

A Supplement to

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CME ACTIVITY

## Oral Contraceptives: Beyond Contraception



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## Educational Medium

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This educational activity has been developed as a print-based monograph for physicians and nurse practitioners. To participate, the clinician will read the articles in the monograph and complete the post-activity test. The estimated completion time for this activity is 2 hours.

## Intended Audience

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The intended audience is obstetricians/gynecologists, reproductive endocrinologists, and physicians whose practice includes a focus in women's health care, and nurse practitioners.

## Physicians' Accreditation Statement

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This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of The Endocrine Society and National Association of Nurse Practitioners in Women's Health. The Endocrine Society is accredited by the ACCME to provide continuing medical education for physicians.

The Endocrine Society designates this educational activity for up to 2 hours in category 1 credit towards the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

## Nurse Practitioners' Accreditation Statement

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Sponsored by the National Association of Nurse Practitioners in Women's Health (NPWH). This program was reviewed by the Continuing Education Committee of NPWH. This activity has been approved by the Continuing Education Approval Program of the National Association of Nurse Practitioners in Women's Health for 2.4 CEUs.

*Instructions:* Nurse practitioners may complete this test for 2.4 CEUs. The questions are based on the clinical articles included in this supplement to *Contemporary OB/GYN*. A CE certificate and correct answers will be provided by NPWH 6 to 8 weeks following receipt of the completed test.

Read the articles carefully. Do not neglect the tables, as they have been selected to enhance your knowledge and understanding. The Post-test questions have been designed to provide a useful link between the articles in this issue and your everyday practice. Read each question, choose the single best answer, and record your answer on the Post-test answer sheet which appears at the end of the Post-test. Retain a copy of your answers so that they can be compared with the correct answers that will be sent to you later.

## Supporter

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This educational activity is supported by an unrestricted educational grant from Wyeth-Ayerst.

## Date of Release

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This educational activity was completed and released on 02/01/2001. Request for CME and CE credit will be accepted until 02/01/2002.

## Representation

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The information presented in this monograph is that of the authors and does not necessarily represent the views, and is independent of, The Endocrine Society and NPWH.

## Disclosure

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# Foreword



Paula J. Adams Hillard, MD

Clinicians have been aware of the noncontraceptive health benefits of oral contraceptives for many years. These have been considered a secondary benefit for individuals who take OCs primarily for contraception. Many women, too, know—often because they have been told by friends or read in magazines—that OCs provide cycle-related benefits, including regular menses, decreased menstrual flow, and relief of dysmenorrhea.

Awareness of other desirable noncontraceptive effects generally has been low, however, even among well-educated people, although two recent polls suggest that women are starting to rely more on the Pill for its health benefits. In a Gallup survey sponsored by the American College of Obstetricians and Gynecologists and conducted in April 2000, 48% of women said that there are noncontraceptive health benefits to Pill use, an increase from 42% in 1993. Yet, about one in three women (32%) still does not think there are any such effects.<sup>1</sup>

Direct-to-consumer advertising has made the public aware that the Pill is a treatment for acne. In fact, relief of acne and menstrual regulation were the most frequently cited noncontraceptive benefits in the recent ACOG-Gallup poll. It has become more acceptable to prescribe OCs as treatment, even for women who do not need contraception. This gives us a new opportunity to educate our patients about the preventive and therapeutic effects of OCs.

Many of these benefits are particularly relevant during the adolescent years and for women who are in their mid-30s or older. Most of the benefits apply to women of all reproductive ages, although this supplement will focus on people at the two "bookends" of reproductive life—adolescents and women over age 30.

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1. ACOG Office of Communications. The Pill at 40: Women say it's safer, has extra benefits but not covered by insurance. 2000. Washington, DC, ACOG. ACOG News Release, May 2, 2000.

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## Learning Objectives

At the conclusion of this activity, the clinician will:

- Review the current knowledge on the noncontraceptive benefits of oral contraceptives
- Obtain an understanding of the benefits for women in their teens and 20s, such as improved menstrual regularity and decreased acne.
- Obtain an understanding of the benefits for women after age 35, such as reduction in perimenopausal bleeding.

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# Adolescents and the noncontraceptive benefits of the Pill

By Paula J. Adams Hillard, MD

*Adolescents are becoming more aware that birth control pills have benefits beyond contraception. Some of this awareness has been fostered by recent print and TV ads: You have probably encountered teens who request the “acne pill.” While the information provided in these advertisements may be less than complete, they have at least served to increase knowledge of one noncontraceptive benefit.*

Clinicians have known for many years that oral contraceptives have many noncontraceptive benefits and therapeutic indications (Table 1). However, several studies have highlighted the lack of awareness of these benefits among the general public. A study by Peipert and associates found that fewer than 20% of students and staff at Yale University were aware that the Pill reduces the risk of ovarian and endometrial cancer, anemia, ectopic pregnancy, benign breast disease, pelvic inflammatory disease (PID), and ovarian cysts.<sup>1</sup> Awareness was highest for dysmenorrhea: 75% had heard that the Pill can help control this symptom. I will start by reviewing the role of OCs in managing this com-

mon adolescent complaint, then discuss other problems that can be prevented or alleviated with these medications.

Not all these indications have been approved by the FDA. The FDA has indicated that “The Food, Drug, and Cosmetic Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens that are not included in approved labeling. Such ‘unapproved’ or, more precisely, ‘unlabeled’ uses may be appropriate and rational.... Accepted medical practice often includes drug use that is not reflected in approved drug labeling.”<sup>2</sup> In the past, the FDA endeavored to restrict

the dissemination of information by pharmaceutical companies on off-label uses of drugs. Whatever the outcome of litigation surrounding this issue, it will not affect the use of a medication for appropriate off-label indications. In fact, the Detailed Patient Labeling included with OCs specifically states the health benefits of oral pills.<sup>3</sup> The clinician, however, must always assess the risk-benefit ratio for each individual adolescent.

Use of OCs as therapy other than for contraception may or may not be covered by insurance policies. If it is not, this may create a financial hardship for some adolescents and their families. The issue of coverage for OCs prescribed for any indication has been brought to public and legislative attention. The Equity in Prescription Insurance and Contraceptive Coverage Act (S1200, HR2120) was introduced in both houses of Congress

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in 1999, and would require all health plans that offer coverage of prescription drugs, devices, and outpatient services to also cover the FDA-approved forms of prescription contraceptives, devices, or outpatient services.<sup>4</sup>

### Easing menstrual pain

As many as 80% of adolescents experience dysmenorrhea; it disrupts daily activities and causes absenteeism from school or work for one quarter to one half of this age group. The etiology of primary dysmenorrhea is prostaglandin-mediated, with elevated levels of prostaglandins found in the menstrual fluid and endometrium of women who experience dysmenorrhea. The prostaglandin-induced uterine contractions result in pain that generally correlates with increases in intrauterine pressure. OCs inhibit ovulation, preventing progesterone-stimulated endometrial prostaglandin production. In addition, reduced endometrial growth produces less menstrual flow with smaller amounts of prostaglandins. Thus OCs are extremely effective in treating primary dysmenorrhea and should be utilized when primary treatment with nonsteroidal anti-inflammatory drugs is ineffective or provides only partial relief. While this noncontraceptive indication is not FDA-approved, relief of dysmenorrhea is well-demonstrated in the literature.

Because adolescents often *are* aware of the benefit that OCs provide in relieving dysmenorrhea, some teens may use this knowledge as a “ticket” to see a health professional, with the real, unstated agenda being the need for contraception. Other teens, especially younger teens, may be so frightened about a visit to a gynecologist that they endure very significant pain and disruption of

TABLE 1

### Noncontraceptive benefits of OCs for women <30

#### Therapeutic

Dysmenorrhea (cycle-related pain, mittelschmerz, menstrual molimina)  
Menorrhagia  
Irregular menses  
PCOS/hyperandrogenism  
Acne  
PMS  
Hypogestrogenism (female athlete triad, hypothalamic amenorrhea)  
Ovarian failure (surgical, caused by chemotherapy)  
Amenorrhea induction (von Willebrand's disease, chemotherapy, bone marrow transplantation)

#### Risk reduction

Anemia  
Pelvic inflammatory disease  
Ectopic pregnancy  
Benign breast disease  
Ovarian cysts  
Ovarian and endometrial cancer

their lives before they will consent to a visit. While the FDA has supported the concept that the pelvic examination may be postponed and OCs prescribed without one if the patient requests this and the clinician believes that it is good medical practice, most adolescents do not know they may have such an option.<sup>3</sup> Deferral of the exam is intended to provide greater access to contraception for sexually active teens, but the clinician should also assess the likelihood of significant physical findings. Primary dysmenorrhea is a diagnosis of exclusion, but few other medical conditions are likely in an adolescent who has a classic history of midline lower abdominal cramping with an onset within the first 1 to 2 years after menarche. A pelvic ultrasound can exclude significant anatomic abnormalities, such as a rare müllerian abnormality. In short, the pelvic examination may be postponed if the teen is not sexually active, if there is no family history of endometriosis, and if

the history is typical, particularly if there are associated menstrual molimina.

### Perimenstrual symptoms

Menstrual molimina are frequent in adolescents with primary dysmenorrhea, and may include irritability, headache, breast tenderness, nausea and vomiting, bowel changes/diarrhea/loose stools, and bloating. Younger women may be more likely to experience these symptoms than women over 30.<sup>5</sup>

Some of the symptoms are prostaglandin-mediated, and others are associated with cyclic hormonal fluctuations. OCs can help with many of these symptoms. Adolescents with severe menstrual or cycle-related complaints may note significant improvement in their quality of life with the use of OCs. Because OCs inhibit ovulation, adolescents with significant pain around the time of ovulation (mittelschmerz) can also benefit from their use. The Pill can even be used for a therapeutic trial when it is

TABLE 2

**Facilitating communication about OCs**

Before you provide a prescription for OCs to an adolescent, give her information that fosters correct use of the Pill. Here are some suggestions for fostering a meaningful discussion:

- Ask the teen what the worst thing is that she has heard about birth control pills.
- Provide her with information about the temporary nature of breast tenderness and bloating and reassure her that 70% to 80% of women do not have this problem. Even if she experiences it during the first cycle, the discomfort likely will ease after two to three cycles.
- Remind the teen not to stop taking Pills without calling your office.
- Communicate the message that if side effects are a problem, she can be switched to another pill; there are about 30 different kinds on the market.
- Instruct the teen to start taking her Pills on the first day of her period and to take one every day at the same time. It may be helpful to put them next to her toothbrush or alarm clock as a reminder.
- Emphasize that if she misses a Pill, she must take it as soon as she notices the slipup.
- Tell the teen that if she runs out of Pills before her next appointment, she can phone your office for a refill.

unclear whether the etiology of pelvic pain is gynecologic or gastrointestinal.<sup>6</sup> Women with dysmenorrhea and cyclic pelvic pain usually respond well to such a trial, while those with cramping that is gastrointestinal in origin do not. Some individuals, particularly adolescents in their early teens who are of a young “gynecologic age” and are just learning to interpret the signs and symptoms of their cycles, are unable to make this distinction.

In addition, unless the young woman herself, her mother, or her physician considers the possibility of gynecologic or cycle-related pain, the timing of the symptoms may initially appear to be random, particularly when the cycles are irregular, the teen does not keep track of her menses, or does not mention that she is menstruating at the time of the onset of pain. This scenario is clinically a very common one; prospective charting of menses and episodes of pain on a “menstrual calendar” will help to show the cyclic association of

pain with menses or ovulation.

Parents frequently complain about mood changes in adolescents; in girls, it is easy to automatically attribute these to premenstrual syndrome (PMS). Mood lability is frequent during adolescence, and the etiologies need to be explored. Developmental issues, including adolescents striving for independence from parents, struggles for control, exploration and testing of limits, feelings of invulnerability, testing relationships, and developing intimacy with a partner, all contribute to the fluctuations in mood that characterize the teenage years.

True clinical depression can occur in teens, with a resultant increased risk for suicide,<sup>7</sup> and an assessment for the problem needs to be done. According to data from the CDC, nearly 1 of every 4 high school girls has seriously considered suicide and 11% have attempted it.<sup>8</sup> Thus, do not attribute mood changes to PMS until you obtain additional history and

determine a teen's risk of suicide by asking her specific questions. Some studies have shown significant improvement in some PMS symptoms in women taking OCs, while others have been less conclusive; the effects may depend on which symptoms (somatic versus mood) are investigated and how.<sup>9,10</sup>

Data do not support the concept that menstrual cycles are typically chaotically irregular, with no pattern whatsoever, during the first 1 to 2 years after menarche. While many cycles in early adolescence are anovulatory, most girls have cycles that fall roughly within the parameters of 21 to 45 days.<sup>11-13</sup> Adolescents whose menstrual cycles often fall outside these parameters should be evaluated for hyperandrogenism/polycystic ovary syndrome (PCOS), eating disorders, and thyroid dysfunction, all of which can cause irregular bleeding. While each of these conditions has many associated medical and psychological ramifications, OCs can be an adjunct to or a mainstay of therapy.<sup>14,15</sup>

**OCs for acne**

About 85% of individuals younger than 25 have significant acne and they make 4.5 million visits to physicians every year for this condition.<sup>16</sup> Acne is not a trivial concern for adolescents; it affects self-esteem and may lead to feelings of social inadequacy, anxiety, or depression. While a number of therapeutic options exist, from topical to systemic medications, recent data have focused on the benefits of OCs for acne that has not responded to these first-line therapies (see “OCs and acne: new findings,” page 7).<sup>17,18</sup>

Treatment with OCs results in suppression of ovarian and adrenal androgen secretion, increased levels of sex hormone-binding globulin (SHBG), and decreased

5 $\alpha$ -reductase activity at the level of the pilosebaceous unit.<sup>17</sup> These changes reduce free testosterone. In 70% to 90% of patients, acne improves.<sup>18,19</sup>

Recent studies have shown that various progestins may have different effects on the mechanisms and markers of androgenicity—a greater or lesser effect on SHBG and a greater or lesser effect on ovarian androgen secretion. The beneficial effect on acne, however, appears well established.<sup>20,21</sup> Low-dose OCs may also offer such benefits. Thus, one can reach the conclusion that most different formulations of OCs result in improved acne for most women.

### **Anemia and other conditions**

OCs very clearly result in decreased menstrual flow, decreased duration of flow, and thus a lower risk of iron deficiency anemia.<sup>22</sup> On this count alone, OCs have the potential to improve health across the world, particularly for very young women.<sup>23</sup>

In adolescents with severe menorrhagia, the possibility of a hereditary bleeding disorder such as von Willebrand's disease should be considered, particularly when an adolescent presents with severe bleeding at menarche.<sup>24</sup> Those with irregular, anovulatory bleeding may present with menometrorrhagia. In these cases, use of OCs will clearly result in regular cycles with decreased flow. Some of these adolescents will have abnormal bleeding due to immaturity of the hypothalamic-pituitary-ovarian axis, while others may have early manifestations of hyperandrogenism or other endocrinologic disease.<sup>25</sup> These conditions should be ruled out prior to the initiation of OCs.

OC therapy will lead to increased clotting factors in teens with coagulopathies, normalization of the

### **OCs and acne: new findings**

A birth control pill containing levonorgestrel and 20- $\mu$ g ethinyl estradiol (EE) reduced acne by almost 30% and inflammatory lesions by about 40% after six cycles, in a recent placebo-controlled trial. The study included 371 women, age 14 and older, with moderate facial acne.

These findings were described by Ken Washenik, MD, PhD, of New York University School of Medicine, NY, at an industry-supported symposium at the American Society for Reproductive Medicine's annual meeting in October 2000. According to the assessments of both clinicians and patients, the OC is significantly more effective against acne than placebo, Dr. Washenik concluded.

The side effects that cause many women to discontinue taking birth control pills can be reduced by lowering the estrogen dose, David F. Archer, MD, Eastern Virginia Medical School, Norfolk, Va., reported at the same symposium. In particular, the common perception that the Pill causes women to gain weight was not borne out in a trial that compared an OC containing 20- $\mu$ g EE with placebo: Mean weight change was the same in the treatment and placebo groups.

Moreover, data do not support the idea that 20- $\mu$ g EE preparations cause more breast tenderness and bleeding than higher-estrogen OCs, Dr. Archer said. He also pointed out that the contraceptive efficacy of low-estrogen pills appears to be just as good.

androgen excess associated with PCOS, and suppression of FSH and LH. Once samples have been drawn to establish or rule out these diagnoses, OCs may be initiated, pending the results of lab testing. Individuals with von Willebrand's disease or PCOS will benefit from ongoing use of OCs. If there are no contraindications, these young women may benefit from continuing to take OCs possibly until they reach menopause, with drug "holidays" only for conception. This aspect of the therapy, as well as issues of daily adherence and correct Pill use, need to be thoroughly discussed with an adolescent and her parent(s).

### **Treatment of hypoestrogenism**

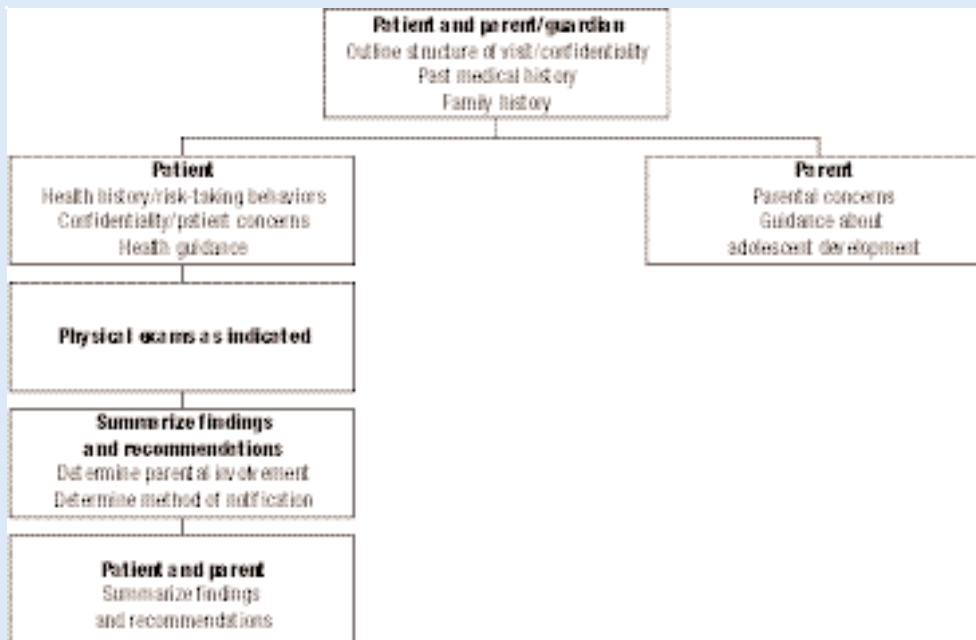
A number of conditions and causes are associated with hypoestro-

genism in adolescence. Adolescents with eating disorders, the female athlete triad (disordered eating, amenorrhea, and osteopenia), hypothalamic amenorrhea, and ovarian failure due to previous surgery or chemotherapy may require hormone replacement therapy (HRT).<sup>26</sup> In teens, low-dose OCs may be preferable to HRT for these indications.

Of primary concern is the fact that hypoestrogenism impairs bone accretion and the attainment of peak bone mass. Data on the efficacy of OCs in correcting this effect in adolescents, however, are controversial.<sup>15</sup> Most of the studies assessing an association between bone mass and OCs have been in women beyond adolescence. While not all these studies show a positive effect, none has shown a decrease in bone mass.<sup>27</sup>

FIGURE 1

Plan for adolescent gynecologic visit



Effects on bone mass may vary by OC formulation, and may be related to the doses and proportions of the estrogen and progestin components.<sup>28</sup> Nonetheless, the potential benefits of estrogen replacement and the low risks of OCs in most otherwise-healthy adolescents would suggest that OCs could potentially be of benefit for hypoestrogenism.

**STDs and other conditions**

Sexually active adolescents make up the age group at greatest risk for gonorrhea and chlamydia, and thus are at risk for the sequelae of these diseases, including PID and ectopic pregnancies.<sup>29</sup> OCs decrease the risk of PID and ectopic pregnancy. This may be important from a public health perspective, but individual teens clearly need to hear the message of dual-method use: OCs provide contraception and have noncon-

traceptive benefits, and condoms or another barrier method also should be used to prevent sexually transmitted diseases.<sup>30,31</sup>

Another therapeutic indication for OCs is suppression of menstruation in women with medical problems that make bleeding problematic. This category includes individuals who have thrombocytopenia or severe anemia, those undergoing chemotherapy or bone marrow/stem cell transplantation, and those with bleeding diatheses. The induction of “therapeutic amenorrhea” using steroid hormonal therapy was first described in the U.S. literature in 1971.<sup>32</sup> Since that time, continuous therapy with OCs has been successfully used for women with hematologic disorders.<sup>33</sup>

Pain related to endometriosis has also been managed with continuous OCs.<sup>34</sup> A recent Cochrane database review reached the conclusion that while there is a

paucity of data relating to use of OCs for treatment of symptomatic endometriosis, some support does exist for their use in this setting, which is commonplace.<sup>35</sup>

**Communication issues**

That OCs reduce the risk of ovarian and endometrial cancer is well established, but this particular benefit is rarely of interest to adolescents. The patient’s mother, however, may appreciate the value of this protective effect for her daughter, particularly if either of these two types of cancer has occurred in the family. OCs have been shown to decrease the risk of ovarian cancer, even among women with known hereditary forms of the disease.<sup>36</sup> Communicating this issue to an adult woman who may herself benefit from OCs may have the secondary benefit that she will then also consider OCs as preventive therapy for her adolescent daughter(s).

Mothers may be more aware of the noncontraceptive benefits of OCs than their daughters and may have experienced the benefits firsthand. They may, however, also have taken older, higher-dose pills that produced more side effects, such as nausea, breast tenderness, and bloating. Therefore it may be helpful to discuss the fact that current OCs contain lower doses of hormones than the ones that they may have taken during their adolescent or young adult years, and thus are less likely to produce side effects (Table 2).<sup>37</sup> For almost all healthy adolescents, the health benefits of OCs outweigh the minimal risks.<sup>38</sup> Conveying this information to both the patient and her mother can provide significant reassurance.

For some adolescents, OCs carry a stigma, even when they have been prescribed for therapeutic and noncontraceptive indications. A clinician may suggest that OCs be thought of as the "hormone pills" that they are. That this is a

common clinical practice can also be communicated. Occasionally a parent will suggest not telling an adolescent that the prescribed pills provide contraception, besides serving noncontraceptive purposes. Most clinicians would consider this level of deception of an adolescent not only dishonest and inappropriately misleading, but also medically risky. In addition, it is likely that the daughter will find out anyway that she is taking birth control pills. More often, a daughter will ask for a prescription for OCs on the pretext of a noncontraceptive indication, when in reality she wants to use them for contraception. While a clinician would always want to encourage information sharing between daughter and mother, the concept of confidential care for adolescents is well established and supported by the American Academy of Pediatrics, the American Medical Association, and the American College of Obstetricians and Gynecologists.<sup>39-41</sup>

Confidentiality is important, but the physician can facilitate communication between mother and daughter without breaching confidentiality. It is desirable, when possible, to interact with both mother and daughter and to answer the questions that each of them may have, encourage adherence to the prescribed regimen, and help ensure the teen's success with OCs. It may be helpful to structure the visit so as to talk with mother and daughter together and also separately (Figure 1).<sup>42</sup>

When talking with a teen alone, it is helpful to establish exactly what information you can share with her mother during the final portion of the visit when you meet both of them to discuss the logistics of successful pill-taking. This is truly the art of medicine and can sometimes be complicated. When the communication is done well, however, both mother and daughter will leave the office feeling that their concerns have been addressed. □

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# Beyond Birth Control: Using the Pill to enhance your health



**B**irth control pills have benefits that go well beyond contraception. Here are some of the desirable effects that you may wish to discuss with your clinician.

## Oral contraceptives can be used to treat

- ▶ Menstrual cramping and pain during ovulation
- ▶ Irregular menses
- ▶ Premenstrual syndrome
- ▶ Acne
- ▶ Polycystic ovary syndrome, a condition that can cause irregular periods and hair growth
- ▶ Estrogen deficiency, including symptoms such as hot flashes and night sweats

## The Pill helps prevent

- ▶ *Ovarian cancer*: This protection is particularly significant for women who have a family history of the disease
- ▶ *Endometrial cancer*: The risk of this disease goes down by as much as 50% after only one year of Pill use
- ▶ *Osteoporosis*: The hormones in the Pill maintain and possibly increase bone mass when used in the years before menopause
- ▶ Pelvic inflammatory disease, which can cause infertility
- ▶ Excessive blood loss
- ▶ Ovarian cysts
- ▶ Benign breast disease
- ▶ Ectopic pregnancy, a dangerous condition that may result in the loss of an ovary

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# OC benefits for the woman over age 30

By Mitchell D. Creinin, MD

*Oral contraceptives provide a unique opportunity for a woman to prevent pregnancy and obtain health benefits by using a single medication. In the first decades after the birth control pill became available in the United States, however, its relative benefits and risks for women 35 years and older were poorly understood. Both clinical observation and research have subsequently taught us that the Pill provides many noncontraceptive benefits with minimal risk in healthy nonsmoking women in their later reproductive years.*

In 1989, the Fertility and Maternal Health Drugs Advisory Committee of the Food and Drug Administration (FDA) received new data and decided that the risks of low-dose combination oral contraceptives were no greater in women aged 40 and over than in younger groups. The committee concluded that the potential health risks associated with pregnancy are greater than the risks of OC use by older women. Less than a year later, the FDA removed from pill labeling all reference to OC-related cardiovascular mortality risks in healthy, nonsmoking women aged 40 and over. By 1994, OC use in women aged 40 to 45 had quadrupled.<sup>1</sup>

Today's low-dose pills supply

four to seven times less estrogen and as much as 20 times less progestin than did those used in the early years. As a result, side effects such as weight gain, nausea, breast tenderness, emotional lability, and headaches have declined markedly. Although cardiovascular complications have become far less significant as well, smoking, especially heavy smoking, remains a contraindication to OC use in women over 35.<sup>2</sup>

The Pill is prescribed therapeutically for multiple noncontraceptive conditions. As the list of potential health benefits has grown, uses that formerly were common but not within labeling, such as treatment of acne and emergency contraception, have

become approved indications. Using a low-dose pill during the perimenopause can provide cycle regularity at a time when irregularity is frequently a problem. Additionally, OCs reduce hot flashes, vaginal dryness, and other hormone-mediated symptoms of the perimenopause. Evidence also suggests OCs help prevent osteoporosis and hip fractures as well as reduce the risk of endometrial and ovarian cancer.<sup>3</sup>

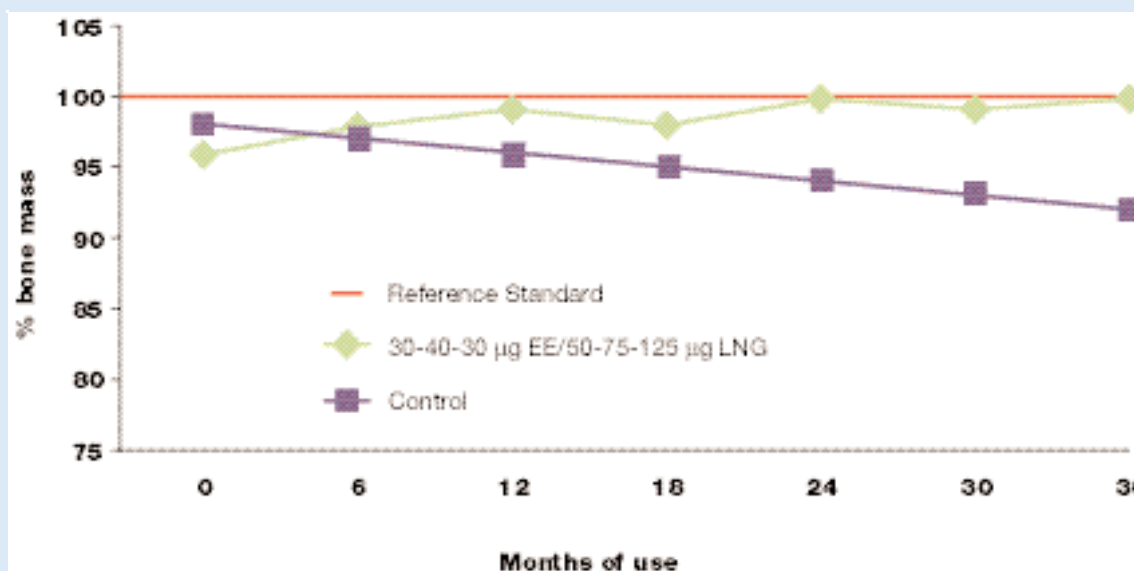
Accordingly, use of OCs is appropriate in women 35 years and older who do not smoke and are free of liver and cardiovascular disease. Potential Pill takers now include groups who until very recently would never have been considered candidates. Not only can older women potentially benefit from the Pill, but also those who have undergone tubal

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FIGURE 1

OCs maintain bone mass in women (41-49 years)



Source: Shargil AA.<sup>13</sup>

ligations, are not sexually active, or are lesbians.

**Contraceptive choices**

Today, the Pill is by far the most popular method of contraception among women aged 20 to 24; 63.4% of this age group use contraception and about one third (33.1%) of these contraceptors choose OCs.<sup>1</sup> Among the roughly 72% of American women aged 30 to 44 who use contraception, the Pill is the method of choice for about 21%. For older age groups, female and male sterilization are the dominant methods in the US, and Pill use is lower—8.1% for contraceptors aged 35 to 39 and 4.2% for those aged 40 to 44.

For women over 30 who are considering contraceptive options, methods other than OCs offer moderate noncontraceptive benefits. While sterilization is an effective method for preventing pregnancy, it does not minimize the effects of hormonal changes during perimenopause. Tubal ligation,

however, may reduce the risk of cervical and ovarian cancer, per-

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mediated  
symptoms of the  
perimenopause.*

haps by as much as two thirds.<sup>4</sup> A causal effect has not been clearly documented, but one hypothesis is that cancer risk decreases because sterilization blocks the migration to the ovaries of vagi-

nally introduced carcinogens, such as talc from sanitary napkins, talcum powder applied to the vulva, or other, unidentified agents.<sup>5</sup>

Vasectomy—the method used by 20.7% of female contraceptors aged 30 to 34, 8.1% of those aged 35 to 39, and 4.2% of those aged 40 to 44—obviously will not affect the hormonal changes of the perimenopause or provide women with protection against cancer and decreased bone density. Nor can male condoms, although they have the advantage of protecting both women and men against the transmission of HIV and other sexually transmitted diseases.

Copper-containing intrauterine devices (IUDs) may protect against endometrial cancer and foster detection of cervical cancer at times of insertion and removal.<sup>4,6,7</sup> These IUDs, however, fail to alleviate perimenopausal vasomotor symptoms and do not protect against ovarian cancer and/or the loss of bone density. In addition, copper-containing IUDs may

increase menstrual bleeding, leading women to discontinue their use.

### Continued benefits from youth through middle age

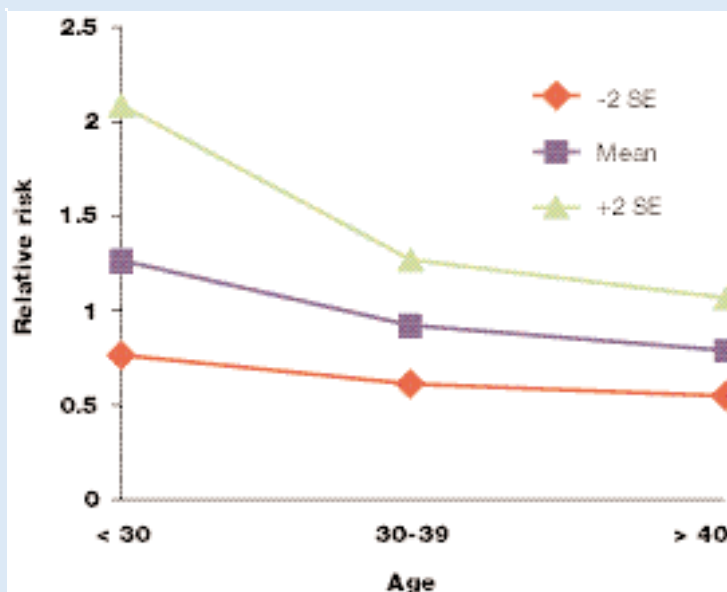
Many noncontraceptive health benefits of OCs that accrue to younger women persist through the perimenopause. For instance, reduced blood flow continues to lower the incidence of iron-deficiency anemia. The likelihood of experiencing a tubal pregnancy is also greatly decreased. Women who take the Pill have a lower risk of rheumatoid arthritis (RA) and those who have first-degree female relatives with the disease get the most protection. Whether OCs can actually prevent RA or inhibit the progression from mild to severe disease, however, is still not known.<sup>8</sup>

An important consideration in the later reproductive years are the cycle-related benefits of OCs. Many women may first experience menstrual irregularities, such as heavy flow and irregular cycles, in midlife. Pill use provides the dual benefits of lighter flow and less cramping. A low-dose pill often relieves breast tenderness and is well tolerated.<sup>9</sup> Healthy nonsmoking women may be encouraged to consider taking OCs for these benefits.

Patients should be counseled from the outset that if one brand causes difficulties, switching to another may help. Just as important to consider is the potential benefit of continuous OC use. In general, women using OCs experience more problems during the placebo week, compared with the days when they take the hormones.<sup>10</sup>

Several conditions that frequently plague older women respond well to OCs. Once other pathologies have been ruled out as causes for heavy, irregular, or

FIGURE 2  
OCs and reduced risk of hip fracture



Source: Michaelsson K, et al.<sup>14</sup>

otherwise abnormal bleeding, the Pill may be used for treatment of menorrhagia, dysmenorrhea, or anovulatory dysfunctional uterine bleeding.

OCs may provide an effective alternative to GnRH analogs in the treatment of endometriosis.<sup>11</sup> Women who need such protection can use a continuous regimen of OCs, with no Pill-free week. OC use diminishes the risk of benign breast disease and protects against the repeated formation of ovarian cysts. In addition, OCs can reduce or eliminate mild hirsutism.<sup>12</sup>

### Prevention of osteoporosis

Pill use by perimenopausal women reduces the risk of osteoporotic fractures, a benefit that obviously grows in importance during the perimenopausal years and beyond. In choosing a birth control method, avoiding bone loss should

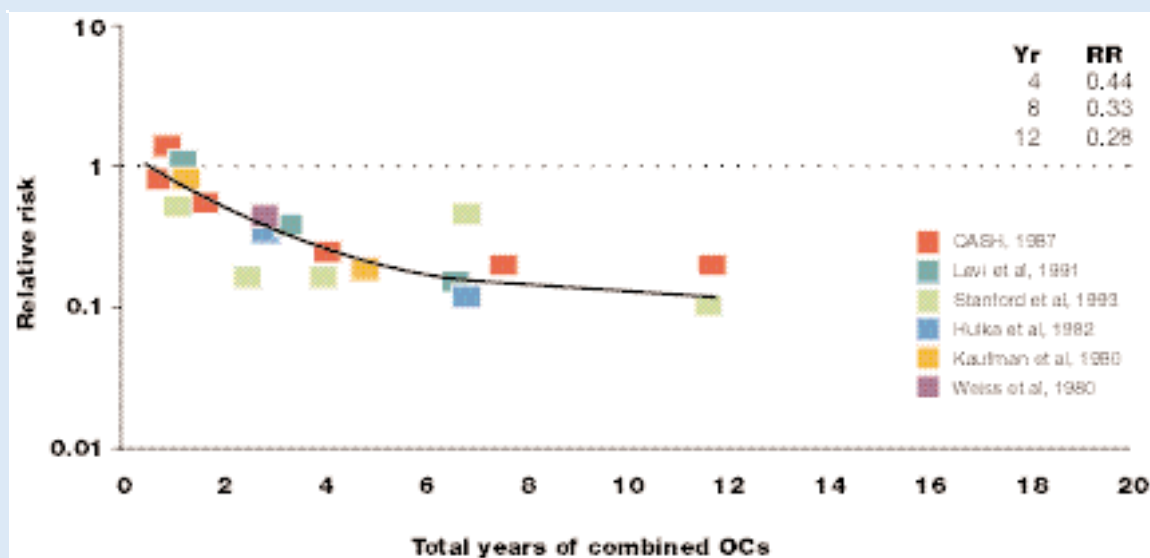
be an important consideration for older women.

Figure 1 shows the results of a 3-year prospective study of 200 perimenopausal women, aged 41 to 49, who needed both contraception and relief from perimenopausal symptoms.<sup>13</sup> One hundred subjects received an OC to provide both birth control and symptom control. Another 100 women used other forms of contraception. After the first year, and for the remainder of the 36-month study, those in the control group lost about 2% of their bone mass per year, while those who took the OC preserved their bone mass or even increased it.

A population-based case-control study of hip fracture in postmenopausal women revealed the protective effects of Pill use.<sup>14</sup> Hip fractures were reduced by 25% for ever-users, compared to those who had never taken the Pill, and the risk of fracture

FIGURE 3

OCs reduce risk of endometrial cancer (by years of use)



Source: Schlesselman JJ.<sup>26</sup>

was lowest for women who used OCs after age 40 (Figure 2). Thus, women who take the Pill later in their reproductive years may enter the menopause with greater bone mass and a lower fracture risk.

Do 20-µg ethinyl estradiol (EE) OCs have the same positive effect on bone mineral density (BMD) as higher-dose pills? Keep in mind that EE doses in these formulations are still considerably higher than the 5 µg of EE used in hormone replacement therapy (HRT). In a longitudinal 2-year follow-up study, researchers compared bone density in healthy oligomenorrheic women aged 40 to 49 with that of age-matched oligomenorrheic women treated with a low-dose OC (20-µg EE/0.15-mg desogestrel).<sup>15</sup> The authors concluded that low-dose OC use prevented the impairment of bone metabolism and concomitant decrease in BMD in perimenopausal oligomenorrheic women. Additional evidence

comes from the 2-year randomized multicenter CHART study using continuous low-dose treatment.<sup>16</sup> This trial involved 265 asymptomatic or mildly symp-

*An important consideration in the later reproductive years are the cycle-related benefits of oral contraceptives.*

tomatic women aged 40 and older who had undergone spontaneous menopause within the last 5 years

and had an intact uterus. The researchers found that continuous use of this OC significantly increased BMD.

**Prevention of cancer**

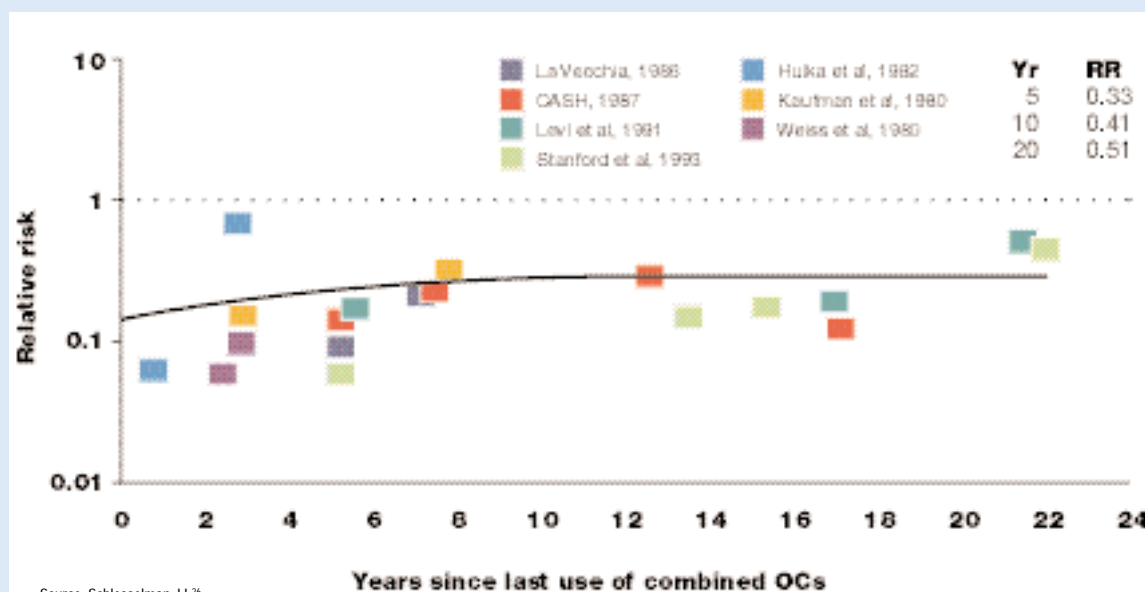
There is strong evidence that OCs reduce the risk of endometrial and ovarian cancer. In all women, but especially in those at high risk for reproductive system cancers, the protection afforded by OCs is unmatched.

**Ovarian cancer.** Since the incidence of ovarian cancer gradually increases during the reproductive years, clinicians should seize opportunities to share information about the protective effects of OCs with their patients, particularly those over age 30.

The Cancer and Steroid Hormone (CASH) study found that even short-term use of high-dose OCs reduced the risk of endometrial and epithelial ovarian cancers by 40%.<sup>17</sup> After 10 years or more of use, risk was reduced by 80%. That protection persisted

FIGURE 4

OCs protect against endometrial cancer after discontinuation



Source: Schlesselman JJ.<sup>26</sup>

for at least 15 years after women stopped taking the Pill. A meta-analysis of 20 studies reported a 10% to 12% decrease in cancer risk for each year of OC use, reaching 50% reduced risk after 5 years of use.<sup>18</sup>

Taking the Pill for at least 5 years reduces the risk for ovarian cancer in nulliparous women to the same level as (or less than) that of parous women. Older nulliparas should routinely be advised of that advantage. And patients who have one or more first-degree relatives with a history of ovarian cancer can counteract their own increased risk by taking OCs for 10 years or more.

A recent population-based case-control study (767 cases, 1,367 controls) sponsored by the National Cancer Institute focused on the protective effects of low-dose OCs against ovarian cancer.<sup>19</sup> Women aged 20 to 69, who had been diagnosed with epithelial ovarian cancer between May 1994 and July 1999, were compared with community con-

trols. Risk reduction in women taking low-estrogen, low-progestin pills was identical to that in women who had taken high-estrogen, high-progestin pills. The adjusted risk of ovarian cancer in ever-users was reduced by 40% over that of never-users, with protection beginning as soon as 1 to 4 years of exposure and escalating with longer duration of use. In fact, these authors conclude that reduced risk continues for at least 30 years after discontinuation.

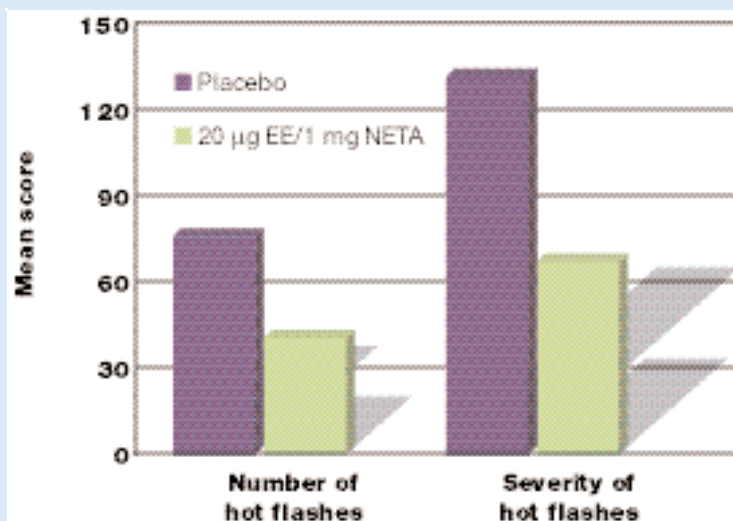
For women who are at high risk for ovarian cancer, the protection provided by OC use is particularly significant. About 10% of invasive ovarian cancer cases are hereditary. The lifetime risk for ovarian cancer is 45% higher in carriers of a mutation in the BRCA1 gene and 25% higher in carriers of the BRCA2 gene. A case-control study evaluated 207 women with hereditary ovarian cancer risk (detected via molecular testing for mutation of either

BRCA1 or BRCA2) and 161 of their sisters (controls).<sup>20</sup> The investigators found that OC use may reduce the risk of ovarian cancer in women with either mutation. Past use of OCs reduced the risk of ovarian cancer by 50% in women with a positive family history. Risk reduction increased with the duration of OC use: 20% for short-term use (up to 3 years) and 60% for long-term use (6 or more years). How many other drugs do we know of that lower cancer risk by such high percentages?

When counseling women who have BRCA mutations about the protective effect of OCs against ovarian cancer, a discussion of breast cancer risk may be in order. A new cohort study reported in the *Journal of the American Medical Association* concluded that women who have first-degree relatives with breast cancer and used OCs during or prior to 1975, when formulations typically contained higher doses of estrogen and progestin,

FIGURE 5

Effect of OCs on hot flashes in perimenopausal women



Source: Casper RF, et al.<sup>30</sup>

have a high risk for breast cancer, with a relative risk (RR) of 3.3.<sup>21</sup> But this finding is not relevant for the current low-dose formulations; in fact, the authors of the study call for further research to investigate the effect of today's OCs on women with a familial predisposition to breast cancer.

Several mechanisms have been proposed to explain the association between use of OCs and reduction in ovarian cancer.<sup>22–24</sup> These include:

- Suppression of gonadotropins that stimulate the ovary;
- Avoidance of “incessant ovulation”;
- Induction of progestin-induced apoptosis (programmed cell death) of the ovarian epithelium.

Skipping ovulation might be protective because it means avoiding a possible key step in the pathogenesis of ovarian cancer: disruption of the ovarian epithelium during ovulation. Suppression of ovulation occurs rapidly

with low-dose OCs, including 20-µg EE formulations. A study of the 20-µg EE/100-µg levonorgestrel OC documented suppression of ovarian activity during Pill use, with return of such activity after discontinuation of the Pill.<sup>25</sup> Normal serum levels of progesterone were noted 1 month after discontinuation.

**Endometrial cancer.** Reducing the risk of endometrial cancer is another important benefit of OC use (Figure 3).<sup>26</sup> One year of use reduces the risk by 50%, with the greatest benefit after 3 years of use. Endometrial protection continues for at least 15 years after cessation (Figure 4). According to the CASH study, the Pill is equally protective for all three major histologic subtypes of endometrial cancer: adenocarcinoma, adenoacanthoma, and adenosquamous cancers.

A review of 13 case-control and three cohort studies confirmed the reduced RR for endometrial cancer among OC users in all

but one case-control study and one cohort study. Among the 13 case-control studies, most showed about a 50% reduction (RR 0.5), and one cohort study reported an 80% reduction (RR 0.2).<sup>24</sup> However, these studies predominantly include high-dose OCs. Unlike the evidence about ovarian cancer, no data exist for endometrial cancer to confirm that low-dose OCs provide preventive benefits.

One possible explanation for the protective effect of OC use against endometrial cancer is the “unopposed” estrogen hypothesis. Without OC use, the endometrium is exposed to unopposed estradiol for 14 days (follicular phase) during the cycle, but with OC use, the endometrium is exposed for only 7 days and proliferation is suppressed. The altered physiologic environment affords reduced endometrial exposure to unopposed estradiol. This benefit should be maintained with low-dose OCs as well.<sup>24,27</sup>

**Other cancers.** The connection between Pill use and other neoplasms remains under intense scrutiny. For example, a reduced risk of colorectal cancer in women who take OCs has been suggested.<sup>28</sup> A number of studies have reported a 30% to 40% reduction in the incidence of colon cancer in women taking OCs.

The contradictory findings of numerous studies on a possible link between OCs and breast cancer have served to fan the anxiety many women feel about taking hormones. OCs seem to increase the risk of breast cancer slightly during use and immediately afterward, although the risk reverts to that of never-users 10 years after cessation.<sup>29</sup> Such a time course suggests the possibility of diagnosis bias or a promotional effect of OC use; however, it is unlikely that use

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of OCs induces new breast cancers.

### **Easing perimenopause**

Use of a combination OC minimizes the estrogen surges that induce perimenopausal disturbances such as hot flashes, sleep disturbances, and night sweats. Perimenopausal women on OCs who experience unpleasant vasomotor symptoms during the Pill-free week may benefit from taking the Pill continuously. Moreover, OCs relieve perimenopause-related vaginal dryness and sleep disturbances.

Psychological and cognitive symptoms during the perimenopause include irritability, anxiety, poor concentration and forgetfulness, and depression. All warrant evaluation for depression and thyroid disorders before OCs or other treatment is started. In addition, some symptoms may reflect stressors inherent in life transitions, such as college-bound children or a husband in “midlife crisis.” Sexual effects may include decreased vaginal lubrication that leads to itching, irritation, dyspareunia, and decreased libido, perhaps associated with vaginal atrophy. Although it is sometimes assumed that sexual symptoms will respond to hormone therapy, that is not always the case.

Low-dose pills are proving to be effective in relieving many of these perimenopausal symptoms. A double-blind, randomized, placebo-controlled Canadian study examined the effects of 20- $\mu$ g EE /1-mg norethindrone acetate in 132 perimenopausal women aged 40 to 55 over 24 weeks (6 cycles).<sup>30</sup> The treated group experienced numerous positive effects: fewer and less severe hot flashes, decreased variability of bleeding episodes, lower rates of bleeding severity, reduction in the incidence and duration of clots and flooding, and improved

quality of life, including measures of sleep, energy, and depression (Figure 5).

### **Transition to HRT**

The gradual transition to menopause typically extends from 2 to 8 years, with the average age of initiation at 51 years. Only 1% of women reach menopause before age 40; 5% do so after age 55.

The perimenopausal period is characterized by decreasing but volatile production of ovarian estradiol, decreasing inhibin levels as ovarian function declines, and rising levels of serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH). These changes come with shortened cycle length (although cycles sometimes get longer at first), oligomenorrhea and anovulatory uterine bleeding, and follicle depletion due to ovarian failure. Menopause is positively established after 12 months of amenorrhea, usually reflecting the permanent cessation of ovarian function.

Pill use masks amenorrhea and the other signs and symptoms that classically demonstrate menopause. Determining the moment at which it is safe to abandon contraception therefore becomes an issue in women who are taking OCs. Once a woman no longer requires cycle control or contraception, she may benefit from moving to lower-potency hormones. By switching to HRT, she reduces her risk for thromboembolic disease, a risk that grows with age. Changing from OCs to HRT, however, is not always the best choice. Adherence to HRT is notoriously poor; discontinuation within a year is fairly common. The decision has to be tailored to each individual.

For a patient who desires to switch to HRT, some authors have recommended measuring serum

FSH on day 7 of the Pill-free interval.<sup>31</sup> Because FSH levels can fluctuate throughout the cycle, however, this method has proved unreliable. One week is too brief for FSH to return to menopausal values in most women who are taking OCs that contain 30 to 35  $\mu$ g of EE.<sup>32</sup> Perimenopausal women can have an elevated FSH level (greater than 30 mIU/mL) and can subsequently have an ovulatory cycle.<sup>33</sup>

Other laboratory findings, both taken on day 7 of the Pill-free interval, have been evaluated. A serum FSH to LH ratio of greater than 1 or an estradiol of less than 20 pg/mL (73 pmol/L) typically indicates menopause.<sup>32</sup> These markers, however, just like FSH, may indicate an anovulatory phase of the perimenopause and hence cannot definitively diagnose menopause. For this reason, it is important to be flexible with the transition to HRT and consider waiting until an age such as 55, when the chance of pregnancy is almost negligible. It is reasonable to continue prescribing OCs until age 55 when reliable lab findings are not available.

If a woman switches from OCs to HRT, the clinician should keep in mind the potential for a change in the vaginal bleeding pattern.<sup>34</sup> Unexpected bleeding may lead to unnecessary testing and patient anxiety. To help avoid this, counsel the patient about potential changes in bleeding patterns before the transition to HRT.

### **Recognition of OC benefits**

Over the years, OCs have become more widely accepted and used. This trend has been driven in part by increased OC use in women over age 30, particularly among those aged 35 to 44.<sup>3</sup> Increased OC use reflects the recognition that the Pill offers both contraceptive

and noncontraceptive benefits. In a nationwide survey of 943 women taking the Pill, most of those who expressed satisfaction with the method were aware of its desir-

able noncontraceptive effects.<sup>35</sup>

In short, evidence suggests that OCs can improve the quality of life of many women. Appropriate candidates should be offered

a discussion of the noncontraceptive as well as contraceptive benefits to be derived from taking the Pill throughout the perimenopause. □

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# Post-test

## Oral Contraceptives: Beyond Contraception

Please select the single best answer and record your response on the answer sheet page (page 21).

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- The noncontraceptive benefits of oral contraceptives include:**
  - A reduction in dysmenorrhea
  - A reduction in anemia
  - A reduction in pelvic inflammatory disease
  - All of the above
- True or false:** Primary dysmenorrhea is a diagnosis of exclusion.
- True or false:** According to data from the CDC, nearly 1 of every 4 high school girls has seriously considered suicide and 11% have attempted it.
- Adolescent girls whose cycles do not fall within a frequency of 21 and 45 days should be evaluated for:**
  - Hyperandrogenism
  - Eating disorders
  - Thyroid dysfunction
  - All of the above
- True or false:** Treatment of acne with oral contraceptives suppresses ovarian but not adrenal androgen secretion.
- True or false:** Women with von Willebrand's disease should avoid oral contraceptives.
- True or false:** Oral contraceptives decrease the risk of endometrial cancer but not ovarian cancer.
- True or false:** The treatment of acne and emergency postcoital contraception are FDA-approved indications for oral contraceptives.
- True or false:** Cigarette smoking is not a contraindication to using oral contraceptives in women older than age 35.
- True or false:** Tubal ligation does not reduce the risk of cervical or ovarian cancer.
- True or false:** Oral contraceptives may lower the risk of a woman developing rheumatoid arthritis.
- True or false:** Oral contraceptives provide prophylaxis against the recurrence of endometriosis following treatment with surgery or GnRH analogs.
- True or false:** Women who take oral contraceptives later in life may enter the menopause with less bone loss.
- The Cancer and Steroid Hormone (CASH) study found that:**
  - Risk of ovarian cancer was reduced by 80% after 10 years of use of OCs
  - Even after short-term OC use, risk of endometrial cancer is reduced by 40%
  - A nulliparous woman's risk of ovarian cancer is reduced to that of a parous woman if she takes oral contraceptives for at least 5 years
  - All of the above
- True or false:** About 40% of cases of invasive ovarian cancer are hereditary.
- Several mechanisms have been proposed to explain the association between use of oral contraceptives and reduction in ovarian cancer. They include:**
  - Suppression of gonadotropins that stimulate the ovary
  - Promotion of "incessant ovulation"
  - Suppression of apoptosis of the ovarian epithelium
  - All of the above

17. **True or false:** One year of oral contraceptive use reduces the risk of endometrial cancer by 20% with the greatest benefit after 3 years of use.
18. **True or false:** Use of oral contraceptives may increase the risk of colon cancer in women.
19. **True or false:** Oral contraceptive use decreases a woman's risk of developing breast cancer.
20. **Oral contraceptives preserve fertility by:**
- A. Suppressing polycystic ovary syndrome
  - B. Suppressing endometriosis
  - C. Preventing pelvic inflammatory disease
  - D. All of the above
21. **The perimenopausal period is characterized by:**
- A. Increasing inhibin levels
  - B. Rising serum FSH
  - C. Declining serum LH
  - D. All of the above
22. **True or false:** In patients with factor 5 Leiden mutation, the risk of thromboembolism should be assessed prior to prescribing oral contraceptives.
23. **True or false:** A serum FSH to LH ratio of greater than 1 sampled on day 7 of the pill-free interval is consistent with menopause.

*Questions were written by David B. Seifer, MD, Professor of Obstetrics and Gynecology,  
UMDNJ-Robert Wood Johnson Medical School, New Brunswick, N.J.*



# Answer sheet

## Oral Contraceptives: Beyond Contraception

### Instructions

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In order to complete this program successfully, you must:

- Complete the post-test.
- Complete the program evaluation.
- Fax or mail your completed answer sheet to:  
The Endocrine Society  
CME Services  
Attn: Gwen Laster  
4350 East West Highway, Suite 500  
Bethesda, MD 20814  
FAX: 301-941-0259

In order to ensure scoring, the answer sheet must be received by 2/01/02.

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- |     |      |       |   |   |     |      |       |   |   |
|-----|------|-------|---|---|-----|------|-------|---|---|
| 1.  | A    | B     | C | D | 13. | True | False |   |   |
| 2.  | True | False |   |   | 14. | A    | B     | C | D |
| 3.  | True | False |   |   | 15. | True | False |   |   |
| 4.  | A    | B     | C | D | 16. | A    | B     | C | D |
| 5.  | True | False |   |   | 17. | True | False |   |   |
| 6.  | True | False |   |   | 18. | True | False |   |   |
| 7.  | True | False |   |   | 19. | True | False |   |   |
| 8.  | True | False |   |   | 20. | A    | B     | C | D |
| 9.  | True | False |   |   | 21. | A    | B     | C | D |
| 10. | True | False |   |   | 22. | True | False |   |   |
| 11. | True | False |   |   | 23. | True | False |   |   |
| 12. | True | False |   |   |     |      |       |   |   |

Please cut here →

