

Prescribing Oral Contraceptives for Women Older Than 35 Years of Age

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This paper addresses the use of combined oral contraceptives in women older than 35 years of age, including the potential risks and benefits, pretreatment assessment, common side effects and their management, appropriate follow-up, and diagnosis of menopause. The case-based discussion also focuses on issues that

pertain to women who smoke, have hypertension, or have dyslipidemia.

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A 42-year-old woman comes to see you to discuss birth control. She has not had sexual intercourse since her divorce 5 years ago but is now in a relationship and wishes to become sexually active. She tolerated oral contraceptives in the past and wonders whether she can use them again.

WHAT ARE THE POTENTIAL RISKS ASSOCIATED WITH ORAL CONTRACEPTIVE USE DURING THE LATE REPRODUCTIVE YEARS?

Many women and practitioners believe that oral contraceptives are associated with substantial risks, especially in women older than 35 years of age. This may explain why only 4% of women in this age category use combined oral contraceptives (1). Combined oral contraceptives contain both estrogen and progestins; in this paper, we refer to these oral contraceptives. Most of the concern regarding oral contraceptive use stems from earlier studies of oral contraceptive formulations with high doses ($>50 \mu\text{g}$) of ethinyl estradiol that were associated with substantial adverse health outcomes. These findings are largely unsubstantiated by more recent studies of lower-dose formulations ($\leq 35 \mu\text{g}$). Thus, clinicians should not only counsel women about potential risks associated with oral contraceptive use but also address misperceptions.

Oral contraceptives increase the risk for venous thromboembolism (Table 1) (3, 18–22). Estrogen augments hepatic production of clotting factors (especially factor VII, factor X, and fibrinogen) (23), which leads to elevation of these factors in women taking oral contraceptives (24). Because the thromboembolic risk associated with oral contraceptives is higher in formulations containing $50 \mu\text{g}$ of estrogen than in those containing $35 \mu\text{g}$ (25, 26), authors have speculated that oral contraceptives containing $20 \mu\text{g}$ of estrogen should have lower risk. However, studies have not found lower rates of venous thromboembolism in women who use oral contraceptives containing $20 \mu\text{g}$ of estrogen compared with formulations containing 30 to $35 \mu\text{g}$ of estrogen (4, 27–29). Two studies have found increased risk for venous thromboembolism in female smokers who used oral contraceptives (30, 31) and one study did not (4). Age does not seem to influence the thromboembolic risk associated with oral contraceptive use (5, 27).

Overall, it should be recognized that the absolute risk for venous thromboembolism is low; thus, there would be approximately only 1 extra case of venous thromboembolism for every 10 000 oral contraceptive users per year (23).

Oral contraceptives contain different progestins. The newest progestins (desogestrel, gestodene, and norgestimate) are often called third-generation progestins (Table 2). Despite several advantages (such as improved lipid profile and reduced androgenicity), oral contraceptives containing desogestrel and gestodene have been associated with an increased risk for venous thromboembolism (3, 18–20, 27, 32–36). Two large case-control studies (3, 35) suggested that women using oral contraceptives that contain desogestrel and gestodene had approximately 50% greater risk for deep venous thrombosis or pulmonary embolus than users of second-generation progestin oral contraceptives that contain levonorgestrel. After publication of these studies, medical safety committees in several countries warned against prescribing oral contraceptives that contain desogestrel and gestodene. However, subsequent analyses uncovered bias and systematic errors that call the initial findings into question (18–20, 33, 37).

Oral contraceptives that contain desogestrel and gestodene were recently found to induce activated protein C resistance similar to that seen in patients with factor V Leiden mutation (21). Although women who are homozygous or heterozygous for factor V Leiden mutation and who use oral contraceptives have a greatly augmented risk for venous thromboembolism (21, 32), genetic screening of all potential oral contraceptive users is not cost-effective and, therefore, not recommended (38).

Myocardial infarction is rare in premenopausal women. Estimates of risk vary in current oral contraceptive users (Table 1); however, most studies of oral contraceptives containing less than $50 \mu\text{g}$ of estrogen that adjusted for cardiac risk factors demonstrated increased risk (7–9, 39). A World Health Organization (WHO) study showed a dose-dependent relationship between smoking and risk for myocardial infarction, with significantly greater risk in current oral contraceptive users who smoked more than 10 cigarettes per day (7). Studies also showed increased risk for myocardial infarction in oral contraceptive users with hypertension, diabetes, or dyslipidemia (7, 8, 39). In addi-

Table 1. Estimates of Risk for Low-Dose Oral Contraceptives*

Risk	Type of Evidence	Approximate Risk in All Women (Reference)†	Approximate Risk in Women Older Than 35 Years (Reference)†
Venous thromboembolism	Randomized, controlled trial Retrospective cohort	10% increase (2) Fivefold increase (2)	Age does not influence risk (3–5)
Myocardial infarction	Case–control studies	No increased risk to fivefold increase (6–8)	No increased risk (9) to 3.5-fold increase‡ (7)
Ischemic stroke	Case–control studies Meta-analysis	No increased risk (10–12) Twofold increase (13)	No increased risk§ (10–12) Twofold increase (13)
Breast cancer	Case–control studies Reanalysis of 54 studies	No increased risk (14) 24% increased risk¶ (15)	No increased risk (16)
Gallstones	Retrospective cohort	10% increased risk (17)	No increased risk** (17)

* Low-dose oral contraceptives are those with <50 µg of ethinyl estradiol.
 † Risks are expressed as changes in relative risk for disease.
 ‡ Risk is for European centers of this multinational, case–control trial.
 § In reference 12, blood pressure was checked before initiation of oral contraceptive use.
 || Includes reanalysis of 10 prospective and 44 case–control studies (15).
 ¶ Includes risk with all doses of oral contraceptives because risk did not differ (15).
 ** Age group from 40 to 44 years of age.

tion, although risk for myocardial infarction seems decreased with third-generation compared with first- and second-generation progestins, studies have not shown a statistically significant difference (8, 39).

An increased risk for ischemic stroke in women taking oral contraceptives has been reported (10–13, 40–56). The original studies noting an increased risk for stroke were conducted when higher doses of estrogen (80 to 150 µg) and progesterone were widely used (12, 51, 53, 55, 56). In the 1990s, many international case–control studies addressed the issue of stroke and oral contraceptives with only 35 to 50 µg of estrogen. The results of these observational studies varied; some studies found increased risk for stroke, whereas others did not (10–12, 42, 43, 46–49, 56) (Table 1).

In the European arm of a WHO study, the women who used oral contraceptives containing less than 50 µg of estrogen, including those who were older than 35 years of age, showed no increased risk for ischemic stroke as long as their blood pressure was checked before they began taking oral contraceptives (12). However, in women who smoked more than 10 cigarettes per day, the risk for stroke increased 7 times; the increase was almost 10 times in women who reported a history of hypertension (12). This study also showed no difference in risk for stroke among

the generations of progestins. Two major studies in the United States also found no increased risk for stroke in women taking oral contraceptives with less than 50 µg of estrogen, even in smokers and women older than 35 years of age (10, 11, 57). In these studies, too few women received treatment for hypertension to permit analysis of the risk for stroke. By contrast, a recent meta-analysis found that when studies using less than 50 µg of estrogen were analyzed and controlled for smoking and hypertension, the risk for ischemic stroke increased twofold (13).

Recent studies demonstrated an increased risk for ischemic stroke in women younger than 45 years of age with migraines (48, 58, 59). Migraines with aura are associated with a greater risk for ischemic stroke than are migraines without aura (58, 59). Studies also find an increased risk for ischemic stroke in oral contraceptive users with migraines (57–59). In addition, an International Headache Society task force states that there is an “apparent synergism” of migraine and oral contraceptives for ischemic stroke (60). Therefore, although the WHO states that prescribing oral contraceptives to women with migraines without focal neurologic symptoms is considered safe in women younger than 35 years of age, oral contraceptives are not usually recommended in women with migraines who are 35 years of age or older (61). Prescribing oral contracep-

Table 2. Third-Generation Progestin Oral Contraceptives Available in the United States*

Name (Manufacturer)	Type	Ethinyl Estradiol, µg	Progestin (mg)
Desogen (Organon, West Orange, NJ)	Monophasic	30	Desogestrel (0.15)
Ortho-Cept (Ortho-McNeil, Raritan, NJ)	Monophasic	30	Desogestrel (0.15)
Mircette (Organon)	Monophasic†	20, 10	Desogestrel (0.15)
Cyclessa (Organon)	Triphasic	25	Desogestrel (0.1, 0.125, 0.15)
Ortho-Cyclen (Ortho-McNeil)	Monophasic	35	Norgestimate (0.25)
Ortho-Tri-Cyclen (Ortho-McNeil)	Triphasic	35	Norgestimate (0.18, 0.215, 0.25)
Ortho-Tri-Cyclen Lo (Ortho-McNeil)	Triphasic	25	Norgestimate (0.18, 0.215, 0.25)

* Norgestimate is sometimes classified as a second-generation progestin, but many authors consider it a third-generation progestin because of its lower androgenicity and other properties.
 † Contains 10 µg of ethinyl estradiol per day on days 3 to 7 of placebo week.

tives to women with migraines with focal neurologic symptoms is contraindicated, regardless of age (61).

The relationship between oral contraceptive use and risk for breast cancer remains controversial. Most studies find no overall risk or a slight increased risk in women using oral contraceptives (Table 1) (14–16, 62–74). Two large case–control studies showed no overall increased risk for breast cancer in current or former oral contraceptive users, regardless of the duration of oral contraceptive use (14, 16). In contrast, the Collaborative Study on Hormonal Factors in Breast Cancer, a large secondary analysis of worldwide epidemiologic data in 54 studies, did demonstrate an increased risk for breast cancer in current oral contraceptive users that decreased with time after discontinuation of oral contraceptive use (15, 74). Of interest, breast cancer in women taking oral contraceptives was usually localized to the breast and was not as advanced as in women who never took oral contraceptives. In addition, the risk for breast cancer was not influenced by age at first use or duration of use (15, 74). Although a more recent report suggests an increased risk for breast cancer in oral contraceptive users with a first-degree family history of breast cancer, many of these women probably used oral contraceptives with higher doses of estrogen than those currently used (75). It is widely recommended that a positive family history of breast cancer should not be considered a contraindication to oral contraceptive use (15, 16, 61, 66, 71, 74, 76–78).

The incidence of symptomatic gallstone disease in women increases with age, parity, and oral contraceptive use (Table 1) (79). A large retrospective cohort study found a slightly increased risk for symptomatic gallstones in oral contraceptive users of all ages; however, the risk was lower in women older than 35 years of age than in women age 15 to 19 years (17). The risk for gallstones in oral contraceptive users is lower than the risk associated with parity (80).

A WHO working group developed evidence-based eligibility criteria for use of oral contraceptives containing 35 μg of estrogen or less (61). To decrease the risk for serious complications, health care providers should review the WHO's absolute contraindications (Table 3) with every patient before prescribing oral contraceptives.

WHAT ARE THE POTENTIAL BENEFITS OF ORAL CONTRACEPTIVE USE IN WOMEN DURING THE LATE REPRODUCTIVE YEARS?

A recent survey reported that in the United States, 41% of pregnancies in women age 35 to 39 years and 51% of pregnancies in women 40 years of age and older are unintended (81). Combined oral contraceptives are one of the most effective methods of birth control. The failure rate in the first year of use ranges from 0.1% to 5%, depending on adherence to prescribing guidelines (77).

In addition to preventing pregnancy, oral contracep-

Table 3. Absolute Contraindications to Oral Contraceptive Use (Unacceptable Health Risk)*

Pregnancy
Postpartum <6 weeks and breastfeeding
Age > 35 years and heavy smoker (>15 cigarettes/d)
Systolic blood pressure > 160 mm Hg, diastolic blood pressure > 99 mm Hg
Hypertension with vascular disease
Diabetes with neuropathy, retinopathy, nephropathy, or vascular disease
History of deep venous thrombosis or pulmonary embolism
Major surgery with prolonged immobilization
History of ischemic heart disease
History of stroke
Complicated valvular disease (with atrial fibrillation, pulmonary hypertension, bacterial endocarditis)
Severe headaches with focal neurologic symptoms
Current breast cancer
Active viral hepatitis, severe cirrhosis, benign or malignant liver tumors

* Adapted with permission from Improving Access to Quality Care in Family Planning: Medical Eligibility Criteria for Contraceptive Use. 2nd ed. Geneva, Switzerland, World Health Organization, 2000:1-12 (61).

tives have many health benefits that are particularly relevant for women older than 35 years of age. Oral contraceptive use clearly reduces the risk for ovarian cancer (82–84) by suppression of ovulation and reduced gonadotropin secretion. The landmark Cancer and Steroid Hormone Study group reported a 40% reduction in risk for ovarian cancer; a protective effect occurs in only 3 to 6 months and increases to an 80% risk reduction after 10 years of use (82). A recent meta-analysis of 17 case–control and 3 cohort studies confirmed this protective effect; risk was reduced by 10% to 12% after 1 year and by approximately 50% after 5 years of use (83). Oral contraceptive users also have a lower risk for endometrial cancer. A meta-analysis of 10 case–control studies and 1 cohort study showed a risk reduction of 56% with 4 years of use, 67% with 8 years of use, and 72% with 12 years of use (85). Protection seems to continue for many years after discontinuation of use (85).

New data suggest that oral contraceptives may decrease the risk for colon cancer. Although a review found that 3 of 4 cohort studies and 5 of 11 case–control studies reported reductions in the risk for colon cancer (86), it is premature for clinicians to recommend oral contraceptives for this purpose. None of the studies supporting the protective effects of oral contraceptives against cancer included formulations containing only 20 μg of ethinyl estradiol; therefore, it is unknown whether lower doses of estrogen provide these benefits.

Erratic fluctuations in ovarian hormonal secretion are characteristic of perimenopause, the period of 2 to 8 years preceding the cessation of menses, and may result in hot flashes, mood swings, insomnia, menstrual irregularity, or vaginal dryness (87–89). Oral contraceptives relieve most symptoms (90–94), but effects on dysphoria vary (95–97). Standard hormone replacement therapy regimens, which are 4 to 10 times less potent than oral contraceptives, may not reliably prevent pregnancy.

It is estimated that women older than 40 years of age

make more than 700 000 visits per year to physicians for acne (98). Acne significantly improved in two randomized, placebo-controlled trials using triphasic norgestimate with 35 µg of ethinyl estradiol for 6 months (99, 100). This oral contraceptive is the first to be approved by the U.S. Food and Drug Administration for the treatment of moderate acne. However, all oral contraceptive formulations, especially those with third-generation progestins, may improve acne through an estrogen-induced increase in sex hormone-binding globulin and a decrease in free testosterone levels. Of note, acne worsens in 5% of oral contraceptive users (101). The reduced androgen levels associated with oral contraceptive use are also thought to be responsible for improvement in hirsutism (102); this effect, in addition to a decrease in menstrual bleeding, explains why oral contraceptives are an effective treatment for the polycystic ovarian syndrome (103).

Two recent evidence-based reviews support the association between low-dose oral contraceptive use and favorable effects on bone mineral density (104, 105). Three of the prospective trials that focused on perimenopausal women found that oral contraceptive users maintained or increased bone density compared with nonusers (93, 106, 107). However, only three studies have examined the relationship between oral contraceptive use and fracture rates, and the data conflict (108–110); therefore, more studies are needed to examine fracture rates in perimenopausal and postmenopausal women.

You discuss these risks and benefits with the patient and learn that she is generally healthy. Her menses are regular, every 29 to 30 days, with moderate flow and mild premenstrual symptoms. She has no personal or family history of deep venous thrombosis, pulmonary embolism, or migraine headaches. Her only medication is ibuprofen, which she uses several days per month for moderate dysmenorrhea. She does not take any other over-the-counter medications or herbal products. She smokes three to four cigarettes per day, only on weekends. She drinks one to two alcoholic beverages per week and does not exercise. Her mother has hypercholesterolemia and was diagnosed with coronary artery disease at age 60 years. She has no family history of breast or gynecologic cancer.

WHICH PHYSICAL EXAMINATION AND LABORATORY TESTS SHOULD BE DONE BEFORE PRESCRIBING OF ORAL CONTRACEPTIVES TO A WOMAN OLDER THAN 35 YEARS OF AGE?

Expert medical opinion regarding routine examinations before prescribing of oral contraceptives has changed over the past 10 years. Required examinations may decrease access to oral contraceptive use, augment beliefs that oral contraceptives are dangerous, and deny women who desire hormonal contraception the right to choose which preventive screening measures they undergo (111). Many professional organizations, including the WHO and Amer-

ican College of Obstetricians and Gynecologists, now state that pelvic examinations are not needed before oral contraceptive use begins because taking a medical history and measuring blood pressure will reveal contraindications to use (111–113). Routine breast examinations and mammography in women younger than 50 years of age are controversial (114) and are not required before initiation of oral contraceptive use (111). Routine fasting lipid panels are recommended for women younger than 45 years of age only if the patient has a family history of dyslipidemia or has other cardiovascular risk factors (115). Any of these preventive services can be offered at the initial or a future visit, but not performing these examinations and tests should not preclude prescribing oral contraceptives.

On examination, the patient is slender, her heart rate is 80 beats/min, and her blood pressure is 138/88 mm Hg. The remainder of her physical examination, including a breast and pelvic examination, is normal. Her Papanicolaou smear is normal. A fasting lipid panel reveals a total cholesterol level of 5.59 mmol/L (216 mg/dL), low-density lipoprotein (LDL) cholesterol level of 3.75 mmol/L (145 mg/dL), high-density lipoprotein (HDL) cholesterol level of 1.06 mmol/L (41 mg/dL), and triglyceride level of 1.69 mmol/L (150 mg/dL).

SHOULD THE PATIENT'S SLIGHTLY ELEVATED DIASTOLIC BLOOD PRESSURE PREVENT PRESCRIBING OF ORAL CONTRACEPTIVES?

Oral contraceptives can increase both systolic and diastolic blood pressure by 4 to 9 mm Hg from baseline (116–118). Blood pressure usually returns to pretreatment levels in 3 to 6 months if oral contraceptive use is discontinued (119). According to the WHO, oral contraceptives are absolutely contraindicated only if blood pressure is 160/100 mm Hg or greater; however, because of the increased risk for stroke and myocardial infarction in oral contraceptive users with hypertension, physicians should be cautious before prescribing oral contraceptives in women with even mild elevations of blood pressure (61). No data show that treatment of hypertension modifies cardiovascular risks in oral contraceptive users, although the risks are reduced in women who do not use oral contraceptives. This patient's blood pressure should not prohibit her from initiating oral contraceptive use; however, her blood pressure should be monitored more frequently after initiation of use and she should be encouraged to stop smoking (61, 77, 116, 120, 121).

SHOULD THE PATIENT'S MILD DYSLIPIDEMIA PREVENT PRESCRIBING OF ORAL CONTRACEPTIVES?

Oral contraceptives are considered safe for patients with mild dyslipidemia if lipid levels are closely monitored after initiation of use (77, 122). The American College of Obstetricians and Gynecologists recommends that if the

LDL cholesterol level is 4.14 mmol/L (160 mg/dL) or higher, HDL cholesterol level is less than 0.91 mmol/L (35 mg/dL), or triglyceride level is greater than 2.82 mmol/L (250 mg/dL), oral contraceptive use should be postponed until the lipid abnormality is better controlled (76). If a woman has a poor response to lipid-lowering therapy, alternative contraception should be considered (76, 120, 122).

The effect of oral contraceptives on lipid levels depends on the estrogen dose relative to the progestin dose, in addition to the androgenicity of the progestin (120). Estrogen tends to have beneficial effects by decreasing LDL cholesterol levels and increasing HDL cholesterol levels; however, triglyceride levels also increase. Progestins seem to have the opposite effect, that is, they cause HDL cholesterol levels to decrease and LDL cholesterol levels to increase. Third-generation progestins, especially norgestimate, seem to be most beneficial because HDL cholesterol levels increase and LDL cholesterol levels remain stable or slightly decreased; however, triglyceride levels mildly increase (53, 120, 123–127). Available data have not linked these favorable effects on lipids to a reduction in cardiovascular risk.

DOES THE PATIENT'S SMOKING STATUS PREVENT PRESCRIBING OF ORAL CONTRACEPTIVES?

Approximately 25% of oral contraceptive users between 35 and 45 years of age smoke; most of these women smoke heavily (>15 cigarettes per day) (128). This is unfortunate because the combination of oral contraceptives and smoking substantially increases the risk for cardiovascular disease (7, 12, 39, 56, 129). The estimated absolute risk for death from cardiovascular disease in oral contraceptive users who smoke is 3.3 per 100 000 women between 15 and 34 years of age compared with 29.4 per 100 000 women between age 35 and 44 years (130).

Consensus panels consistently recommend exercising caution in prescribing oral contraceptives for women older than 35 years of age who smoke (40, 61, 77). It is generally agreed that oral contraceptives are absolutely contraindicated in heavy smokers (>15 cigarettes per day) who are older than 35 years (40, 61). In light smokers (\leq 15 cigarettes per day) who are older than 35 years of age, oral contraceptives may be considered (40, 61); however, the data comparing cardiovascular risk in light and heavy smokers are sparse (130). A careful investigation for other risk factors for cardiovascular disease is essential before oral contraceptives are prescribed to any older woman who smokes. Most important, all women who smoke should be strongly encouraged to quit. This patient does not smoke heavily enough for oral contraceptive use to be absolutely contraindicated. She should be warned about her increased risk for cardiovascular disease.

You discuss the need for close monitoring of blood pressure and lipid levels with the patient. You strongly advise her to quit smoking, adopt a low-fat diet, and begin to exercise. She is receptive to these lifestyle changes and chooses a quit date for smoking cessation. You and the patient agree that oral contraceptives are a reasonable contraceptive option for her.

WHICH ORAL CONTRACEPTIVE SHOULD BE PRESCRIBED? ARE ANY ORAL CONTRACEPTIVES PARTICULARLY WELL SUITED FOR WOMEN OLDER THAN 35 YEARS OF AGE?

Many oral contraceptive formulations are available. Decisions regarding oral contraceptive choice should depend on many factors, including health risks, noncontraceptive benefits, and cost. Many insurers do not routinely cover oral contraceptives, and the monthly cost can range from \$16.40 to \$31.64 (average wholesale price) (131).

A pill with the lowest effective estrogen dose should be selected. Because oral contraceptives containing 20 μ g of estrogen do not seem to exhibit adverse coagulation effects in vitro (132), these types of oral contraceptives should be considered for any patient who smokes. However, no evidence confirms reduced cardiovascular risk with estrogen formulations containing 20 μ g, although cardiovascular risk is clearly reduced in oral contraceptives with less than 35 μ g compared with those containing 50 μ g of estrogen or more. There is currently no evidence that the type of progestin in oral contraceptives affects a woman's risk for stroke or myocardial infarction, but it may influence her venous thromboembolism risk.

You write the patient a prescription for an oral contraceptive with 20 μ g of ethinyl estradiol. You discuss some of the most common side effects of oral contraceptives with the patient, who is particularly concerned about the potential for weight gain.

WHAT ARE THE COMMON SIDE EFFECTS OF ORAL CONTRACEPTIVES?

About 25% of women experience minor side effects while using oral contraceptives, most commonly during the first 3 months (133). Because these side effects can lead to nonadherence or discontinuation of oral contraceptive use, patient education about expected common side effects and ways to prevent them is essential (134, 135). The most common reason patients discontinue use is abnormal menstrual bleeding, followed by nausea, weight gain, mood changes, breast tenderness, and headache (134).

Categorizing side effects by the hormonal influence that produces them may help practitioners choose and change oral contraceptives. In our patient, using an oral contraceptive containing 20 μ g of estrogen will probably decrease the likelihood of many bothersome side effects (136) but may increase the risk for breakthrough bleeding

(137). Nausea and headaches are related to excessive estrogen. Nausea usually disappears after the second or third cycle and can be decreased by taking the pill with food or at bedtime. Headaches are typically related to vasospasm (migraines) or fluid retention. Persistent, recurrent, or severe headaches should be evaluated because they may be a harbinger of more serious complications. Headaches related to fluid retention are typically associated with edema, bloating and weight gain, or breast symptoms. Breast symptoms include tenderness, swelling, and nipple discharge and occur most often before menses begin; they are also associated with higher estrogen or progestin doses. Caffeine restriction and decreased salt intake may help.

Weight gain, mood changes, and decreased libido are of major concern to women using oral contraceptives (134). Theoretically, oral contraceptives can cause weight gain by two mechanisms: The progestin component may increase appetite, and estrogen may cause cyclic weight gain from fluid retention. However, studies of oral contraceptive users show that most have little to no change in weight (136, 138–140). Women should obtain accurate information about the side effects of oral contraceptives and should be encouraged to continue healthy eating patterns and regular exercise. Negative mood changes and decreased libido are related to progestin excess and develop in fewer than 20% of women (141).

AFTER INITIATION OF ORAL CONTRACEPTIVE USE IN A WOMAN OLDER THAN 35 YEARS OF AGE, HOW FREQUENTLY SHOULD SHE BE FOLLOWED?

Most authors recommend annual follow-up visits for most women (77, 142). Blood pressure should be checked in all oral contraceptive users at least annually (77, 116, 117, 120, 121). However, because our patient's diastolic blood pressure was borderline, her blood pressure should be checked every 2 to 3 months for several visits. If her blood pressure remains controlled, oral contraceptive use can be continued. However, if her blood pressure is consistently greater than 140/90 mm Hg or ever exceeds 160/100 mm Hg, oral contraceptive use should be discontinued indefinitely or until the blood pressure is controlled (76, 77, 143). Lipid profiles do not need to be monitored in women without a history of dyslipidemia. However, this patient does have a mild lipid abnormality; therefore, lipids should be rechecked in 3 to 6 months and then yearly if they are stable (76, 120, 122). Although some studies suggest an increased risk for cervical cancer with oral contraceptive use, there is insufficient evidence to support more frequent Papanicolaou smear screening for women using oral contraceptives (143).

All women should be counseled about symptoms that should be immediately reported to a health care provider (77). To assist patient recall, the acronym "ACHES" (abdominal pain, chest pain, headaches, eye problems, severe calf or thigh pain) may be helpful. Abdominal pain could

indicate mesenteric venous thrombosis, gallstones, or hepatic adenoma. Chest pain or shortness of breath may indicate pulmonary embolism or myocardial infarction. Severe headaches may indicate new or worsening migraines or impending stroke. Eye problems, such as loss of vision, blurry vision, or flashing lights, may indicate embolism to the eye. Finally, severe calf or thigh pains may point to deep venous thrombosis or thrombophlebitis.

Two months after starting oral contraceptive use, the patient calls you because of some spotting 1 week before her usual menses. She also tells you that she quit smoking just after her last office visit.

HOW IS BREAKTHROUGH BLEEDING MANAGED? IS A DIAGNOSTIC EVALUATION OF BREAKTHROUGH BLEEDING DIFFERENT IN A WOMAN OLDER THAN 35 YEARS OF AGE?

Breakthrough, or intermenstrual, bleeding occurs in 10% to 30% of women in the first month of oral contraceptive use (144–146). The bleeding typically resolves after the first few cycles, so initial reassurance and encouragement to continue taking oral contraceptives are warranted (77, 145). No study demonstrates one oral contraceptive formulation to be superior to another in rates of breakthrough bleeding, although bleeding seems to increase with lower hormone doses (77, 144, 146–148). Likewise, the data conflict about the relative potencies of different progestins and how these relate to breakthrough bleeding (53, 145, 146, 149–152).

Consistent use of oral contraceptives, including taking the pills at the same time each day, reduces irregular bleeding (145, 152). The antiestrogenic effects of smoking may impair the efficacy of oral contraceptives and increase the frequency of breakthrough bleeding (153). One study revealed that 29% of women taking oral contraceptives who were previously well regulated and were experiencing new breakthrough bleeding had *Chlamydia trachomatis* (154). Less frequent causes of breakthrough bleeding include medication interactions, impaired absorption, ectopic pregnancy, miscarriage, endometriosis, endometritis, fibroids, polyps, endometrial cancer, and cervical dysplasia (77, 145, 149, 151).

This patient has breakthrough bleeding during the first 2 months after starting to use an oral contraceptive containing 20 µg of estrogen. Because such breakthrough bleeding is common, the patient should be reassured and reminded to take the pill at the same time each day and avoid missing pills. If this patient frequently missed pills, a pregnancy test should be done. If she continues to have irregular bleeding after 3 to 4 months, additional evaluation (including cervical cultures and a Papanicolaou smear) may be warranted. Often, simply switching to a different oral contraceptive formulation is effective in decreasing irregular bleeding (77, 155). In addition, nonsteroidal anti-

inflammatory medications or a short course of exogenous estrogen therapy may alleviate bleeding (155). This patient's age does not warrant a different approach to the evaluation and management of breakthrough bleeding.

The patient's breakthrough bleeding stops after her third month of taking oral contraceptives, and she has no other side effects. At her 3-month follow-up visit, her blood pressure is 132/84 mm Hg. Over the next year, she tries to follow a low-fat, low-cholesterol diet, and her lipid levels are slightly improved. She continues to take oral contraceptives for the next several years. When she turns 50 years old, she wonders whether she has entered menopause.

HOW IS MENOPAUSE DIAGNOSED IN A PATIENT TAKING ORAL CONTRACEPTIVES?

Although oral contraceptive use is safe into the early fifties, it does not prevent menopause. Women who are still fertile risk pregnancy until menopause, which occurs on average by age 51 years (87). Conceptions have been reported as late as age 56 years (87), so it is important to ensure that contraception is no longer necessary before discontinuing oral contraceptive use. Follicle-stimulating hormone and luteinizing hormone levels increase and estradiol levels decrease gradually after age 35 years (88, 89, 92). Follicle-stimulating hormone levels consistently higher than 30 IU/L in a nonmenstruating woman have been considered diagnostic of menopause (110, 156); however, these levels occasionally fail to increase in postmenopausal women, even after discontinuation of use of active pills for 14 days (156). Moreover, perimenopausal women may experience elevated follicle-stimulating hormone levels and amenorrhea followed by resumption of ovulatory cycles (157).

The risks and benefits of hormone replacement therapy should be thoroughly discussed with each patient. Published guidelines are available for transitioning women if they wish to begin hormone replacement therapy (77, 155, 158). If a woman does not require contraception and wishes to initiate hormone replacement therapy, it is recommended that she switch to either cyclic or continuous combined hormone replacement therapy at age 50 years or greater. If contraception is still required, a woman may safely continue taking oral contraceptives until age 55 years, when conception is extremely unlikely. At this point, a woman can switch to standard hormone replacement therapy if she selects this option (158).

SUMMARY

Oral contraceptives can be safely prescribed to many women older than 35 years of age until menopause. Numerous benefits unrelated to contraception may be attractive to women of this age group. Although more studies that focus on perimenopausal women are needed, existing data support oral contraceptive use in most women older

than 35 years of age. Clinicians should educate women in this age group about the benefits of oral contraceptives while addressing misperceptions to allow more women this therapeutic option.

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