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May 4, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

**Re: "Draft Labeling for Industry on Labeling for Combined Oral Contraceptives;
Availability" (Docket No. 2000D-1350)**

On behalf of the American College of Obstetricians and Gynecologists (ACOG) an organization representing over 40,000 physicians dedicated to improving women's health care, I am pleased to provide comments on the Food and Drug Administration (FDA) draft guidance for industry on combined oral contraceptives (COCs) (69 Federal Register 44, 10457-10458).

ACOG supports actions by the FDA that increase the usefulness and clarity of labeling of drug products for physicians and patients. It is critical that there be clear and accurate labeling for drug products that require daily use and have a small margin for error, such as COCs. ACOG provided comments in 2000 on the previous revision of this guidance, and we are pleased that some of these comments have been addressed in the current draft. We find the new approach for the patient labeling to be particularly useful and a significant improvement over the previous draft.

We believe, however, that specific areas of the current draft guidance need further clarity and updated literature support. At present, certain areas of the document appear to stray from the science and some changes could be interpreted as politically motivated. Our most significant concerns include outdated evidence for vascular risks, inappropriate requirement of pelvic examination and laboratory tests as a prerequisite for prescribing COCs, and a failure to recognize the substantial noncontraceptive health benefits of COCs.

As we did in our 2000 comments, we are enclosing a copy of the evidence-based ACOG Practice Bulletin "The Use of Hormonal Contraception in Women with Coexisting Medical Conditions," which differs from the draft guidance in several areas—particularly contraindications. These areas of difference and our other clinical recommendations and comments are as follows.

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C21

LABELING FOR PACKAGE INSERT

Indications and Usage

The wording of the indication for the use of COCs is inappropriate and poorly reflects the current scientific knowledge of the excellent effectiveness of COCs with correct use. In addition, to say that COCs are “indicated for use by women to *lower the risk* of becoming pregnant” (italics added), rather than “for the prevention of pregnancy,” as in the 2000 draft, places an unequal and unfair burden on COCs. No pharmaceutical agent is 100% effective, and to single out COCs in this way will inappropriately diminish women’s confidence in the effectiveness of these products. Used as directed, COCs are extremely effective in preventing pregnancy. We strongly recommend that the language in the 2000 draft be reinstated.

We also recommend that a current version of Hatcher and Trussell’s failure rates (as appeared in the 2000 version) be used instead of the simplified chart in this draft. This simplification overestimates the effectiveness of typical use of COCs and underestimates the effectiveness of condom use in preventing pregnancy.

Contraindications

We note with appreciation that several of our comments provided on the 2000 draft of the guidance have been incorporated.

We continue to believe, however, that for some women the use of COCs in women with a history of venous thromboembolism (VTE) ought to be individualized. Women who have had a single episode of VTE in the remote past associated with a nonrecurring risk factor (eg, after immobilization following a motor vehicle accident) may not be at increased risk for VTE.

Although the addition of congenital hypercoagulopathies to this draft of the guidance is consistent with current evidence, we have some concern that this may lead to inappropriate screening of women in order to determine whether they are so affected. As noted in the enclosed Practice Bulletin, screening would identify approximately 5% of COC candidates as having factor V Leiden mutation, but the great majority of these women will never experience VTE, even if they use COCs. It has been estimated that screening more than 1 million COC candidates for thrombophilic markers would, at best, prevent 2 COC-associated deaths. We suggest that it be clarified under “Warnings” that screening of women of unknown status is not recommended.

The addition of “other hormone-sensitive cancer” to this draft requires further explanation as to which cancers are meant. If gynecologic cancers are meant, standard treatment for these cancers generally involves hysterectomy or oophorectomy, which would leave a woman sterile and in no need of contraception. If other cancers are intended, they should be specified.

In addition, we suggest that “active” liver disease be specified on line 108 and that line 111 indicate that superficial thrombophlebitis is not included.

Warnings

This draft appropriately recognizes that the decision to use COCs in women with medical conditions is not made in a vacuum but should take into consideration the woman's risk of pregnancy and possibility of use of other contraceptive methods. We suggest, therefore, that lines 148 and 176 include the risk of thromboembolic disease associated with pregnancy (60/100,000 women) vs. the 10-15 cases/100,000 women per year among users of older, low-dose COCs.

The decision whether to discontinue COCs before surgery appears to be properly nuanced. We do recommend, however, that the "elective surgery of a type associated with an increase in risk of thromboembolism" be defined as major surgery; discontinuation of COCs is not necessary before laparoscopic tubal sterilization or other brief surgical procedures. The possibility of other prophylactic measures, such as heparin, should be considered as well.

The data on vascular risks appear to be quite old, and a new literature search would be beneficial. For example, at line 183, the relative risk of heart attack for current OC users ("two to six") appears incorrect unless the data refer to older, higher-dose pills. There is little to any increased risk for healthy users of the currently available low-dose pills. See, for example Pettiti et al 2003 N Engl J Med. Similarly, the risk of stroke appears not to reflect current data. We recommend that lines 199-200 say: "Some observational studies show an increased risk of stroke among women using COCs. However, other studies have found no increase in the overall risk of arterial stroke (either ischemic or hemorrhagic) among current low-dose OC users." (See Pettiti DB et al N Engl J Med 1996;335:8-15 and WHO Collaborative study of cardiovascular disease and steroid hormone contraception. Lancet 1996;348:498-505)

In the section on liver disease, it should be noted that liver tumors are extremely rare among young women—stating only the attributable risk without the absolute risk is distorting. Also, it should be noted that WHO data show no increased risk of liver cancer with OC use (Leon DA, Int J Cancer 1989;43:254-9).

Regarding diabetes, newer data indicate that COCs do not enhance the progression of diabetes (see, for example, Klein BEK et al, Diabetes Care 1990;13:895-8 and Garg SK et al, JAMA 1994;271:1099-1102). Regarding high blood pressure, the Nurses Health Study II found only 42 cases of elevated blood pressure per 10,000 person-years of low-dose COC use. (Chasan-Taber L, et al. Am J Epidemiol, 1996 Aug 1;94:483-9).

Precautions

In the general section, we oppose the new requirements for physical examinations and laboratory tests. Although preventive services, such as cervical cytology, are an important part of women's health care, it is questionable whether they are useful in informing the decision whether to prescribe COCs. Making such services a prerequisite to obtaining COCs undeniably poses a barrier to obtaining necessary services for those who most critically need reliable contraception.

ACOG recommends that the physical examination may be deferred at the woman's request or in appropriate circumstances, particularly in young teens. We strongly urge that this section incorporate the following language from the FDA Advisory Committee Recommendation: "Physical examination may be deferred until after initiation of oral contraceptives if requested by the woman and judged appropriate by the clinician."

As medicine continues to limit the morbidity and mortality associated with human immunodeficiency virus (HIV) infection yet infections continue to occur, more HIV-positive women of reproductive age will need effective means of contraception. We believe that providing information on drug interactions of COCs with anti-HIV protease inhibitors will be useful to clinicians in prescribing contraception for HIV-positive women. However, non-nucleoside reverse transcriptase inhibitors (NNRTIs) may have a similar effect, and one of these (nevirapine) is in common use in the obstetric-gynecologic community as it is used to prevent maternal-fetal transmission—a current government priority. We recommend that NNRTIs be addressed here as well. Similarly, more women are turning to complementary and alternative therapy, and it will be beneficial for clinicians to know the drug interactions of herbal products such as St. John's wort with COCs.

Adverse Experiences

Because breakthrough bleeding is relatively common, it should be added to the side effects, as it is in the patient labeling.

Possible Health Benefits

Use of COCs has many significant well-established noncontraceptive health benefits for women, and the omission of several of these is inexplicable. There is abundant high-quality evidence supporting the role of COCs (including lower-dose formulations) in protecting against endometrial cancer and ovarian cancer and decreasing the incidence of ectopic pregnancy. (CDC CASH study, JAMA 1983;249:1600-4, JAMA 1983;249:1596-9; Grimes DA and Economy KE, Am J Obstet Gynecol 1995;172:227-35; Schlesselmann JJ, Obstet Gynecol 1995;85:793-801; Franks AL et al, Am J Obstet Gynecol 1990;163:1120-3; Marchbanks P, et al. JAMA 1988;259:1823-7.) Failing to include these well-supported benefits would suggest that something other than the scientific evidence is motivating the FDA process. Additionally, benefits should be described as being "beyond preventing pregnancy," not "beyond lowering of risk of becoming pregnant" as in the current draft.

PATIENT LABELING

The approach to patient labeling in this draft is clearer than the same section in the 2000 draft. Requiring manufacturers to address just the formulation that is packaged (ie, 21-day pack or 28-day pack) will help women understand the important information in this section. The inclusion of illustrations of the pill pack and the direction in which pills are taken will also be helpful.

The section on how well pills work is important to giving patients a clear understanding of what to expect with pill use. As the section notes, the failure rate is dependent on whether use is “typical” or “perfect,” so—as for the package insert—we suggest that the Hatcher and Trussell data be provided here instead of the simplified table. Because COCs are quite effective in preventing pregnancy, this section appears to be overly negative.

The section on management of missed pills will be crucial for women’s effective use of COCs. We are very pleased that the directions on what women should do if they miss a pill(s) have been made more explicit, but we have concerns that the current labeling would require excessive use of both back-up contraception and additional pills. For example, the management recommended in the current draft when women missed two active pills is very similar to the Yuzpe regimen of emergency contraception. This regimen is clearly effective in women who have had unprotected intercourse around the time of ovulation, but it is also associated with significant side effects. Whether it is warranted in this circumstance is less certain. We encourage FDA to reexamine this important issue, perhaps by consulting some of the international groups that have done work in this area.

In the “Who Should Not Take (OC Name)?” section, women cannot be expected to know which cancers are hormonally sensitive and which are not; specific cancers should be mentioned instead. Line 572 should specify “active” liver disease. While previous heart attack is a clear contraindication, “chest pains” are insufficiently specific to serve as a contraindication and ought to be deleted. In addition, angina is not addressed in the package insert. “Severe migraine headaches” may not be specific enough to guide women; we recommend that the neurologic effects be included (ie, “Severe migraine headaches with aura, numbness, weakness, or visual changes”).

In the “Side Effects” section, the most frequent side effect is breakthrough bleeding—it ought to be listed first. Also, the less common side effects do not match the similar section in the package insert. The two inserts should be in agreement.

In the “Most Serious Risks” section, reference to blood clots in the eyes and gallbladder problems should be reconsidered. The package insert indicates that COCs have been associated with retinal vein thrombosis on the basis of case reports. This level of evidence may be insufficient to warrant including effects on the eyes. Similarly, the current draft of the package insert now describes the risk on gallbladder disease as “minimal,” so it may be preferable to omit gallbladder disease. At line 682, it should be specified that pain is in one leg. At line 684, “or sudden neurologic symptoms like visual changes, weakness, numbness” ought to be added. Line 686 ought to specify “sudden severe headache unlike any previous headaches.”

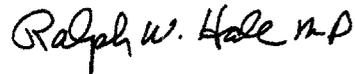
CONCLUSION

Combined oral contraceptives remain the most popular reversible form of contraception for women. Ensuring that the labeling of COCs is clear and accurate is vitally important to the appropriate prescribing and use of these products. ACOG appreciates the opportunity to

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comment on the FDA draft guidance on COCs. As an organization dedicated to improving women's health care, we welcome the opportunity to work further with the FDA on this issue and would be pleased to discuss our views in more detail.

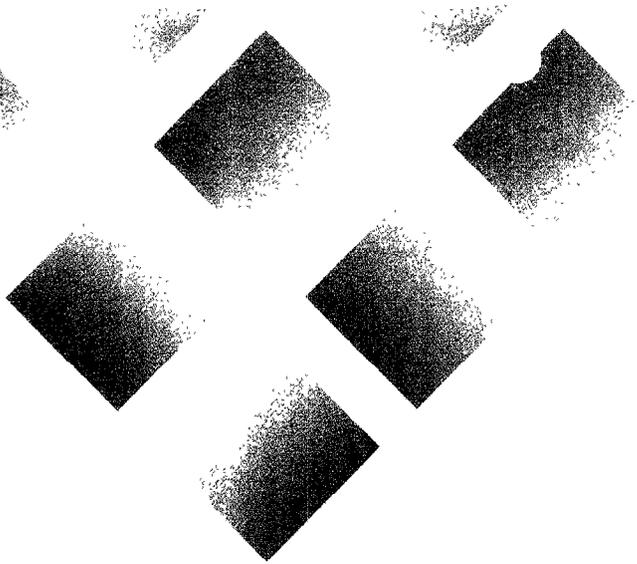
Sincerely,

A handwritten signature in black ink that reads "Ralph W. Hale MD". The signature is written in a cursive style.

Ralph W. Hale, MD, FACOG
Executive Vice President

Attachment

cc: Paula J. Adams Hillard, MD, FACOG
Herbert Peterson, MD, FACOG



ACOG PRACTICE BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR
OBSTETRICIAN-GYNECOLOGISTS

NUMBER 18, JULY 2000

This Practice Bulletin was developed by the ACOG Committee on Practice Bulletins—Gynecology with the assistance of Andrew M. Kaunitz, MD. The information is designed to aid practitioners in making decisions about appropriate obstetric and gynecologic care. These guidelines should not be construed as dictating an exclusive course of treatment or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to the institution or type of practice.



The Use of Hormonal Contraception in Women with Coexisting Medical Conditions

Although numerous studies have addressed the safety and effectiveness of hormonal contraceptive use in healthy women, data are far less complete for women with underlying medical problems or other special circumstances. Because recommendations vary widely, substantial confusion exists with respect to contraceptive guidelines for women with coexisting medical conditions or other concerns. Using available scientific evidence, this Practice Bulletin will provide information to facilitate contraceptive counseling and selection for women with coexisting medical conditions.

Background

Decisions regarding contraception for women with coexisting medical problems may be complicated. In some cases, medications taken for certain chronic conditions may alter the effectiveness of hormonal contraception, and pregnancy in these cases may pose substantial risks to the mother as well as her fetus. Package labeling approved by the U.S. Food and Drug Administration for progestin-only oral contraceptives (OCs) is occasionally the same as that for combined estrogen-progestin preparations. For instance, current labeling for norethindrone progestin-only OCs no longer lists a history of thromboembolism as a contraindication (1). Such a history, however, remains listed as a contraindication in package labeling for norgestrel progestin-only pills and for depot medroxyprogesterone acetate (DMPA) injections.

Sometimes, simultaneous use of two contraceptive methods is appropriate. For instance, although hormonal contraception provides effective birth control

for women at risk for human immunodeficiency virus or other sexually transmitted diseases (or those currently infected), such patients also should be encouraged to use male or female condoms correctly and consistently to prevent disease. For women concomitantly using major teratogens, such as isotretinoin or thalidomide, simultaneous use of two methods of contraception (eg, OCs and condoms) also may be appropriate.

This Practice Bulletin will focus on selection of hormonal contraceptives for women with coexisting medical problems. However, practitioners should recognize that the use of other nonhormonal forms of contraception, such as intrauterine devices, represent a safe, effective choice for many women.

Clinical Considerations and Recommendations

This document will address the use of combination OCs in women who have the following conditions and risk factors:

- Older than 35 years
- Smoke tobacco products
- Hypertension
- Diabetes
- Migraine headaches
- Fibrocystic breast changes, fibroadenoma, or family history of breast cancer
- Uterine fibroids
- Lipid disorders
- Breastfeeding/postpartum
- Take concomitant medication
- Anticipate surgery
- Venous thromboembolism (VTE)
- Systemic lupus erythematosus (SLE)
- Sickle cell disease

In addition, the document will review clinical settings in which the use of progestin-only contraceptives represent safe alternatives for women with contraindications to combination OCs (see the box). The effect of DMPA use on bone mineral density (BMD) will be reviewed, particularly with respect to adolescent candidates. Practitioners should be aware that patients who have any of the previously mentioned conditions or risk factors and use OCs require close monitoring and follow-up evaluation.

Indications for Contraception Methods Other Than Oral Contraceptives

In women with the following conditions, use of progestin-only oral contraceptives, depot medroxyprogesterone acetate,* or implants may be safer than combination oral contraceptives. An intrauterine device also represents an appropriate contraceptive choice for women with these conditions.

- Migraine headaches
- Older than 35 years and smoke cigarettes
- History of thromboembolic disease
- Coronary artery disease
- Congestive heart failure
- Cerebrovascular disease
- Less than 2 weeks postpartum[†]
- Hypertension with vascular disease or older than 35 years
- Diabetes with vascular disease or older than 35 years
- Systemic lupus erythematosus with vascular disease, nephritis, or antiphospholipid antibodies
- Hypertriglyceridemia

* Because of its long duration of action and potential for hypoestrogenic effects, depot medroxyprogesterone acetate may be less appropriate than other progestin-only contraceptives for some women with these listed conditions.

[†]Use of an intrauterine device may not be an appropriate contraceptive choice.

► *Is combination OC use safe for women older than 35 years?*

Use of combination OCs is safe in healthy, nonsmoking women older than 35 years. Recent large U.S. population-based case-control studies found no increased risk of myocardial infarction (2) or stroke (3) among healthy, nonsmoking women older than 35 years who use OCs formulated with less than 50 µg of estrogen.

Perimenopausal women benefit from the more regular menses and positive effect on BMD (4, 5) offered by combination OCs. In addition, use of combination OCs may reduce vasomotor symptoms in perimenopausal women (6). Furthermore, the reduced risk of endometrial and ovarian cancers associated with OC use is of particular importance to older women of reproductive age.

As increasing numbers of women in their late 40s and early 50s use combination OCs, the question of when women no longer need contraception and can consider transitioning to hormone replacement therapy will arise

more frequently. Assessment of follicle-stimulating hormone levels to determine when older OC users have become menopausal and thus no longer need contraception is expensive and may be misleading (7–10). Until a well-validated tool to confirm menopause is available, an alternative approach is for healthy, nonsmoking women doing well on combination OCs to discontinue OCs routinely between the ages of 50 and 55 years. By age 55, the likelihood that a woman has reached menopausal status is at least 85% (11, 12).

► ***Is combination OC use safe for women who smoke cigarettes?***

Smoking represents the single most important preventable cause of death and disability in U.S. women (13). At every opportunity, women should be encouraged to quit smoking, regardless of hormonal contraception use.

Numerous epidemiologic studies conducted from the 1960s through the 1980s observed high relative risks of myocardial infarction among women who used OCs formulated with 50 µg or more of estrogen and smoked cigarettes, compared with women who neither smoked nor used OCs (14). The absolute rates of myocardial infarction in this study increased substantially among OC users who smoked and were in their mid-30s or older. Accordingly, package labeling for combination OCs was modified to warn clinicians and OC users of the risks associated with smoking among OC users in general and particularly among those aged 35 years and older.

Data are sparse on U.S. women older than 35 years who smoke and use OCs. Recently, epidemiologic studies assessing the risk of arterial events among U.S. women using contemporary OCs formulated with less than 50 µg of estrogen have been published. These large case-control studies found no evidence that use of these lower-dose contemporary formulations increased risks of myocardial infarction (2) or stroke (3) in nonsmokers or in women who smoked, regardless of their age. Reflecting current U.S. clinical practice, these studies included few OC users who were older than 35 years or who smoked. Therefore, unless other studies confirm the safety of contemporary combination OCs in older women who smoke, practitioners should prescribe combination OCs to such women with caution, if at all. Nonetheless, the recent U.S. studies provide evidence that combination OCs should not be denied to women younger than 30 years who smoke cigarettes (15). When considering OCs for women who are between the ages of 30 and 35 years and are smokers, the number of cigarettes smoked and the competing risk of pregnancy should be taken into account. In women who are older than 35 years and are smokers, the risk of using OCs is likely to exceed the risk of pregnancy.

► ***Is combination OC use safe for women with chronic hypertension?***

Hypertension is a common condition associated with increased maternal and fetal risks should pregnancy occur, which emphasizes the importance of effective contraception for women with chronic hypertension.

Use of OCs appears to increase blood pressure, even with contemporary OC preparations. A small clinical trial found that an OC containing 30 µg of ethinyl estradiol and 150 µg of progestin increased the ambulatory blood pressure of normotensive women (approximately 8 mm Hg systolic and 6 mm Hg diastolic) (16). A small cross-sectional study of Italian women with mild hypertension found that those using combination OCs (most with 30 µg of estrogen) had ambulatory systolic blood pressures approximately 7 mm Hg higher than those not using OCs (17).

It is unclear if the use of contemporary OCs in women with hypertension increases the risk of vascular events. A large Danish case-control study of women with cerebral thromboembolism found that the risk of stroke was increased threefold in hypertensive women whether or not they used OCs (18). A large World Health Organization study conducted in developing and European countries observed that combination OC users with a history of hypertension had an increased risk of myocardial infarction and stroke (19). A pooled analysis of two U.S. population-based, case-control studies on OC use and myocardial infarction (2) and stroke (3) suggests that current OC use may not substantially increase the risk of stroke or myocardial infarction in women with hypertension. However, the studies included too few women who were hypertensive or older than 35 years to draw firm conclusions.

In healthy women of reproductive age, the incidence of myocardial infarction or stroke with use of low-dose OCs is extremely low. Although the relative risk of these conditions is increased in women with hypertension, the absolute risk remains low. In view of the increased risk of myocardial infarction and stroke associated with hypertension and uncertainty regarding additional risks of OCs, the decision to use OCs in these patients should be weighed against the risk of pregnancy associated with hypertension, and the noncontraceptive benefits of OCs should be taken into account. Women with well-controlled and monitored hypertension who are aged 35 years or younger are appropriate candidates for a trial of combination OCs formulated with 35 µg or less of estrogen, provided they are otherwise healthy, show no evidence of end-organ vascular disease, and do not smoke cigarettes. If blood pressure remains well-controlled with careful monitoring several months after initiating OCs, use can be continued.

Although coronary artery disease, congestive heart failure, and cerebrovascular disease are uncommon in women of reproductive age, the risk of pregnancy and delivery in these women can be substantial, making effective contraception important. Inadequate data are available to address the use of OCs in women with these conditions; therefore, given the increased risk of venous thromboembolism with combined OCs, their use is contraindicated. However, progestin-only contraceptives such as DMPA, progestin-only OCs, or levonorgestrel implants may be appropriate.

► ***Is combination OC use safe for women with diabetes?***

Pregnancy in women with diabetes is associated with an array of serious maternal and perinatal complications, which emphasizes the importance of effective contraception in this patient population. In theory, the steroids in combination OCs might impair carbohydrate metabolism and accelerate the occurrence of vascular disease in diabetic women. Fortunately, current combination OCs do not appear to have this effect. In a cross-sectional U.S. study, 43 women with type 1 (formerly insulin-dependent) diabetes who used combination OCs for 1–7 years (mean duration, 3.4 years) were compared with a similar number of women with type 1 diabetes who were not using OCs. The overall mean age and duration of diabetes was 23 and 14 years, respectively, in this study group. Hemoglobin A_{1c} values were similar in the OC users and nonusers, which suggests that OC use did not affect control of diabetes. Likewise, the degree of nephropathy and retinopathy was similar in both groups, which suggests that OC use did not accelerate the development of diabetic vascular disease (20).

Although studies of OC use in women with type 2 (formerly non-insulin-dependent) diabetes have not been reported, two recent papers offer reassurance that combination OC use does not precipitate this disease. A prospective cohort study, which followed more than 98,000 U.S. women nurses, found that use of combination OCs did not significantly increase the risk of developing type 2 diabetes over a 4-year follow-up period; likewise, past use did not appear to increase risk (21). In a California population of Hispanic women with gestational diabetes followed for up to 7 years postpartum, use of combination OCs did not accelerate the development of type 2 diabetes. The use of progestin-only pills by the relatively small subgroup of women who nursed their infants was associated with a significantly increased risk of developing type 2 diabetes (22), an unexpected finding that is difficult to interpret.

Although the above data support the use of combination OCs in women with diabetes, based on theoretical

concerns, such use should be limited to nonsmoking, otherwise healthy women with diabetes who are younger than 35 years and show no evidence of hypertension, nephropathy, retinopathy, or other vascular disease. Practitioners who provide contraception to women with diabetes should coordinate care with the physician treating the diabetes and follow such patients closely. Appropriate follow-up includes monitoring blood pressure, weight, and lipid status. Regardless of hormonal contraception use, women with the following risk factors should undergo blood glucose screening every 3 years: history of gestational diabetes, family history of diabetes in parents or siblings, obesity (body weight greater than 120% of ideal) or hypertension, and member of high-risk ethnic groups (African American, Hispanic, Native American).

► ***Is combination OC use safe for women with migraine headaches?***

Headaches are a frequent occurrence in women of reproductive age. Most of these headaches are tension headaches, not migraines (23). Some women with migraines experience improvement in their symptoms with the use of OCs, while some women's symptoms worsen. However, in women using OCs, most migraines occur during the hormone-free interval. Because the presence of true migraine headaches affects the decision to use OCs, careful consideration of the diagnosis is important.

A large hospital-based case-control study performed at five European centers found that women with classic migraines (with aura) had a statistically significant fourfold increased risk of ischemic stroke; women with simple migraine (without aura) had a threefold increased risk that was not statistically significant (24). Women with a history of migraines using OCs (<50 µg of estrogen) had a greater than sixfold increased risk of ischemic stroke (not statistically significant [OR 6.6; 95% CI, 0.8–55]) when compared with women who were not using OCs and who had no migraine headaches. Compared with women who did not smoke, did not use OCs, and had no history of migraines, women who smoked, were using OCs, and had a history of migraines had a 34-fold increased risk of ischemic stroke (OR 34.4; 95% CI, 3.3–361).

A pooled analysis of two large, U.S. population-based case-control studies also observed a statistically significant twofold elevated risk of ischemic stroke, as well as hemorrhagic stroke (not statistically significant) among current users of OCs who reported migraine headaches compared with women with migraines who did not use OCs (3). A large Danish population-based case-control study found that among women with a history of migraine headaches, the risk of stroke was elevated

approximately threefold ($P < 0.01$) (18). Neither study categorized migraines by type. The additional risk of thrombotic stroke attributable to women with migraines using OCs has been estimated as 8 per 100,000 women at age 20 years, and 80 per 100,000 women at age 40 years (25).

Although cerebrovascular events rarely occur among women with migraines who use combination OCs, the impact of a stroke on a woman of reproductive age is so devastating that clinicians should consider the use of progestin-only, intrauterine, or barrier contraceptives in this setting. Concerns remain that all women with migraines are at increased risk of stroke. However, because absolute risk remains low, the use of combination OCs may be considered for women with migraine headaches if they do not have focal neurologic signs, do not smoke, are otherwise healthy, and are younger than 35 years.

► ***Does the use of combination OCs increase the risk of breast cancer in women with fibrocystic breast changes, fibroadenoma, or a family history of breast cancer?***

Women with fibroadenoma, benign breast disease with epithelial hyperplasia with or without atypia, or a family history of breast cancer have an increased risk of breast cancer (26). A recently published massive reanalysis of 54 studies assessing the association of OC use and breast cancer risk, however, provides reassurance to these women and to their clinicians regarding OC use. Overall, this reanalysis found that 10 years or more after discontinuing OC use, the risk of breast cancer was identical among these former OC users and those who never used OCs. Small but significantly increased relative risks (RR) were observed in current OC users (RR, 1.24) and those who had used OCs in the previous 1–4 years (RR, 1.16) or 5–9 years earlier (RR, 1.07). The increase in risk was restricted to women with localized disease; there was an associated reduced risk of metastatic disease, which suggests that much if not all of the risk can be attributed to early diagnosis of existing disease (27).

A positive family history of breast cancer in a mother or sister, or both, or a history of benign breast disease should not be regarded as contraindications to OC use. Use of OCs has an identical effect on the risk of breast cancer for women with and without each of these two risk categories (27)

► ***What are the effects of combination OC use in women with uterine leiomyomata?***

Use of combination OCs reduces menstrual blood loss in women with normal menses as well as in those with men-

orrhagia (28). A Swedish study conducted in the 1960s using high-dose oral contraceptives, which are not currently used, noted OC use significantly reduced bleeding in women with menorrhagia associated with uterine fibroids (29). Oral contraceptive use also reduces dysmenorrhea (28). Some practitioners routinely employ the use of combination OCs as first-line medical management in women with menorrhagia or dysmenorrhea associated with uterine leiomyomata. Several large epidemiologic studies have observed that OC use does not induce the growth of uterine fibroids and may decrease bleeding disorders in these women (30–32).

► ***Is combination OC use safe for women with lipid disorders?***

The term “dyslipidemia” includes disorders of lipoprotein metabolism that lead to atherosclerosis. These abnormalities arise from genetic and secondary factors and are caused by excessive entry of lipoproteins into the bloodstream, an impairment in their removal, or both.

The estrogen component of combination OCs enhances removal of low-density lipoprotein (LDL) and increases levels of high-density lipoprotein (HDL) cholesterol. Both of these actions can have a favorable effect on a woman’s risk of coronary artery disease. Oral estrogen also increases triglyceride levels; however, in the setting of concomitantly increased HDL and decreased LDL levels, the moderate triglyceride elevations caused by oral estrogen use do not appear to increase the risk of atherogenesis. Numerous epidemiologic studies of past use of OCs find no increased risk of cardiovascular disease, arguing against any adverse long-term effect of OCs on the risk of atherogenesis (33). The progestin component of combination OCs antagonizes these estrogen-induced lipid changes, which increases LDL levels and decreases HDL and triglyceride levels. Accordingly, among women taking combination OCs with an identical dose of estrogen, the choice (and dose) of the progestin component affects net lipid changes. It is not known whether the differential lipid effects of distinct OC formulations have any clinical significance in women with normal baseline lipid levels or those with lipid disorders.

Using guidelines from the National Cholesterol Education Program (34), experts have recommended that most women with controlled dyslipidemia can use combination OCs formulated with 35 µg or less of estrogen. In contrast, in women with uncontrolled LDL cholesterol greater than 160 mg/dL or multiple additional risk factors for coronary artery disease (including smoking, diabetes, obesity, hypertension, family history of premature coronary artery disease, HDL level <35 mg/dL, or triglyceride level >250 mg/dL), use of alternative contraceptives

should be considered (35). Fasting serum lipid levels should be monitored as frequently as each month after initiating combination OC use in dyslipidemic women; less frequent monitoring is appropriate once stabilization of lipid parameters has been observed.

Ongoing communication with the patient's primary care physician (or internist) is appropriate, and the importance of a low-fat diet, daily exercise, and the achievement of ideal body weight should be emphasized (22). Concomitant hormonal contraception and lipid-lowering therapy may be appropriate in some women.

► ***What hormonal contraceptive options are available for postpartum and lactating women?***

Postpartum women remain in a hypercoagulable state for weeks after childbirth. Product labeling for combination OCs advises deferring use until 4 weeks postpartum in nonbreastfeeding women. Because first ovulation after delivery can occur in as little as 25 days (36), some practitioners initiate the use of combination OCs in nonbreastfeeding women as early as 2 weeks after childbirth, although no data support or refute the safety of this approach. Because progestin-only OCs, DMPA, and implants do not contain estrogen, these methods may be safely initiated immediately postpartum (37).

Combination OCs are not recommended as the first choice for breastfeeding mothers because of the negative effect of contraceptive doses of estrogen on lactation. The estrogenic component of combination OCs can reduce the volume of milk production and the caloric and mineral content of breast milk in lactating women (38). However, use of combination OCs by well-nourished breastfeeding women does not appear to result in infant development problems (38). Their use can be considered once milk flow is well established.

Progestin-only contraceptives do not impair lactation and, in fact, may increase the quality and duration of lactation (39). In nursing women using progestin-only OCs, very small amounts of progestin are passed into the breast milk, and no adverse effects on infant growth have been observed (40). Product labeling for progestin-only pills may suggest that fully breastfeeding women begin tablets 6 weeks postpartum and advise partially breastfeeding women to begin at 3 weeks.

Like other progestin-only methods, DMPA use does not adversely affect breastfeeding (38). Product labeling for DMPA advises initiation of use within the first 5 days postpartum if not breastfeeding and, if exclusively breastfeeding, at 6 weeks postpartum. When initiated immediately postpartum, however, use of DMPA does not adversely affect lactation (38) or infant development (41).

Product labeling for progestin subdermal implants indicates that insertion should be deferred until 6 weeks postpartum in lactating women. Studies of the effects of implant use on lactation and infant development investigated outcomes of insertion at least 30 days postpartum (42, 43). Although the results of these studies have been reassuring, data assessing immediate postpartum implant insertion in breastfeeding women are needed. Given the lack of procoagulation effect and the apparent safety in nursing mothers with DMPA and implants, their immediate postpartum use in both lactating and nonlactating women appears reasonable.

► ***What hormonal contraceptive options are available for women taking concomitant medications?***

For women with seizure disorders, the frequency of seizures may increase during pregnancy (44). In addition, the risk of birth defects is intrinsically increased in these women (44). Finally, many anticonvulsants are teratogens (44). Each of these observations emphasizes the importance of providing effective contraception for women with seizure disorders.

Anticonvulsants that induce hepatic enzymes can decrease serum concentrations of the estrogen or progestin component of OCs, or both (45) (see the box, "Interaction of Anticonvulsants and Combination Oral Contraceptives"). This effect has been observed with phenobarbital (46), phenytoin, carbamazepine (47), felbamate (48), and topiramate (49). Therapeutic doses of vigabatrin do not induce hepatic enzymes. Nonetheless, a small clinical trial found ethinyl estradiol levels lower than during placebo use in two of 13 volunteers taking this anticonvulsant (50). Although each of these studies demonstrated reduced serum levels of OC steroids during anticonvulsant use, and many of them demonstrated associated breakthrough bleeding, investigators did not observe ovulation or accidental pregnancy during anticonvulsant use. Although some clinicians prescribe OCs containing 50 µg of ethinyl estradiol to women taking these anticonvulsants, no published data support the enhanced contraceptive efficacy of this practice. Use of condoms in conjunction with OCs or use of DMPA or an intrauterine device may be considered for such women (see the box).

In contrast to the above anticonvulsants, use of valproic acid (51), gabapentin (52), and tiagabine (53) does not appear to decrease serum levels of contraceptive steroids in women using combination OCs. Practitioners should be aware, however, that studies of the latter agents were performed using anticonvulsant doses lower than those used in clinical practice (54).

Interaction of Anticonvulsants and Combination Oral Contraceptives

Anticonvulsants that decrease steroid levels in women taking combination oral contraceptives

Barbiturates (including phenobarbital and primidone)

Phenytoin

Carbamazepine

Felbamate

Topiramate

Vigabatrin

Anticonvulsants that do not decrease steroid levels in women taking combination oral contraceptives

Valproic acid

Gabapentin*

Lamotrigine*

Tiagabine*

*Pharmacokinetic study used anticonvulsant dose lower than that used in clinical practice.

Although there have been many anecdotal reports of OC failure in women taking concomitant antibiotics, pharmacokinetic evidence of lower serum steroid levels exists only for rifampin (55) and griseofulvin (56) (see the box, "Interaction of Antiinfective Agents and Combination Oral Contraceptives"). Because OC steroids are strikingly reduced in women concomitantly taking rifampin, such women should not rely on combination OCs, progestin-only OCs, or implants for contraceptive protection. Pharmacokinetic studies have not demonstrated lowered

Interaction of Antiinfective Agents and Combination Oral Contraceptives

Antiinfective agents that decrease steroid levels in women taking combination oral contraceptives

Rifampin

Griseofulvin

Antiinfective agents that do not decrease steroid levels in women taking combination oral contraceptives

Tetracycline

Doxycycline

Ampicillin

Metronidazole

Quinolone antibiotics

OC steroid levels with concomitant use of tetracycline (57), doxycycline (58), ampicillin or metronidazole (59), or quinolone antibiotics (60–62).

Serum progestin levels during use of progestin-only OCs and implants are lower than during combined OC use. Accordingly, these low-dose progestin-only contraceptives are not appropriate choices for women using concomitant liver enzyme inducers (40, 63). The contraceptive efficacy of DMPA in women taking hepatic enzyme inducers has not been explicitly studied. A potential advantage of using DMPA in women with seizure disorders is DMPA's intrinsic anticonvulsant effect (23).

► Is hormonal contraceptive use safe for women with a history of thromboembolism?

The estrogenic component of combination OCs, which increases hepatic production of serum globulins involved in coagulation (including factor VII, factor X, and fibrinogen), increases the risk of VTE in users. Beginning in 1995, European studies clarified that, compared with nonusers, current users of OCs formulated with 35 µg or less of estrogen experience a threefold to fourfold increased risk of VTE. This risk, in absolute terms, remains lower than the increased risk of VTE during pregnancy.

The goal of screening OC candidates with respect to VTE risk is to identify those women for whom the VTE risk associated with OC use outweighs OC benefits. In addition to current use of exogenous estrogens, risk factors for VTE include pregnancy and the puerperium, personal or family history of VTE, obesity, surgery, and certain familial coagulation disorders. Although cigarette smoking, hypertension, and diabetes represent risk factors for arterial disease, including myocardial infarction and stroke, they do not increase VTE risk (64). Likewise, the presence of superficial varicose veins does not increase VTE risk (64). Health risks (including VTE) associated with pregnancy, noncontraceptive OC benefits, and the potential for effective use of contraceptives that do not increase VTE risk (eg, progestin-only OCs and intrauterine and barrier methods) should all be factored into risk-benefit considerations. Practitioners should be aware that package labeling for DMPA and for certain brands of progestin-only OCs inappropriately indicates that a history of VTE contraindicates the use of these progestin-only methods.

Women with a documented history of unexplained VTE or VTE associated with pregnancy or exogenous estrogen use should not use combination OCs unless they are currently taking anticoagulants. An OC candidate

who had experienced a single episode of VTE years earlier associated with a nonrecurring risk factor (eg, VTE occurring after immobilization following a motor vehicle accident) may not currently be at increased risk for VTE. Accordingly, the decision to initiate combination OCs in such a candidate can be individualized.

► ***Should women awaiting surgery discontinue combination OC use?***

Venous thromboembolism with pulmonary embolism remains a major cause of fatalities associated with surgical (including gynecologic) procedures. Findings of a large British prospective cohort study suggested that the risk of postoperative VTE was approximately twice as high ($P>0.05$) in OC users as in nonusers (65). A prospective study found that, among women taking OCs formulated with 30 µg of estrogen, OC-induced procoagulant changes did not substantially resolve until 6 or more weeks after OC discontinuation (66). Accordingly, the risks associated with stopping OCs 1 month or more before major surgery should be balanced against the risks of an unintended pregnancy (67). In current OC users having major surgical procedures, heparin prophylaxis should be considered (67). Because of the low perioperative risk of VTE, it currently is not considered necessary to discontinue combination OCs before laparoscopic tubal sterilization or other brief surgical procedures.

► ***Is OC use safe in women with hypercoagulable states?***

Women with factor V Leiden mutation who use OCs experience a risk of VTE 30 times higher than non-OC users who are not carriers of the mutation (68). A clotting assay can determine activated protein C resistance, and a polymerase chain reaction test can identify the presence of factor V Leiden mutation. Such screening would identify approximately 5% of U.S. OC candidates as having factor V Leiden mutation; however, the great majority of these women will never experience VTE, even if they use combination OCs (69). Given the rarity of fatal VTE, one group of investigators concluded that screening more than 1 million combination OC candidates for thrombophilic markers would, at best, prevent two OC-associated deaths (70). Some practitioners may choose to test for factor V Leiden mutation in women with a positive family history of VTE who are considering OC use or pregnancy. In this setting, the clinician should weigh factors including age of onset of thrombosis in affected family members, the clinical setting, and severity of thrombotic episodes. The risks, benefits, and financial implications of such selective testing, however, are unknown.

Women using warfarin for chronic anticoagulation may experience menorrhagia and, rarely, hemoperitoneum following rupture of ovarian cysts. In addition, warfarin is a teratogen. Because use of combination OCs can reduce menstrual blood loss (28) and does not increase the risk of recurrent thrombosis in well-anticoagulated women (69, 71), some authorities recommend their use in such patients. Because intramuscular injection of DMPA consistently suppresses ovulation (72), DMPA represents another potential contraceptive choice in anticoagulated women.

► ***Does the use of emergency contraception increase the risk of VTE?***

Use of postcoital (emergency) contraception may increase in the United States with the recent availability of a dedicated product. A recent retrospective cohort analysis from Britain found no cases of thromboembolism in more than 100,000 episodes of postcoital contraception use with the Yuzpe regimen (73).

► ***Are hormonal contraceptives safe for women with SLE?***

Because the risks of maternal and perinatal morbidity as well as mortality can be high in pregnancies complicated by SLE, effective contraception is an important component of the care of such women. Particular concerns about hormonal contraception use in women with SLE relate to the increased risk of venous and arterial thrombosis in women with this disease. A small retrospective cohort study noted that while combination OC use was associated with flare-ups in SLE patients with renal disease, progestin-only OC use was not associated with increased disease activity (74). One retrospective cohort study of 85 women with SLE noted that among 31 patients using combination OCs, increased disease activity was not precipitated by OC use. However, deep vein thrombosis was diagnosed in two OC users; both of these women had antiphospholipid antibodies (75). A small prospective cohort study found that use of progestin-only OCs or contraceptive injections was not associated with increased SLE activity (76).

Existing data from observational studies suggest that combination OC use should be avoided in SLE patients with a history of vascular disease, nephritis, or antiphospholipid antibodies, although progestin-only methods are safe alternatives. Data are insufficient to address the use of combination OCs among women with stable or inactive disease who have no history of thrombosis, nephropathy, or antiphospholipid antibodies (77). If such women do not wish to use progestin-only methods, use of combination OCs with close monitoring can be considered in selected cases.

► ***Is hormonal contraceptive use safe for women with sickle cell disease?***

In persons with sickle cell disease, abnormal hemoglobin precipitates and becomes rigid when subjected to oxygen deprivation. Vasoocclusive episodes in those with sickle cell disease, however, differ from intravascular thrombosis (78). Pregnancy in women with sickle cell disease carries increased risks of maternal complications and is associated with elevated rates of spontaneous abortion, intrauterine growth restriction, and neonatal mortality.

No well-controlled study has assessed whether VTE risk in OC users with sickle cell disease is higher than in other combination OC users. Accordingly, recommendations regarding use of combination OCs in this patient population vary widely. On the basis of studies of pregnant women with sickle cell disease, small observational studies of women with sickle cell disease who use combination OCs, and theoretical considerations, the consensus is that pregnancy carries a greater risk than combination OC use.

Two controlled studies have assessed the use of DMPA in women with sickle cell disease (79, 80). Both of these found that use of DMPA reduced the incidence of painful crises. Accordingly, DMPA may be a particularly appropriate contraceptive for women with sickle cell disease.

► ***What are the effects of DMPA on bone density?***

Use of DMPA in contraceptive doses suppresses ovarian production of estradiol. Thus, there has been concern that women using DMPA for contraception might develop osteopenia. A New Zealand study of women who used DMPA for at least 5 years found significantly reduced bone density in the lumbar spine and femoral neck compared with premenopausal controls (81). A subsequent study performed by the same investigator noted that among women who had used DMPA for at least 3 years, deficits in BMD of the lumbar spine were reversible following DMPA discontinuation (82). Five recent cross-sectional studies suggest that DMPA use decreases BMD of the spine (83–87). In the largest of these studies, the median duration of DMPA use was 12 years. In this study, initiation of DMPA use before age 21 years and use for more than 15 years were identified as risk factors for osteopenia (84). None of these cross-sectional studies found evidence of osteoporosis or fractures in DMPA users.

Information on the effects of DMPA use on BMD during adolescence is limited. However, a small study compared BMD of the lumbar spine in females aged 12–21 years. In this prospective cohort study, BMD in those using

no hormones was compared with those using DMPA, OCs, or implants. After 1 year of use, bone density in DMPA users decreased 1.5%, whereas it increased 1.5% in OC users, 2.5% in levonorgestrel implant users, and 2.9% in those using no hormones. None of those who initially selected an OC continued after 2 years. However, follow-up BMD measurements at 2 years showed a total decrease of 3.1% in DMPA users and total increases of 9.5% in non-hormone users and 9.3% in implant users (88).

The rate-of-loss trends in BMD seen with DMPA seem to be similar to those noted during lactation (89, 90) in that no long-term decrease occurs. Two recent cross-sectional studies of menopausal women found no long-term BMD declines in former DMPA users. In these reports, BMD in former DMPA users was not significantly different from never-users (91, 92). Estrogen supplementation (eg, conjugated estrogen, 1.25 mg daily, or equivalent doses of other estrogens) can be considered for long-term users of DMPA, including adolescents. However, no data address the effect of such an add-back regimen on BMD in women using DMPA. Caution should be exercised in prescribing DMPA for adolescents, women known to be at high risk for low BMD, and perimenopausal women.

Summary

The following recommendations are based on good and consistent scientific evidence (Level A):

- Women with fibroadenoma, benign breast disease with epithelial hyperplasia with or without atypia, or a family history of breast cancer are at little or no additional risk of breast cancer because of OC use. Therefore, OCs can be prescribed for such women if they are otherwise appropriate candidates.
- Progestin-only preparations are safe and preferable forms of hormonal contraception for lactating women. Combination OCs are not recommended as the first choice for breastfeeding mothers because of the negative impact of contraceptive doses of estrogen on lactation. However, use of combination OCs by well-nourished breastfeeding women does not appear to result in infant development problems; therefore, their use can be considered once milk flow is well established.
- Hormonal contraceptive effectiveness is compromised by the use of the antibiotics rifampin and griseofulvin; thus, women taking these antibiotics should use nonhormonal contraceptives.
- Progestin-only preparations are appropriate for women at increased risk for VTE. Combination OCs

are not recommended for women with a documented history of unexplained VTE or VTE associated with pregnancy or exogenous estrogen use, unless they are taking anticoagulants.

- ▶ Combination OCs should be prescribed with caution, if ever, to women who are older than 35 years and are smokers. Women younger than 30 years who smoke and are otherwise healthy generally can be prescribed combination OCs.
- ▶ If desired, healthy, nonsmoking women doing well on combination OCs may continue their use until menopause.

The following recommendations are based on limited or inconsistent scientific evidence (Level B):

- ▶ Women with well-controlled and monitored hypertension aged 35 years and younger are appropriate candidates for a trial of combination OCs formulated with 35 µg or less of estrogen, provided they are otherwise healthy with no evidence of end-organ vascular disease and do not smoke cigarettes. If blood pressure remains well-controlled several months after initiating OCs, use can be continued.
 - ▶ The use of combination OCs by women with diabetes should be limited to such women who do not smoke, are younger than 35 years, and are otherwise healthy with no evidence of hypertension, nephropathy, retinopathy, or other vascular disease.
 - ▶ Women with migraine headaches who have focal neurologic signs are not appropriate candidates for OC use. Combination OCs can be used by women with simple migraine headaches (ie, no focal neurologic signs) if they do not smoke, are younger than 35 years, and are otherwise healthy. If such women experience increased frequency or severity of headaches or develop headaches with focal neurologic signs or symptoms, they should discontinue OC use.
 - ▶ Combination OCs may be beneficial in treating dysmenorrhea and menorrhagia in women with uterine fibroids.
 - ▶ The risks associated with stopping OCs 1 month or more before major surgery should be balanced against the risks of an unintended pregnancy. In current OC users undergoing major surgical procedures, heparin prophylaxis should be considered. Because of the low perioperative risk of VTE, it generally is considered unnecessary to discontinue combination OCs before laparoscopic tubal sterilization or other brief surgical procedures.
- ▶ Progestin-only OCs and contraceptive injections appear to be the hormonal contraception methods of choice for women with SLE. Use of combination OCs in women with SLE can be considered if the women have stable or inactive disease and no history of thrombosis, nephropathy, or antiphospholipid antibodies.

The following recommendations are based primarily on consensus and expert opinion (Level C):

- ▶ Most women with controlled dyslipidemia can use combination OCs formulated with 35 µg or less of estrogen. In women with uncontrolled LDL cholesterol greater than 160 mg/dL, a triglyceride level greater than 250 mg/dL, or multiple additional risk factors for coronary artery disease, alternative contraceptives should be considered.
- ▶ DMPA has noncontraceptive benefits and is the contraceptive method of choice for many women with sickle cell disease.
- ▶ Progestin-only contraceptives may be appropriate for women with coronary artery disease, congestive heart failure, or cerebrovascular disease. However, combination oral contraceptives are contraindicated in these women.

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The MEDLINE database, the Cochrane Library, and ACOG's own internal resources and documents were used to conduct a literature search to locate relevant articles published between January 1985 and March 1998. The search was restricted to articles published in the English language. Priority was given to articles reporting results of original research, although review articles and commentaries also were consulted. Abstracts of research presented at symposia and scientific conferences were not considered adequate for inclusion in this document. Guidelines published by organizations or institutions such as the National Institutes of Health and the American College of Obstetricians and Gynecologists were reviewed, and additional studies were located by reviewing bibliographies of identified articles. When reliable research was not available, expert opinions from obstetrician-gynecologists were used.

Studies were reviewed and evaluated for quality according to the method outlined by the U.S. Preventive Services Task Force:

- I Evidence obtained from at least one properly designed randomized controlled trial.
- II-1 Evidence obtained from well-designed controlled trials without randomization.
- II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
- II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments also could be regarded as this type of evidence.
- III Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the highest level of evidence found in the data, recommendations are provided and graded according to the following categories:

Level A—Recommendations are based on good and consistent scientific evidence.

Level B—Recommendations are based on limited or inconsistent scientific evidence.

Level C—Recommendations are based primarily on consensus and expert opinion.

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ISSN 1099-3630

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12345/43210

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