Transitional Management: The Use of Oral Contraceptives in Perimenopause

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A number of perimenopausal women and their health care providers choose to either decline or prematurely discontinue use of oral contraceptives (OCs), despite the availability of formulations that can prevent pregnancy and address perimenopausal symptoms. This lack of use is due to several factors. First, many women erroneously believe that irregular menses signal the end of fertility, obviating the need for contraception. Second, although OCs may be used safely by healthy nonsmoking women until their mid-50s, many are afraid to use OCs after age 35. They may associate OC use at older ages with increased risk of cardiovascular disease (CVD)--or mistakenly fear that OCs can cause breast cancer or weight gain. The result of these misperceptions is many perimenopausal women needlessly experience vasomotor symptoms and irregular bleeding. Furthermore, these patients deny themselves highly effective protection against pregnancy and future health risks. This article discusses the use of OCs during perimenopause to provide for a healthy transition to the permanent cessation of menses.

what is PERIMENOPAUSE?

Perimenopause is a time of transition, characterized by unstable endocrine physiology and highly variable (and often unpredictable) hormone profiles. It is marked by menstrual, ovarian, and hypothalamic-pituitary changes that include shortened cycle length and irregular, unpredictable menses. During this time, women may also experience breast tenderness (at times of high ovarian hormone production), vasomotor symptoms (when background estrogen levels are low), and emotional liability. On average, perimenopausal symptoms tend to begin affecting women in their mid-40s--about 5 years before the cessation of menses. Women with a history of heavy smoking often experience perimenopausal symptoms earlier than do nonsmoking women; some panel members report that current or past heavy smokers often present in their late 30s with classic perimenopausal symptoms. Although menstrual cycle length begins to shorten during perimenopause, the potential for ovulation and pregnancy persists for a number of years.

OC UNDERUTILIZATION

Use of OCs decreases dramatically as women reach age 40. Whereas 21% of women aged 35 to 39 years use OCs, only 11% of women aged 40 to 44 and 4% of those aged 45 to 50 take them. Several factors contribute to the significant decrease in utilization of OCs in women over age 40.

Ovulation Changes
The menstrual irregularities of perimenopause often lead women to believe that their fertility has ceased; consequently, they stop using contraception. However, although ovulation is unpredictable and less frequent during perimenopause, the potential for conception is present, and contraception is still necessary to prevent unintended pregnancy.

Vascular Issues
These women may remember the vascular risk associated with early high-dose OCs (i.e., >50 µg estrogen), and may therefore believe that OC use in older reproductive-age women can lead to
vascular mortality—particularly stroke, myocardial infarction, and deep-vein thrombosis. However, detailed epidemiologic assessments and low-estrogen formulations (i.e., 250 µg estrogen) indicate that the arterial disease associated with OCs accretes primarily to women over age 35 who smoke.

**Patient Concerns**

Fear of cancer may deter older reproductive-age women from using OCs—despite evidence that OCs can significantly reduce the long-term risk of endometrial and ovarian cancer. A growing body of data indicates that OCs may actually help to protect women against colorectal cancer. In addition, no significant or overwhelming evidence exists that OC use in this age group increases a woman’s long-term risk of breast cancer—even in high-risk women with a positive family history or prolonged duration of use.

**Body Weight**

The widespread notion that OCs cause weight gain is another concern among American women. Patients should be informed of a recent placebo-controlled trial that provided high-quality evidence that use of a low-dose OC containing norgestimate does not cause weight gain.

**NONCONTRACEPTIVE BENEFITS**

In addition to the therapeutic use of OCs in the treatment of abnormal menstrual bleeding and vasomotor instability, OCs offer long-term benefits for general health.

**Cancer Risk Reduction**

The risks of endometrial and ovarian cancer decrease with OC use in a duration-dependent manner; such protection has been documented for 10 to 30 years after cessation of OC use. Thus, perimenopausal use of OCs can provide postmenopausal protection against these malignancies for women into their 60s and 70s.

**Bone Health**

One noncontraceptive benefit associated with OC use that is of particular interest to perimenopausal women is preservation of bone mineral density (BMD). BMD peaks between the ages of 20 and 40 years, followed by an age-associated loss of approximately 1% per year, so that most women at menopause are 10% to 12% below their peak BMD. The rate of bone loss can accelerate during perimenopause, potentially lowering the threshold for fracture risk. Hip fractures play a major role in morbidity and mortality in women aged 75 years or older. Many patients are unaware that about 20% of elderly women with hip fractures die within 1 year postfracture. The protective effect of OCs on BMD is strongly dependent on the age at initiation of OC use, as well as on duration of use. However, a recent Swedish case-control study showed that any OC use by women in their 40s reduced the risk of postmenopausal hip fracture by 30% compared with never-users. In a meta-analysis of 13 studies of low-dose OC use and BMD, 9 showed a positive effect of OC use on BMD, and 4 did not show an association. None of the studies showed a decrease in BMD with OC use. The effect of estrogens on bone mass is dose related; the optimum dose may be 25-35 µg of ethinyl estradiol (EE) or its equivalent.

**TREATING PERIMENOPAUSAL SYMPTOMS**

**Menstrual Problems**

OCs can also be used to treat abnormal perimenopausal menstrual bleeding. Anovulation, which increases in frequency as women age, can manifest as dysfunctional uterine bleeding (DUB) that includes menorrhagia, metrorrhagia, menometrorrhagia, and polymenorrhea. The first and only reported randomized, placebo-controlled trial of an OC in the treatment of anovulatory DUB showed that patients taking the triphasic OC norgestimate/35 µg EE had significantly fewer abnormal bleeding patterns compared with placebo. This OC formulation can therefore serve as an appropriate first-line therapy in the treatment of primary dysmenorrhea, menorrhagia, and anovulatory bleeding in perimenopause—regardless of whether contraception is desired.

**Vasomotor Instability**

A hallmark of perimenopause, this is manifested as daytime hot flashes and nighttime sweats—frequently accompanied by heart palpitations, anxiety, stiffness, and nausea. The physiologic mechanism for vasomotor instability in perimenopausal women is thought to be an abnormality in the body's "set point" for cooling. A recent randomized, placebo-controlled trial evaluated the effect of a norethindrone acetate/20 µg EE on hot flashes in symptomatic perimenopausal women. This study showed an approximate 50% reduction in the number and severity of hot flashes with the OC as compared with placebo. Given this significant symptom relief, perimenopausal women experiencing vasomotor symptoms may elect to use this therapeutic intervention.
Table 1 summarizes the benefits of OC use that are of particular interest to perimenopausal women. Included in this summary is the treatment of acne, the only noncontraceptive indication listed in any OC prescribing information.

<table>
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<th>Benefits of OC Use in Perimenopause</th>
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<tr>
<td>Effective contraception (if needed)</td>
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<tr>
<td>Regulation of menses*</td>
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<tr>
<td>Preservation of BMD/reduced fracture risk later in life</td>
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<tr>
<td>Treatment of DUB, menorrhagia, and/or dysmenorrhea*</td>
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<tr>
<td>Prevention of endometrial hyperplasia</td>
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<td>Reduction in vasomotor symptoms*</td>
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<td>Prevention of ovarian and endometrial cancer</td>
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<td>Protection against colorectal cancer</td>
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<td>Treatment of acne</td>
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OC = oral contraceptive; BMD = bone mineral density; DUB = dysfunctional uterine bleeding.

*These indications represent off-label uses of OCs. Only the triphasic norgestimate/35-µg ethinyl estradiol OC is approved by the Food and Drug Administration for treatment of moderate acne.

EVALUATION & MANAGEMENT

Disease Screening
As women enter the perimenopausal years, they become more receptive to health strategies focused on disease prevention. Preservation of BMD during perimenopause can reduce the risk of osteoporotic fractures later in life. Due to the risk of declining BMD during perimenopause, there is a role for selective bone density evaluation and calcium supplementation. Smoking cessation counseling should be offered to all women who smoke, and, if needed, lifestyle changes in diet and exercise should be recommended to reduce CVD risk. The American College of Obstetrics and Gynecology (ACOG) states that regular cholesterol screening is appropriate in perimenopausal women. Many clinicians find that fasting lipid panels (which include lipoprotein and triglyceride levels) are more useful than total cholesterol assessment.

Because various professional societies have different recommendations for cancer screening, clinicians should use their clinical experience and evaluation of the literature to determine appropriate cytology screening schedules for perimenopausal women. The position taken by ACOG is that after three consecutive normal papanicolaou tests in a low-risk patient, clinicians may use their discretion to determine when cervical cytology is needed again. Mammography screening for breast cancer should be performed every 1 to 2 years between ages 40 and 50; thereafter, it should be performed annually. Colorectal cancer is the third most common malignancy in both women and men, and risk increases with age. Fecal occult blood testing is appropriate for perimenopausal women. For women aged 50 or older, sigmoidoscopy or colonoscopy for colon cancer screening is appropriate. With regard to endometrial cancer, abnormal menstrual bleeding is common in perimenopausal women, and ACOG guidelines support office endometrial sampling to rule out hyperplasia.

Transition to Hormone Replacement
OCs can play an important role in the management of symptoms related to perimenopause; many women in their late 40s and early 50s experience a number of contraceptive and noncontraceptive benefits with OC use. In the past, to determine when a woman using OCs had reached menopause and the use of OCs was no longer necessary, the level of follicle-stimulating hormone (FSH) was assayed during the pill-free interval. It is accepted that evaluation of FSH levels during perimenopause is undependable as a means of evaluating ovulation. If a woman is satisfied with the OC she is using, it is safe and appropriate to continue use until her mid-50s--when her risk of ovulation and conception is very low--and then make a seamless transition to hormone replacement therapy (HRT). With the availability of new HRT regimens, women doing well on combination OCs can switch to HRT using the same progestin.

Complementary and Alternative Medicines
Patients may inquire about, or use, complementary or alternative medicines to manage perimenopausal or menopausal symptoms. These interventions include vitamins, herbs, botanicals, and amino acids. Despite the lack of sufficient studies to support the use of such over-the-counter (OTC) products, they are often marketed without clinical trials or review by the US Food and Drug
Administer (FDA).

Nonprescription alternative and botanical products that have some documented success in the treatment of vasomotor symptoms include soy protein isoflavones, isoflavone isolates, black cohosh, topical progesterone cream, and vitamin E. Botanicals with no proven therapeutic effect include evening primrose oil, dong quai, and ginseng.

Nonprescription alternatives and botanicals that patients may use to treat perimenopausal depression, mood disorders, and affective symptoms include St John's wort, kava kava, inositol, vitamin B6, and ginseng. There have been recent reports that St John's wort can have multiple drug-herb interactions due to its effects on the cytochrome P450 system. These interactions could extend to a reduction in the efficacy of OCs by decreasing therapeutic levels of serum steroids. Although some OTC remedies do address somatic menopausal complaints and may be appropriate for some women, no one alternative to estrogen offers as many noncontraceptive benefits as OC use or has been shown to effectively reduce the long-term risks associated with estrogen deficiency.

Women considering the use of OTC products, particularly herbs and botanicals, should be aware of the dearth of hard data to substantiate many of the claims made. Few studies have been performed to demonstrate safety and efficacy. There is also a lack of standardization with regard to dose and content; therefore, consistency within these formulations is not ensured. Although some agents have been determined by the FDA to be safe and efficacious for certain disease states, this judgment has not been made regarding the treatment of perimenopausal symptoms. Thus, these agents are considered experimental in this setting.

Other Agents

Some prescription medications are also used in the treatment of perimenopausal symptoms. Nonsteroidal prescription agents used to treat vasomotor instability include clonidine; a combination of belladonna alkaloids, ergotamine tartrate, and phenobarbital (Bellaregal®); veralipride (a substituted benzamide not available in the United States); paroxetine hydrochloride; and venlafaxine. Review of data concerning these products has shown that all these products reduce symptoms of vasomotor instability to varying degrees.

Education and Counseling

When counseling women concerning the use of OCs during perimenopause, it is best to use open-ended questions to elicit attitudes toward OCs; then counseling can be tailored to the patient's individual concerns, baseline knowledge, and cultural perspective. Counseling should occur in a calm and private environment (preferably not the examination room), and the focus should be limited to a few high-priority "take-home" messages. For women who are appropriate candidates for OC use during perimenopause, some specific messages that may facilitate treatment are shown in Table 2.

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CONCLUSION

Perimenopause is marked by a number of menstrual, ovarian, and hypothalamic-pituitary changes. The resulting symptoms--including menstrual irregularities--can negatively affect a woman's life. At the same time, perimenopausal women may still be at risk for unintended pregnancy, as many may not realize that they retain fertility until menopause.

To maximize long-term health in perimenopausal women, it is important for clinicians to address smoking cessation, cancer screening, cholesterol screening, and bone loss prevention measures. Perimenopausal women also should be counseled about the vasomotor symptoms, bleeding irregularities, and conception risk that may accompany this life stage. Women should be informed that OC use until menopause or the mid-50s is both safe for healthy, nonsmoking women and effective in easing perimenopausal symptoms. OC use during perimenopause can also help reduce the risks of bone density loss and future fractures, endometrial cancer, ovarian cancer, and
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By extending their use of OCs until they switch to HRT, most women can enjoy improved health outcomes throughout their reproductive life cycle and beyond. Use of OCs during perimenopause offers both contraceptive and noncontraceptive benefits; this approach represents a safe and appropriate therapy for the majority of women during these transitional years.

References:
23. Castracane VD, Gimpel T, Goldzieher JW. When is it safe to switch from oral contraceptives to colorectal cancer later in life.

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