OBG MANAGEMENT

BY JOSEPH S. SANFILIPPO, MD, MBA

Sizing up a new generation of OCs

Ultra-low-dose formulations are thought to offer a number of advantages over earlier oral contraceptives, including a reduced risk of thromboembolism and stroke, and fewer concerns about breast cancer. But what does the evidence show?

The first combination oral contraceptive (OC), approved by the FDA in 1960, contained 150 μg mestranol and 10,000 μg norethynodrel. In the years since its introduction, equally effective but lower-dose OCs have been developed that are associated with fewer unpleasant side effects. Since 1988, no OC has contained more than 50 μg ethinyl estradiol (EE_2) or its biologic equivalent. EE_2 now is the only estrogen used in OC formulations.

Ultra-low-dose OCs, formulated with estrogen doses as low as 15 to 25 μg, have been proven clinically effective. In addition, newer progestins with less androgenic activity continue to become available. The latest are "third-generation" progestins that have minimal progestational side effects. One of them is drospirenone, which exhibits both antiandrogenic and antimineralocorticoid activity. Today the primary differences between OC preparations center on their androgenic, mineralocorticoid, and sex-hormone-binding globulin effects. **TABLE 1** lists the androgenic qualities of each progestin.

KEY POINTS

- Oral contraceptives formulated with estrogen doses as low as 15 to 25 μg have been proven clinically effective and generally are associated with a lower incidence of estrogen-related side effects.
- In general, ultra-low-dose pills have resulted in bleeding patterns consistent with those of higher-dose preparations.
- One study of women taking 20 μg ethinyl estradiol (EE_2) and 100 μg levonorgestrel over 2 years found no significant changes from baseline levels of triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoprotein A-1 and B.
- The enhanced hepatic enzyme activity associated with some anticonvulsants can limit the efficacy of OC therapy.

Mechanism of action

OCs inhibit ovulation by suppressing the secretion of gonadotropin-releasing hormone (GnRH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH), thereby halting ovarian follicular development. While this decreases endogenous production of estrogen and progesterone, the serum levels of these hormones remain high, as they are the main ingredients of the pills.

Ultra-low-dose OCs became clinically available in the 1990s. Several formulations now are offered in the United States and internationally, all of them containing EE_2. The dosing is 15, 20, or 25 μg in monophasic pills.

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One biphasic formulation containing 20 μg EE_2 has reduced the pill-free interval to 2 days, followed by 5 days of 10 μg EE_2. (Two other ultra-low-dose OCs have reduced the pill-free interval to 5 days.) Triphasics include formulations that have 25 μg of EE_2 and increasing amounts of desogestrel (100, 125, and 150 μg), as well as those that contain 30 to 40 μg EE_2 and increasing amounts of levonorgestrel (50, 75, and 125 μg). Another triphasic contains 20, 30, and 35 μg of EE_2 and 1,000 μg norethindrone. See **FIGURE 1** for a more complete listing.

The progestin content of monophasic formulations typically is 150 μg desogestrel or 75 μg gestodene, although one brand contains 100 μg norethindrone and another contains 100 μg levonorgestrel. A recently approved monophasic OC contains 30 μg EE_2 and 3,000 μg drospirenone. (As mentioned earlier, the progestin has antiandrogenic and antimineralocorticoid activity.) When desogestrel is the progestin in low-dose triphasics, it is administered in the amount of 100 μg on cycle days 1 through 7, increasing to 125 μg on days 8 through 14, and 150 μg on days 15 through 21.

Interestingly, a number of the 20-μg-EE_2 formulations have been noted to have follicular-phase levels of circulating estradiol. When low-dose pills were evaluated with respect to the pulsatile character of gonadotropin secretion, the LH pulse frequency during the treatment cycle was significantly inhibited, compared with the control cycle. Overall, gonadotropin secretion is at a low level during treatment with these contraceptives.[1]

The 20-μg preparations also have been associated with reduced ovarian activity. With the 15-μg formulations, there is greater variation in the interval between cessation of OCs and the resumption of ovulation. Researchers have hypothesized that the gradually decreasing estradiol levels (with the 15-μg formulations) are responsible for this problem, as well as for occasional breakthrough ovulation.[2]

TABLE 1

Androgenicity of progestins in OC formulations

LOW	MEDIUM	HIGH
Norgestimate	Norethindrone	Norethynodrel
Gestodene	Norethindrone acetate	Norgestrel
Desogestrel	Ethynodiol diacetate	Levonorgestrel
Drospirenone		

Overall failure rates are interpreted in terms of women-years of use, known as the Pearl index. When compliance is adequate, OC therapy has a failure rate of less than 1 in 100 women-years, i.e. a Pearl index of less than 1.

Benefits

Davis and colleagues reported an overall improvement in dysfunctional uterine bleeding—i.e., a lower incidence of spotting and breakthrough bleeding—with OCs containing more than 35 μg EE_2 plus norgestimate.[3] Unfortunately, data are limited on bleeding patterns associated with formulations containing less than 35 μg of EE_2. In general, ultra-low-dose pills have resulted in bleeding patterns consistent with those of higher-dose preparations. Breakthrough bleeding occurs more often in the first 3 to 4 cycles and decreases with longer duration of use in patients given OCs for dysfunctional uterine bleeding.[3] OCs containing norethindrone acetate appear to have the least favorable bleeding profile (i.e., the highest incidence of breakthrough bleeding) even when taken correctly.[4]

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A 40% reduction in the risk of ovarian malignancy has been reported with OC therapy, as has a decrease in borderline epithelial ovarian cancer. Most data concern preparations containing 30 μg or more of EE_2.[5] The effect appears to accrue within several cycles of OCs and last 10 to 15 years after the pills are

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TABLE 2

Noncontraceptive benefits of OC therapy

MENSTRUAL IMPROVEMENTS
Regularity
Improvement in dysmenorrhea
Reduced flow
Restoration of regular menses in oligoanovulatory women
REDUCED INCIDENCE OF BENIGN CONDITIONS
Fibrocystic breast disease
Pelvic inflammatory disease
Ectopic pregnancy
Rheumatoid arthritis
REDUCED INCIDENCE OF GYNECOLOGIC MALIGNANCIES
Ovarian malignancy
Epithelial ovarian cancer
Endometrial adenocarcinoma
INCREASED BONE MINERAL DENSITY

discontinued.[6] In a study involving 282 women taking OCs containing 35 μg or less of EE_2, Royar and colleagues noted a 52% reduction in ovarian cancer risk in women who had ever used OCs.[7]

A 50% reduction in the risk of endometrial adenocarcinoma also has been reported with OC therapy.[8] This risk reduction appears to persist for up to 15 years after discontinuation of OCs. Other noncontraceptive benefits are included in **TABLE 2.**

Ultra-low-dose pills also have been associated with a lower incidence of dysmenorrhea. However, no randomized clinical trials (RCTs) have shown this benefit to be greater than placebo. Data are limited regarding their effects on cancers, as well as benign gynecologic conditions such as fibrocystic breast disease, ovarian cysts, chlamydial and gonococcal infections, and pelvic inflammatory disease (PID).

A common misconception is that OC therapy will inhibit height if initiated during adolescence. However, once menarche occurs, endogenous estrogen production stimulates epiphyseal closure. It is this—and not OCs per se—that determines height.

During perimenopause, low-dose OCs have a number of benefits, such as the reduced risk of ovarian and endometrial cancer mentioned earlier, a lower incidence of acute PID, and maintenance of bone mineral density (BMD). Even the 20-μg pill has been shown to prevent bone turnover.[4] In a meta-analysis of 13 studies, 9 showed OCs to have a positive effect on BMD, and none noted a decrease in BMD.[10] This information is important because 20 million individuals are affected by osteoporosis and 1 million annually experience BMD-related fractures. Consequently, barring contraindications, OCs are a reasonable option for perimenopausal women.

In menopausal patients, OCs have been shown to help maintain BMD by preventing the acceleration of resorption that accompanies aging.[9]

Adverse effects

Thromboembolic disease and cancer often are mentioned as 2 of the gravest potential effects of OC use. Low-dose OCs (those containing less than 35 μg EE_2) are associated with a lower risk of thromboembolism than higher-dose formulations.[11] Thus, the incidence of thromboembolic phenomena appears to be related to the dose of estrogen. However, ultra-low-dose OCs do not appear to be associated with any significant difference in the incidence of venous thromboembolism (VTE). Additional research is needed.

Stroke. Epidemiologic studies regarding smoking and OC use in women over 35 have questioned whether the risk of arterial events is greater with formulations containing more than 50 μg EE_2. The evidence is conflicting regarding those containing less than 50 μg EE_2, with one large study finding a slightly increased risk of stroke with low-dose pills (an increase of approximately 2 per

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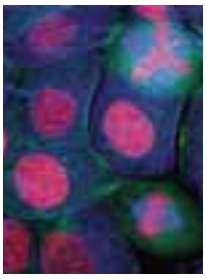
100,000)[12,13] and another finding a slight increase in the risk of thromboembolic stroke.[14] Two similar trials found no increased risk of ischemic or hemorrhagic stroke among women taking a low-dose OC, although there was a possible association between hemorrhagic stroke and the use of OCs containing norgestrel.[15,16] A meta-analysis concluded that a healthy nonsmoker's risk of stroke would increase with low-dose OC use from 4.4 to 8.5 per 100,000.[17] That is, among this population, it would take 24,000 women on OCs to cause 1 additional ischemic stroke per year.

Cancer. The overall incidence of breast cancer does not appear to rise with OC therapy. Although several studies suggest an increased risk with recent or current OC use, detection bias likely accounts for these findings.[18] Women who had taken OCs and then discontinued them for 10 years or more had no increased risk of breast cancer, although a small but significant increase in the relative risk (RR, 1.24) associated with current OC use has been reported.[19] The increased risk was found primarily in women with localized breast disease. Interestingly, the incidence of metastatic disease was lower in current OC users, possibly a reflection of earlier diagnosis.[19]



A possible link between OCs and cervical cancer continues to be debated. Factors such as smoking, early age at first sexual encounter, and multiple sexual partners may predispose an individual on OCs to cervical cancer.[8] I prescribe OCs to women with these risk factors only after obtaining informed consent.

Weight gain. There is no greater risk of weight gain with OC therapy than with placebo.[20] Although there are no specific data regarding ultra-low-dose pills, one would expect the risk of weight gain associated with them to be small.[21]

Acne. Researchers conducted an RCT using a regimen of 20 μg EE_2 and 100 μg levonorgestrel to evaluate the pill's effect on acne. They placed 350 patients (all of whom were older than 14 years of age) on the OC or placebo for 6 cycles. Inflammatory, noninflammatory, and total lesion counts at cycle 6 were significantly lower with the regimen than with placebo.[22]

Coexisting medical conditions

Hypertension. OCs increase blood pressure—in general, by an average of 8 mm Hg systolic and 6 mm Hg diastolic, according to reports. In patients with preexisting hypertension, an additional 7-mm Hg increase in both systolic and diastolic blood pressure should be expected.[20,23] Hypertension remains a relative contraindication to OC use.

The lipid profile. Most data concern 35- and 50-μg OC preparations. The National Cholesterol Education Program (NCEP) recommends that women with controlled dyslipidemia be placed on OC formulations containing 35 μg estrogen or less. In one study, researchers found that 2 years of OC therapy with 20 μg EE_2 and 100 μg levonorgestrel did not cause significant changes from baseline levels of triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and apolipoprotein A-1 and B.[24] The changes in lipid concentration were less than those associated with higher doses of estrogen. Further, when lipid values were elevated, they returned to baseline after 12 to 24 cycles of OC use. OCs are not recommended in women who have elevated LDL cholesterol (more than 160 mg/dL) or additional risk factors for coronary artery disease, including smoking, diabetes, obesity, hypertension, family history of premature coronary artery disease, HDL cholesterol less than 35 mg/dL, or triglyceride levels exceeding 250 mg/dL.[25]

Oral contraceptives are **not recommended** in women who have elevated LDL cholesterol.

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Diabetes. In one study involving 43 women with type 1 diabetes mellitus who used OCs for a mean duration of 3.4 years, hemoglobin A1C values did not differ significantly from those of the controls. The authors concluded that 35-μg OC formulations posed no additional risks for these women.[26] We lack data on ultra-low-dose OCs and diabetes.

Migraine. In a European multicenter case-control trial, women with a history of migraine headaches who used OC formulations containing less than 50 μg estrogen had a 6-fold increased risk of ischemic stroke compared with nonusers with no migraine history, although this difference was not statistically significant.[27] Two other studies also found an increased risk of stroke among OC users with a history of migraines.[11,28]

When smokers with a prior history of migraine were placed on OC therapy, they exhibited a 34-fold increased risk of ischemic stroke in association with the development of migraine headaches compared with nonsmokers who did not use OCs or have a history of migraines.[27]

A pooled study of patients from Kaiser Permanente in northern and southern California and 3 Washington State counties found that ischemic stroke patients—and, to a lesser extent, hemorrhagic stroke patients—were more likely than controls to report a history of migraines.[11] Minimal data exist on migraine headaches and ultra-low-dose pills.

Seizure disorders. The enhanced hepatic enzyme activity associated with the use of phenobarbital, phenytoin, carbamazepine, felbamate, and topiramate can limit the efficacy of OC therapy.[29,30] Patients who must remain on 1 or more of these anticonvulsants may require a higher-dosage OC, since there is evidence of increased metabolic clearance of the estrogen and progestin.[29] Clinicians also should be aware that progestin-only therapy, such as with depot medroxyprogesterone acetate (DMPA), increases the threshold for seizures.

Sickle cell disease. With its associated hemoglobinopathy, sickle cell disease can produce vaso-occlusive abnormalities. Unfortunately, no well-controlled studies regarding the potential for VTE in OC users with sickle cell disease have been reported. Researchers have found that the use of alternative contraceptives such as DMPA is safe and effective.[31,32] Sickle cell anemia remains a relative contraindication to OC use, although the risks of pregnancy in this population also must be considered. The sickle cell trait does not appear to be a contraindication.

Leiomyomata. Research has shown that uterine myomas do not significantly increase in size when a woman takes a low-dose OC.[29] While we lack studies involving ultra-low-dose pills, one would expect a similar effect.

Postpartum and lactating women. Combination pills are not the contraceptive of choice for breastfeeding mothers, as there is evidence that even low-dose formulations can decrease milk production.[33] There also is controversy over when to initiate OCs in the postpartum period among nonbreastfeeding women to avoid an increased risk of thromboembolism.[33] Theoretically, lower-dose pills would be associated with less risk. The World Health Organization (WHO) recommends that combined pills be initiated no sooner than 6 months after delivery when lactation is planned.[34]

In select patients, low-dose OCs can be initiated 6 weeks postpartum, provided the woman is breastfeeding exclusively—no bottle supplements—and both mother and infant are in good health. If the patient is not breastfeeding, OCs can be initiated as early as 2 weeks postpartum.

Although new contraceptives have been introduced—including a vaginal ring containing EE_2 and etonogestrel (3-keto-desogestrel), and a transdermal contraceptive containing EE_2 and norelgestromin (17-deacetylnorgesti-

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FIGURE 1

Selected ultra-low- and low-dose formulations

ORAL CONTRACEPTIVE	ESTROGEN		PROGESTIN		
	DOSE (µg)	CYCLE DAYS	TYPE	DOSE (µg)	CYCLE DAYS
MONOPHASICS					
Alesse, Levlite*	20	1-21	LNG	100	1-21
Loestrin 21 1/20, Loestrin Fe 1/20	20	1-21	NETA	1,000	1-21
Desogen, Ortho-Cept	30	1-21	DSG	150	1-21
Levlen, Levora, Nordette*	30	1-21	LNG	150	1-21
Loestrin 21 1.5/30, Loestrin Fe 1.5/30	30	1-21	NETA	1,500	1-21
Lo-Ovral*	30	1-21	NG	300	1-21
Yasmin	30	1-21	DRO	3,000	1-21
Brevicon, Modicon, Genora 1/35, Nelova 0.5/35E	35	1-21	NOR	500	1-21
Demulen 1/35, Zovia 1/35E	35	1-21	EDDA	1,000	1-21
Ovcon 35	35	1-21	NOR	400	1-21
Nelova 1/35E, Norinyl 1+35, Ortho-Novum 1/35	35	1-21	NOR	1,000	1-21
Ortho-Cyclen	35	1-21	NGM	250	1-21
BIPHASICS					
Mircette	20 0 10	1-21 22-23 24-28	DSG	150	1-21
TRIPHASICS					
Estrostep 21, Estrostep FE	20 30 35	1-5 6-12 13-21	NOR	1,000	1-21
Tri-Levlen, Trivora-28, Triphasil*	30 40 30	1-6 7-11 12-21	LNG	50 75 12.5	1-6 7-11 12-21
Ortho Novum7/7/7	35	1-21	NOR	500 750 1,000	1-7 8-14 15-21
Ortho Tri-Cyclen	35	1-21	NGM	180 215 250	1-7 8-15 16-21
Tri-Norinyl	35	1-21	NOR	500 1,000 500	1-7 8-16 17-21

DRO = drospirenone; DSG = desogestrel; EDDA = ethynodiol diacetate; LNG = levonorgestrel; NETA = norethindrone acetate; NG = norgestrel; NGM = norgestimate; NOR = norethindrone

*These pills can be used for the Yuzpe emergency contraceptive regimen (200 µg ethinyl estradiol + 1 mg LNG or 2 mg NG, divided in 2 and taken 12 hours apart). Only the yellow tablets of Tri-Levlen and Triphasil may be used.

mate)—no studies demonstrating their safety and efficacy in lactating women are available.

Conclusion

According to preliminary evidence, the new generation of OCs has many advantages over the higher-dose pills. Ultra-low-dose formulations are effective and generally associated with a lower incidence of estrogen-related side effects. Although more research is needed, these OCs are safe for healthy nonsmokers. However, in other populations, such as women with risk factors for coronary artery disease, they may not be advisable.

It is important to know the androgenicity of different progestins, as well as their effect on sex-hormone-binding globulin, since this is paramount to determining the amount of free, clinically significant androgen levels in the circulation.

Patients also should be counseled about the noncontraceptive benefits of OCs, including a lower incidence of ovarian and endometrial cancers, PID, and dysmenorrhea, and enhanced BMD. ■

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