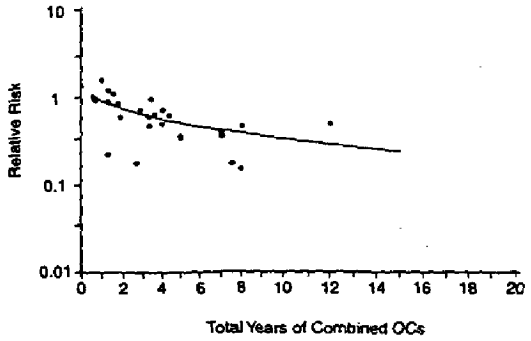

Figure 3. Relative risk of endometrial cancer by total years of oral contraceptive (OC) use. Reproduced with permission from the American College of Obstetricians and Gynecologists from Schlesselman. Net effect of oral contraceptive use on the risk of cancer in women in the United States. Obstet Gynecol 1995;85:793–801.[17]

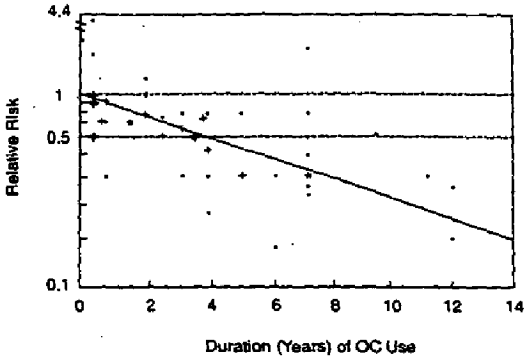

Figure 4. Relative risk of ovarian cancer by oral contraceptive (OC) use: findings of 15 studies. Study categories, indicating category weights ranging from smallest (weight in bottom 25% of range) to largest (weight in top 25% of range): squares = 1 (smallest); pluses = 2; dark crosses = 3; stars = 4 (largest). Adapted with permission from the American College of Obstetricians and Gynecologists from Hankinson et al. A quantitative assessment of oral contraceptive use and risk of ovarian cancer. Obstet Gynecol 1992;80:708–14.[21]

tion persists for at least two decades after OC discontinuation,[20] OC users in their mid-30s or older can reduce their risk for those decades during which they would otherwise experience a peak incidence of this common gynecologic malignancy.[17]

The epidemiologic evidence regarding the protection provided by OC use, as summarized in Figure 3, is provided by studies based on experience with OCs containing at least 35 μg EE. At doses of 35 μg EE and higher, the degree of protection appears independent of estrogen dose.[19,20] The effect of OCs containing ≤30 μg EE upon endometrial cancer has not been analyzed.

Ovarian Cancer

In general, primary prevention (that is, avoidance) of disease is preferable to secondary or tertiary prevention (early detection and treatment, respectively).[45] Perhaps in no disease is this more true than for ovarian cancer. It is estimated that more than 26,000 women in the United States were diagnosed with this lethal disease in 1996.[44] Often asymptomatic until late in its development (stage III or IV), ovarian cancer causes more deaths in the United States than any other gynecologic cancer.[44] Fewer than 45% of women survive 5 years after diagnosis.[44]

OCs have been well-documented as protecting against ovarian cancer,[17,21–25] although few women are aware of this fact. No other prescription drugs have been shown to confer such potent protection against a lethal malignancy.[45] As seen in Figure 4, the beneficial effect of OC use on the incidence of ovarian cancer appears to be duration-dependent[22,25] and may be related to suppression of ovulation, although other mechanisms are also possible.[21] Risk is reduced by approximately 40% after 4 years of use; after 10 to 12 years, it is reduced by as much as 60% to 80%.[17,22,23] The protective effect of OCs lasts for at least 20 years after discontinuation.[17,23] Therefore, OC users in their mid-30s and older can reduce their risk for those decades in life when they would otherwise experience peak risk for this lethal malignancy. For every 100,000 women between the ages of 20 and 54 in the United States who never use OCs, approximately 369 will develop ovarian cancer. For every 100,000 women using OCs for 8 years, 193 fewer cases would be expected to occur.[17]

Almost all the epidemiologic evidence regarding the protection against ovarian cancer provided by OC use is based on experience with OCs containing at least 30 μg EE. No studies have analyzed the effects of 20-μg EE formulations upon ovarian cancer[21,23] and it has not yet been determined whether the prophylactic effect is maintained when the estrogen dose is reduced below 30 μg.

Benign Breast Disease

Previous studies of benign breast disease in users of formulations containing 50 μg or more of estrogen found a decreased risk among users compared with nonusers.[28,29] Current use of high-dose formulations was associated with reductions in the risk of benign

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