OBG MANAGEMENT

Is hormonal contraception right for your perimenopausal patient?

In healthy patients, combination OCs and other hormonal methods have a lot to offer—as long as you're mindful of risks in selected subgroups.

Andrew M. Kaunitz, MD
Dr. Kaunitz is Professor and Associate Chairman, Department of Obstetrics and Gynecology, at the University of Florida College of Medicine in Jacksonville, Fla. He serves on the OBG MANAGEMENT Board of Editors.

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CASE
Perimenopausal complaints, and a request for contraception At her annual visit, M.B., a healthy 48-year-old divorced woman, reports that her periods are increasingly erratic and that she has begun experiencing occasional hot flushes. Although her previous husband had a vasectomy, she has started to date and is concerned about contraception. A close friend became pregnant at the age of 46 and chose to have an abortion. M.B. hopes to avoid the same fate and asks specifically about birth control pills. Is this an appropriate option for her? What do you tell her?

Although only 11% of women 40 to 44 years old reported using oral contraceptives (OCs) in 2002 in the United States, that figure represents a 5% increase over 1995,[1,2] and all indications are that the percentage is still rising.

In lean, nonsmoking, healthy perimenopausal women, OCs offer users not only effective contraception, but also benefits that include a reduction in heavy menstrual bleeding; regularization of the menstrual cycle; protection against ovarian, endometrial, and colorectal cancer; prevention of bone loss (with possible prevention of postmenopausal osteoporotic fractures); and some degree of relief from vasomotor symptoms. Although an increased risk of venous thromboembolism (VTE) is well documented in OC users, concerns also exist that use of the pill might increase the risk of myocardial infarction (MI), stroke, and breast cancer in older reproductive-age women.

IN THIS ARTICLE

CONTINUED

To explore the range of hormonal contraceptive options and their risks and benefits in perimenopausal women in more depth, OBG MANAGEMENT recently caught up with Andrew M. Kaunitz, MD, an expert in both contraception and menopause and a member of the OBG MANAGEMENT Board of Editors. He describes and interprets the robust data in this field to answer our many questions—although he points out that perimenopausal women have been underrepresented in studies of OC use in particular and hormonal contraception in general.

Why hormonal contraception?

OBG MANAGEMENT: *Why is effective contraception important in this age group? Aren't perimenopausal women less fertile than younger women?*

Kaunitz: Older women are less fecund, but irregular menstrual cycles make it difficult to predict when ovulation is occurring, making unplanned pregnancy a real possibility in sexually active women.

Pregnancy itself is fraught with risks in this age group. Pregnancy-related mortality among women 40 years or older in the United States is five times higher than among 25- to 29-year-olds. Older women are also more likely to have comorbidities such as hypertension and diabetes, further increasing the risks of pregnancy.[3,4] In addition, perimenopausal women are more likely than any reproductive age group except adolescents to opt for induced abortion when they do become pregnant, with 304 abortions for every 1,000 live births in women 40 years or older in the United States.[5]

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OBG MANAGEMENT: *Why should a perimenopausal woman consider hormonal contraception?*

Kaunitz: It is highly effective and offers a range of noncontraceptive benefits, and older women are more likely to use it properly, making contraceptive failure less likely than in younger patients.

Nor are combination OCs the only option for this age group. Progestin-only OCs, the levonorgestrel-releasing intrauterine system, the etonogestrel implant, and injectable depot medroxyprogesterone acetate (DMPA) are alternatives. Although the vaginal patch and ring have not been studied extensively, they may be appropriate in some instances. Until further data specific to these combination estrogen–progestin methods are available, let's assume for our discussion that they carry the same risk–benefit profile as combination OCs.

Thromboembolism is the greatest risk

OBG MANAGEMENT: *What is the greatest risk of OC use in perimenopausal women?*

Kaunitz: That would be VTE. The risk rises sharply after 39 years of age among users of combination OCs, with approximately 100 cases for every 100,000 person-years, compared with 25 cases for every 100,000 person-years among adolescents.[6] This already elevated risk almost doubles among obese women older than 39 years.[7] In these women, progestin-only or intrauterine contraceptives are better options than combination OCs.[8]

Also, avoid prescribing combination OCs for women with a known thrombophilic defect. However, because screening for thrombophilia is not cost-effective, routinely evaluating candidates for combination contraception with testing for familial thrombophilic disorders is not recommended.

OBG MANAGEMENT: *Does the dosage of estrogen determine the risk of VTE?*

Kaunitz: That is the general assumption—that higher dosages of estrogen pose a greater

risk—but we lack definitive evidence that OCs formulated with 20 µg of estrogen are any safer in this regard than those that contain 30 to 35 µg.[7,9]

There is some evidence that the progestin plays a role. OCs that contain desogestrel appear to carry almost twice the risk of VTE as those formulated with levonorgestrel or norgestimate.[10]

Risk of MI, stroke may rise in some older women

OBG MANAGEMENT: *Do perimenopausal women who take combination OCs face a heightened risk of MI or stroke?*

Kaunitz: Yes, if they smoke or have hypertension. The reason: In women who use combination OCs, smoking and hypertension are synergistic risk factors for MI and stroke. That means perimenopausal women who smoke or have high blood pressure should avoid combination contraceptives.

Although it is limited, available evidence supports the safety of OCs in older women who do not smoke or have hypertension. One large case-control study from the United States found no increased risk of MI or stroke among this population when they used OCs containing less than 50 µg of ethinyl estradiol.[11,12] However, this study included few women older than 35 years who used OCs and smoked or had hypertension.

A large, prospective study from Sweden that included 1,761 current OC users between 40 and 49 years of age found no increased risk of MI among former or current OC users.[13] It also found that the initiation of OC use in women 30 years of age or older carried no higher risk of MI than did initiation at age 29 or younger.

Avoid OCs in older women who have diabetes

OBG MANAGEMENT: *What about women 35 years of age or older who have diabetes? Is hormonal contraception appropriate for them?*

TABLE How selected health conditions affect choice of contraceptive in women ≥35 years

Condition	Recommendation*
Obesity	Avoid combination contraceptives (OCs, patch, and ring)
Smoking	
Diabetes	Progestin-only† or intrauterine contraceptives are preferred
Migraine	
Hypertension	

* Based on guidelines from the American College of Obstetricians and Gynecologists[8]
† Includes progestin-only OCs, progestin implants, depot medroxyprogesterone acetate, and copper and progestin-releasing intrauterine devices

Kaunitz: Both premenopausal and postmenopausal women who have diabetes have a higher risk of cardiovascular disease, so combination contraceptives are a bad idea when the woman has diabetes and is 35 years of age or older. OCs also should be avoided in women younger than 35 years who have diabetes, unless they are normotensive and free of nephropathy and other vascular disease. Intrauterine contraception and progestin-only formulations tend to be better options for diabetic women.

Avoid combination OCs in perimenopausal migraineurs

OBG MANAGEMENT: *Isn't there evidence that women who have migraine headaches have an elevated stroke risk? How does this affect their choice of contraceptive?*

Kaunitz: One case-control study from a large US health maintenance organization found twice the risk of stroke among OC users who had migraines as among those who did not.[12] However, this study did not distinguish between women who had migraines with aura and those who had migraines without aura.

Another study found an increased risk of stroke among OC users who had migraines with aura, but not among those who had migraines without aura.[14]

Accordingly, both the American College of Obstetricians and Gynecologists (ACOG)

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Both ACOG and the World Health Organization recommend that perimenopausal migraineurs avoid combination estrogen–progestin contraceptives

and the World Health Organization recommend that older women who experience migraines use progestin-only or intrauterine contraception.[8,15]

Does estrogen use increase the risk of breast cancer?

OBG MANAGEMENT: *It's a common assumption that hormonal contraceptives that contain estrogen increase the risk of breast cancer. Is that assumption backed by data?*

Kaunitz: Long-term use of combination estrogen–progestin menopausal hormone therapy modestly increases the risk of breast cancer. Accordingly, many clinicians and women assume that use of hormonal contraception must likewise increase risk. In fact, the evidence does not indicate that combination OCs or progestin-only contraceptives increase the risk of breast cancer. However, studies to date have involved a relatively small number of women older than 45 years.

For example, a large cohort study from the United Kingdom that involved more than 1 million person-years of follow-up found no association between use of OCs and breast cancer, even among long-term users.[16] Most cases of OC use in this study involved OCs formulated with 50 µg or more of ethinyl estradiol. However, this study did not indicate the age at which women used OCs.

In the Women's Contraceptive and Reproductive Experiences (CARE) study, current or previous users of OCs had no increased risk of invasive or in situ breast cancer, compared with never-users.[17,18] This study did include a subgroup of women who had started using OCs after age 40. Nor did the CARE study find an association between progestin-only injectable DMPA or implantable contraceptives and breast cancer.[19]

Last, a population-based case-control study in the United States found no increased risk of death from breast cancer among previous users of OCs, compared with women who had never used them.[20] This study included an analysis limited to women who had begun using OCs at 30 years of age or older.

OBG MANAGEMENT: *What about women who have a family history of breast cancer? Do OCs and other hormonal contraceptives elevate their risk further?*

Kaunitz: Women who have a family history of breast cancer are often cautioned that it would be unsafe for them to use hormonal contraception. However, use of hormonal contraception does not appear to impact the risk of breast cancer in women who have a family history of the disease.

A large prospective study from Canada involving women who had a family history of breast cancer and a mean age of 49 found no increased risk of breast cancer among former or current OC users.[21] This study did not assess risk by *BRCA* mutation status.

A separate study found that the risk of breast cancer increased slightly among women who had a *BRCA1* mutation, with an odds ratio of 1.20 (95% confidence interval, 1.02–1.40), but not among women who had a *BRCA2* mutation.[22] Another study found no significant increase in the risk of breast cancer among women who had either a *BRCA1* or *BRCA2* mutation.[23]

Benefits include improved bleeding patterns

OBG MANAGEMENT: *Many perimenopausal women who have fibroids or adenomyosis experience menorrhagia or dysfunctional uterine bleeding (DUB) and opt for surgery such as endometrial ablation or hysterectomy. Can OCs or other hormonal contraceptives alleviate these patterns without the need for surgery?*

Kaunitz: Yes. OCs can restore physiologic bleeding in older women who have DUB. One study involving women 15 to 50 years of age who had DUB found improved bleeding patterns in more than 80% of women randomized to OCs, compared with less than

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OCs can restore physiologic bleeding patterns in older women who have dysfunctional uterine bleeding

50% of women randomized to placebo.[24] In addition, women who have menorrhagia have reported a significant reduction of blood loss after using OCs.[25]

Another effective option for women who have menorrhagia is the levonorgestrel-releasing intrauterine system (LNG-IUS), even in women who have menorrhagia associated with fibroids and adenomyosis.[26–28]

Because long-term use of injectable forms of contraception tends to lead to amenorrhea, some physicians recommend DMPA as a treatment for menorrhagia. Data supporting this strategy are scant, however.[29]

OCs reduce the risk of three cancers

OBG MANAGEMENT: *Oral contraceptives are known to reduce the risk of ovarian, endometrial, and colorectal cancer to varying degrees. Does this benefit hold up for older women, too?*

Kaunitz: Yes. And because the incidence of ovarian cancer, in particular, increases with age, the protection afforded by combination OCs may be especially beneficial for women of older reproductive age.

OBG MANAGEMENT: *Just how much protection against ovarian cancer does OC use afford?*

Kaunitz: Among users of low-dose combination OCs, the risk of epithelial ovarian cancer declines by at least 50%, compared with women who have never used the pill—and, the longer the use, the greater the protection.[16,30,31] Once OCs are discontinued, the protection diminishes over time, but some degree of reduced risk persists for three decades or longer.[31]

OBG MANAGEMENT: *What about endometrial cancer?*

Kaunitz: Not just OCs, but also DMPA, are associated with a significant reduction in the risk of endometrial cancer: 50% with use of OCs formulated with 30 µg or more of estrogen, and 80% with use of DMPA. In the case of OCs, the reduced risk is greater with longer use, and it persists after discontinuation for at least 20 years.[25,32]

OBG MANAGEMENT: *Is the protection against colorectal cancer as great as the protection against these other cancers?*

Kaunitz: No, it isn't, but the protection is still significant. OC use reduces the risk of colorectal cancer by approximately 20%, but the protection against colorectal cancer does not appear to increase with duration of use.[16,33] It also may be that more recent OC use (past 5 years) affords greater protection than use in the more distant past.[16,33]

OCs may reduce fracture risk postmenopausally

OBG MANAGEMENT: *What effect do combination OCs and other forms of hormonal contraception have on the bone loss that accelerates around the time of menopause?*

Kaunitz: One randomized trial found that OC use increases bone mineral density (BMD) in women of older reproductive age.[34] And a population-based, case-control trial from Sweden found a 25% reduction in the risk of hip fracture among postmenopausal women who had a history of OC use. The reduction in risk was even greater when the women had used OCs in their 40s or for an extended duration.[35]

The Women's Health Initiative found no reduction in the risk of fracture among previous users of OCs, but failed to stratify women by the age at which they used OCs.

OBG MANAGEMENT: *Are any hormonal contraceptives associated with bone loss?*

Kaunitz: Yes. Use of intramuscular DMPA (150 mg) or subcutaneous DMPA (104 mg) is linked to a loss of BMD. The good news

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is that BMD recovers after discontinuation of the drug, even in women who begin to use it after 40 years of age.[29,36] However, we lack data on the risk of fracture among postmenopausal women with a history of DMPA use.

OCs may ease hot flushes and other menopausal symptoms

OBG MANAGEMENT: *Is there any evidence that use of combination OCs by perimenopausal women relieves vasomotor symptoms?*

Kaunitz: Yes, but the number of studies demonstrating this association so far has been limited. One small double-blind trial randomly assigned women to use of an OC containing 20 µg of estradiol or to placebo.[37] Although the number and severity of symptoms diminished by about 50% in those taking the OC, the difference was not statistically significant.

A prospective observational study found that 90% of perimenopausal women experienced complete relief after taking an OC containing 30 µg of ethinyl estradiol, compared with only 40% of nonusers.[38]

OBG MANAGEMENT: *What about other forms of hormonal contraception? Are any effective against vasomotor symptoms?*

Kaunitz: One interesting option is to use menopausal doses of estrogen to treat vasomotor symptoms along with an LNG-IUS to prevent endometrial hyperplasia and provide contraception, if needed. This combination produced substantial improvement in a trial involving perimenopausal women who were experiencing vasomotor symptoms.[39] Most of the women became amenorrheic, and there was no endometrial hyperplasia.

DMPA in contraceptive dosages also has relieved vasomotor symptoms in menopausal women, compared with placebo.[40]

OBG MANAGEMENT: *What about women who experience vasomotor symptoms during the 7 placebo days of a 28-pill cycle? What options do they have?*

Kaunitz: Some physicians either switch to a 24/4 OC formulation (Yaz or Lo-Estrin 24), an extended OC formulation with no placebo days (Seasonique), a continuous OC formulation (Lybrel), or simply prescribe pills from a traditional 21/7 pack in a continuous fashion so as to eliminate the hormone-free interval. However, this strategy has been studied to only a limited degree.

At what age should an OC be discontinued?

OBG MANAGEMENT: *Perimenopausal women are, obviously, going to become menopausal at some point. How do you know when that transition occurs if they are taking OCs?*

Kaunitz: It turns out that testing is not useful in this clinical setting. Some people have advocated measuring the follicle-stimulating hormone (FSH) level, but this strategy is unreliable. An elevated FSH level—thought to be indicative of menopause—has been found in older ovulatory women,[41] and a depressed FSH level has been found in postmenopausal women for weeks after discontinuation of OCs.[42]

Rather than use this imperfect science to try and predict the point of menopause, I recommend discontinuing OCs once the woman has attained age 55, arbitrarily assuming that she is menopausal at this age. I use the same approach for women using other hormonal contraceptives.[8,43]

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DMPA in contraceptive dosages has relieved vasomotor symptoms in menopausal women

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