ACOG
PRACTICE
BULLETIN

CLINICAL MANAGEMENT GUIDELINES FOR
OBSTETRICIAN–GYNECOLOGISTS

NUMBER 73, JUNE 2006

(Replaces Practice Bulletin Number 18, July 2000)

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. Using the best available scientific evidence, this Practice Bulletin provides information to help clinicians and women with coexisting medical conditions make sound decisions regarding the selection and appropriateness of various hormonal contraceptives, including the levonorgestrel intrauterine system.

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.

Reaffirmed 2008

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. In addition, differences in content and delivery methods of hormonal contraceptives may affect patients with certain conditions differently. Use of the contraceptive vaginal ring is associated with lower serum ethinyl estradiol levels than is the use of the patch or oral contraceptives (1), but it is unclear how this may affect risk for a particular condition. Practitioners should recognize that other nonhormonal forms of contraception, such as the copper intrauterine device (IUD), remain safe, effective choices for many women with medical conditions (2).

Package labeling approved by the U.S. Food and Drug Administration (FDA) for progestin-only contraceptives is in some cases the same as that for combined estrogen–progestin methods without supporting evidence, further

complicating decisions for women with coexisting medical conditions. For instance, current labeling for norethindrone progestin-only oral contraceptives no longer lists a history of thromboembolism as a contraindication (3). Such a history, however, remains listed as a contraindication in package labeling for norgestrel progestin-only pills and for depot medroxyprogesterone acetate (DMPA) injections.

Addressed in this document is the use of hormonal contraceptives in women who have the following conditions and risk factors:

- Age older than 35 years
- Tobacco smoking
- Hypertension
- Lipid disorders
- Diabetes
- Migraine headaches
- Fibrocystic breast changes, fibroadenoma, or family history of breast cancer *BRCA1* or *BRCA2*
- Uterine leiomyomata
- Breastfeeding postpartum
- Concomitant medications
- Scheduled for surgery
- History of venous thromboembolism
- Hypercoagulable conditions
- Anticoagulation therapy
- Obesity
- Systemic lupus erythematosus
- Sickle cell disease
- Depression
- Human immunodeficiency virus (HIV) (acquisition, transmission, and progression)

In addition, this document provides a review of clinical settings in which the use of progestin-only contraceptives (DMPA, progestin-only pills, and the levonorgestrel intrauterine system) represent safe alternatives for women with contraindications to combination contraceptives (see the box). The effect of DMPA use on skeletal health will be reviewed, particularly with respect to adolescent candidates.

Because the transdermal and vaginal ring combination hormonal contraceptives are new, little if any data address their safety in women with underlying medical conditions. In the absence of specific evidence to the contrary, contraindications to the use of combination oral contraceptives also should be considered to apply to these newer combination methods.

Conditions Where Progestin-only Methods May Be More Appropriate

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

Migraine headaches, especially those with focal neurologic signs

Cigarette smoking or obesity in women older than 35 years

History of thromboembolic disease

Hypertension in women with vascular disease or older than 35 years

Systemic lupus erythematosus with vascular disease, nephritis, or antiphospholipid antibodies

Less than 3 weeks postpartum*

Hypertriglyceridemia

Coronary artery disease

Congestive heart failure

Cerebrovascular disease

*Use of an intrauterine device may not be an appropriate contraceptive choice.

Clinical Considerations and Recommendations

▶ *Is the use of hormonal contraception safe for women older than 35 years?*

Use of combination oral contraceptives is safe in healthy, nonsmoking women older than 35 years. Large U.S. population-based case–control studies have found no increased risk of myocardial infarction (4) or stroke (5) among healthy, nonsmoking women older than 35 years who use oral contraceptives formulated with less than 50 mcg of estrogen. Although European studies have reported an increased risk of myocardial infarction with oral contraceptive use, the prevalence of cigarette smoking is high among women in these studies (including those using oral contraceptives). It is unclear whether these European findings can be applied to healthy, nonsmoking women.

Perimenopausal women may benefit from a positive effect on bone mineral density (6) and a reduction in vasomotor symptoms (7) offered by combination oral

contraceptives. In addition, the reduced risk of endometrial and ovarian cancers associated with oral contraceptive use is of particular importance to older women of reproductive age. However, these benefits must be balanced against the impact of age and obesity as independent risk factors for cardiovascular disease. In particular, it is important to note that the background risk of venous thromboembolism increases with age and, therefore, the role of venous thromboembolism attributable to combination contraception use increases substantially for women aged 40 years and older. Because this risk increases sharply after age 39 years among combination oral contraceptive users, combination contraceptive use should be individualized in women older than 35 years; in particular, caution should be exercised for those who are obese or who have other cardiovascular disease risks (8). Data regarding the impact of oral contraceptive use by women in their late 40s and 50s on breast cancer risk are limited (9). In the absence of further evidence, it is reasonable to assume that use of oral contraceptives among women 50–55 years may have effects on the risk of breast cancer similar to those of combined hormone therapy for this age group.

As increasing numbers of women in their late 40s and early 50s use combination contraceptives, the question of when women no longer need contraception will arise more frequently. Assessment of follicle-stimulating hormone levels to determine when hormonal contraceptive users have become menopausal and thus no longer need contraception is expensive and may be misleading (10–13). Until a well-validated tool to confirm menopause is available, it is appropriate for healthy, nonsmoking women doing well on a combination contraceptive to continue use of contraceptives until age 50–55 years, after weighing the risks and benefits.

▶ *Is the use of hormonal contraception safe for women who smoke cigarettes?*

Numerous epidemiologic studies conducted from the 1960s through the 1980s observed high relative risks of myocardial infarction among women who used oral contraceptives formulated with 50 mcg or more of estrogen and smoked cigarettes, compared with women who neither smoked nor used oral contraceptives (14). The absolute rates of myocardial infarction in this study increased substantially among oral contraceptive users who smoked and were in their mid-30s or older.

More recent large case–control studies assessing the risk of arterial events among U.S. women using oral contraceptives with less than 50 mcg of estrogen found no evidence that use of these lower-dose formulations increased risks of myocardial infarction (4) or stroke (5) in nonsmokers or in women who smoked, regardless of age. Reflecting current U.S. clinical practice, however, these studies included few oral contraceptive users who were older than 35 years or who smoked. A Dutch case–control study observed that oral contraceptive use combined with smoking was associated with an odds ratio for myocardial infarction (13.6) almost twice as high as that observed for smoking alone (7.9) (15). Given the limited amount of conclusive data, practitioners should prescribe combination hormonal contraceptives with caution, if at all, to women older than 35 years who smoke.

▶ *Is the use of hormonal contraception safe for women with chronic hypertension?*

Use of oral contraceptives appears to increase blood pressure, even with contemporary oral contraceptive preparations. In a small nonrandomized clinical trial, normotensive women who began an oral contraceptive containing 30 mcg of ethinyl estradiol and 150 mcg of progestin had ambulatory blood pressure increased by approximately 8 mm Hg systolic and 6 mm Hg diastolic compared with no such increase in women beginning use of a copper IUD (16). A small cross-sectional study of Italian women with mild hypertension found that those using combination oral contraceptives (most with 30 mcg of estrogen) had ambulatory systolic blood pressures approximately 7 mm Hg higher than those not using oral contraceptives (17).

Some studies on the use of combination contraceptives in women with hypertension have reported increases in 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 women with self-reported hypertension whether or not they used oral contraceptives (18). A large World Health Organization case–control study conducted in developing and European countries observed that combination oral contraceptive users with a history of hypertension had increased risks of developing myocardial infarction and stroke, with an odds ratio of 10.7 and 68.1, respectively (19, 20). A pooled analysis of two U.S. population-based, case–control studies on oral contraceptive use and myocardial infarction (4) and stroke (5) suggests that current oral contraceptive 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 a prospective study, DMPA use did not appear to increase baseline blood pressure in 21 normotensive and three hypertensive women for more than 3 months (21).

In another cross-sectional study, DMPA use did not appear to cause more changes in blood pressure than did IUD use (22). A prospective study of 1,787 women found that a new 104-mg formulation of DMPA for subcutaneous injection did not have a significant impact on blood pressure (23). Likewise, use of progestin-only pills does not appear to have a significant impact on blood pressure (24). In a large World Health Organization multicountry case–control study, there was no increased risk of cardiovascular disease overall with use of progestin-only oral or injectable methods (25). In a small subgroup analysis, current progestin-only contraceptive users with a history of hypertension had an increased risk of stroke compared with nonusers with a history of hypertension, but confidence limits were wide because of very small numbers. Another multinational case–control study showed no increase in cardiovascular disease risk associated with progestogen-only pill use (26).

In healthy women of reproductive age, the incidence of myocardial infarction or stroke with use of low-dose oral contraceptives is extremely low. Although the relative risk of these events is increased in women with hypertension, the absolute risk remains low. Because of the increased risk of myocardial infarction and stroke associated with hypertension alone and the likelihood of additional risks of hormonal contraceptives, the decision to use combination hormonal contraceptives in these patients should be weighed against adverse pregnancy outcomes associated with hypertension. The noncontraceptive benefits of oral contraceptives also 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 contraceptives, 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 contraceptive initiation, use can be continued. Progestin-only contraceptives, such as DMPA, progestin-only oral contraceptives, or the levonorgestrel intrauterine system, are appropriate options in women with hypertension.

▶ *Is the use of hormonal contraception 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 oral contraceptives enhances removal of low-density lipoprotein (LDL) and increases levels of high-density lipoprotein (HDL) cholesterol. 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 (27, 28). The progestin component of combination oral contraceptives antagonizes these estrogen-induced lipid changes, which increases LDL levels and decreases HDL and triglyceride levels. Accordingly, among women taking combination oral contraceptives with an identical dose of estrogen, the choice (and dose) of the progestin component may affect net lipid changes. Oral contraceptives formulated with less androgenic progestins increase HDL levels more and triglyceride levels less than formulations with more androgenic progestins (29). Use of the transdermal contraceptive patch increases HDL and triglyceride levels and lowers LDL levels, similar to lipid changes observed in women using oral contraceptives formulated with less androgenic progestins (30). As with use of combination oral contraceptives, use of the contraceptive vaginal ring increases triglyceride levels (31). In contrast to combination oral contraceptives, use of DMPA decreases HDL levels, increases LDL levels and does not increase triglyceride levels (32, 33).

Lipids are surrogate measures, however, and the effect of contraceptives on lipids may not necessarily correlate with effects on cardiovascular disease or mortality (34). Thus, it is not known whether the differential lipid effects of distinct hormonal contraceptive formulations or means of administration have any clinical significance in women with normal baseline lipid levels or those with lipid disorders. Epidemiologic studies of current use of combination oral contraceptives by women with normal lipid levels find an approximate twofold increased risk of cardiovascular disease, with no increased risk with past use (35, 36). Because the absolute risk of cardiovascular events is low, most women with controlled dyslipidemia can use combination oral contraceptives formulated with 35 mcg or less of estrogen. Fasting serum lipid levels should be monitored as frequently as each month after initiating combination oral contraceptive use in women with dyslipidemia; less frequent monitoring is appropriate once stabilization of lipid parameters has been observed. In contrast, in women with uncontrolled LDL cholesterol greater than 160 mg/dL or multiple additional risk factors for cardiovascular disease (including smoking, diabetes, obesity, hypertension, family history of premature coronary artery disease, HDL level less than 35 mg/dL, or triglyceride level greater than 250 mg/dL), use of alternative contraceptives should be considered (2, 37). Use of progestin-only contraceptives does not appear to increase the risk of myocardial infarction (25). Accord-

ingly, use of DMPA and other progestin-only contraceptives is appropriate in women with hyperlipidemia.

Is the use of hormonal contraception safe for women with diabetes?

Steroids in combination oral contraceptives might impair carbohydrate metabolism and accelerate the occurrence of vascular disease in women with diabetes (38). However, current combination oral contraceptives do not appear to have this effect. A study of 43 women with type 1 diabetes who used combination oral contraceptives were compared with a similar number of women with type 1 diabetes not using oral contraceptives (39). Hemoglobin A_{1c} values and the degree of nephropathy and retinopathy were similar in both groups, which suggests that oral contraceptive use neither affected control of diabetes nor accelerated development of vascular disease.

A small Danish study found that use of combination oral contraceptives in women with type 1 diabetes did not impair metabolic control (40, 41). In contrast, a prospective study observed that use of combination oral contraceptives or DMPA resulted in increased fasting blood sugar levels in women with well-controlled diabetes. However, the lack of evidence of impaired glycometabolic control in these women suggests these increased fasting blood sugar levels may not be clinically important (42). Although the previously mentioned observations support the use of combination hormonal contraceptives 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. A clinical trial noted that metabolic control was similar in women with uncomplicated diabetes randomized to a copper or a progestin-releasing IUD (43). Thus, the levonorgestrel intrauterine system is an appropriate option for women with diabetes.

Available data offer reassurance that combination oral contraceptive use does not precipitate type 2 diabetes. Two large U.S. studies observed that use of combination oral contraceptives is not associated with an increased risk of developing diabetes (44, 45). In a California population of Latina women with gestational diabetes monitored for up to 7 years postpartum, use of combination oral contraceptives did not accelerate the development of type 2 diabetes. The use of progestin-only pills by the relatively small subgroup of women who breastfed their infants was associated with a significantly increased risk of developing type 2 diabetes (46). In a case–control study of Navajo women, use of DMPA was associated with an increased risk of a diagnosis of type 2 diabetes compared with users of combination oral contraceptives (47). Because Latina and Navajo women overall are at higher risk for developing diabetes than other women, the generalizability of these findings to lower risk women is uncertain.

Is the use of hormonal contraception 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 (48). Some women with migraines experience improvement in their symptoms with the use of oral contraceptives, whereas some women's symptoms worsen. However, in many women using oral contraceptives, migraines occur during the hormone-free interval. Because the presence of true migraine headaches affects the decision to use oral contraceptives, careful consideration of the diagnosis is important.

Most migraines occur without aura. Nausea, vomiting, photophobia, phonophobia, visual blurring, generalized visual spots, or flashing occurring before or during a migraine headache do not constitute aura. Typical aura lasts 5–60 minutes before the headache and is visual. The following reversible visual symptoms indicate the presence of aura: a flickering uncolored zigzag line progressing laterally to the periphery of one visual field, a laterally spreading scintillating scotomata (area of lost or depressed vision within a visual field, surrounded by an area of normal or less depressed vision or loss of vision) (49).

Most studies have noted a higher risk of stroke in women who have migraine with aura than in those who have migraine without aura (50–55). The assumption is that aura is associated with ischemic changes. However, many studies of oral contraceptives and migraines do not differentiate between migraines with aura and those without. Smoking and hypertension also have been found to be associated with an increased risk of stroke in women with migraines.

A pooled analysis of two large, U.S. population-based case–control studies identified a statistically significant twofold increased risk of ischemic stroke among current users of oral contraceptives who reported migraine headaches compared with women with migraines who did not use oral contraceptives (5). 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 ($P<.01$) (18). Neither study categorized migraines by type. The additional risk of thrombotic stroke attributable to women with migraines using oral contraceptives has been estimated as 8 per 100,000 women at age 20 years, and 80 per 100,000 women at age 40 years (56).

Concerns remain that all women with migraines are at increased risk of stroke if they take combination contraceptives. However, because absolute risk remains low, the use of combination contraceptives 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. Although cerebrovascular events occur rarely among women with migraines who use combination oral contraceptives, the impact of a stroke is so devastating that clinicians also should consider the use of progestin-only, intrauterine, or barrier contraceptives in this setting.

▶ *Does the use of oral contraceptives 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 (57, 58). Consistent with earlier studies, a large Canadian cohort study found that the risk of benign breast disease being diagnosed was lower in oral contraceptive users than in nonusers (59). A meta-analysis of individual patient data from 54 studies assessing the association of oral contraceptive use and breast cancer risk noted that a small increased risk of breast cancer was associated with current or recent use, but oral contraceptives did not further increase risk for women with a history of benign breast disease or a family history of breast cancer (60, 61). A more recent study has supported this finding (62). The meta-analysis of the 54 studies found that 10 or more years after discontinuing oral contraceptive use, risk of breast cancer was identical in former and never users of oral contraceptives. In the studies included in this reanalysis, most women with breast cancer had used older, higher-dose oral contraceptives (61). More recently, the Women's CARE study, a large U.S. population-based case–control study conducted by the National Institutes of Health, found no increased risk of breast cancer with current or past oral contraceptive use compared with never using oral contraceptives (9). No significant differences in overall results were noted for time since last oral contraceptive use, duration of use, age at first use, age at last use, or family history of breast cancer. The Women's CARE study likewise found no increased risk of breast cancer to be associated with use of DMPA (63). A case–control study found that oral contraceptive use before age 30 years and oral contraceptive use for more than 5 years were associated with an increased risk of breast cancer for *BRCA1* carriers, but not in *BRCA2* carriers (64). A more recent cohort study focused on cases of breast cancer diagnosed before age 40 years and included a substantial number of *BRCA1* and *BRCA2* mutation carriers (65). Compared with never using oral contraceptives, using current low-dose oral contraceptive formulations did not increase the risk of breast cancer in carriers of *BRCA1* or *BRCA2* mutations. A history of benign breast disease or a positive family history of breast cancer (including *BRCA1* or *BRCA2* mutations) should not be regarded as contraindications to oral contraceptive use. The *BRCA1* and *BRCA2* mutations are associated with a 45% and 25% lifetime risk, respectively, for epithelial ovarian cancer (66). Because oral contraceptive use reduces ovarian cancer risk in *BRCA1* and *BRCA2* carriers, as it does in noncarriers (66, 67), use of oral contraceptives offers important benefits for women with *BRCA1* or *BRCA2* mutations.

▶ *What are the effects of hormonal contraceptive use in women with uterine leiomyomata?*

Use of combination oral contraceptives reduces menstrual blood loss in women with normal menses as well as in those with menorrhagia (68). A Swedish study conducted in the 1960s using high-dose oral contraceptives noted oral contraceptive use significantly reduced bleeding in women with menorrhagia associated with uterine leiomyomata (69). Oral contraceptive use also reduces dysmenorrhea (68). Several large epidemiologic studies have observed that oral contraceptive use does not induce the growth of uterine leiomyomata and, therefore, may decrease bleeding disorders in these women (70–73).

An epidemiologic study conducted in Thailand suggests that use of DMPA reduces the need for hysterectomy in women with leiomyomata (73). A U.S. epidemiologic study found that use of DMPA was associated with a lowered risk of uterine leiomyomata (74). A small uncontrolled study of South African women with menorrhagia due to leiomyomata found that the use of DMPA, 150 mg intramuscularly per month, resulted in reduced bleeding or amenorrhea in most participants after 6 months of treatment (75).

Clinical trials in Russia, Italy, and Turkey have documented that use of the levonorgestrel intrauterine system reduces menstrual blood loss in women with menorrhagia associated with uterine leiomyomata (76–78). One of these trials (77) reported a 12% expulsion rate, considerably higher than the other two clinical trials.

▶ *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 combina-

tion oral contraceptives advises deferring use until 4 weeks postpartum in nonbreastfeeding women. Because progestin-only oral contraceptives and DMPA do not contain estrogen, these methods may be safely initiated immediately postpartum.

Traditionally, combination oral contraceptives have not been recommended as the first choice for breastfeeding women because of concerns that the estrogenic component of combination oral contraceptives can reduce the volume of milk production and the caloric and mineral content of breast milk in lactating women (79). However, use of combination oral contraceptives by well-nourished breastfeeding women does not appear to result in infant development problems (79). A systematic review of randomized controlled trials concluded that existing data are of poor quality and insufficient to establish an effect of hormonal contraception on lactation (80). Use of combination hormonal contraceptives can be considered once milk flow is well established.

Progestin-only pills and DMPA do not impair lactation (81) and, in fact, may increase the quality and duration of lactation (82). In nursing women using progestin-only oral contraceptives, very small amounts of progestin are passed into the breast milk, and no adverse effects on infant growth have been observed (83). Product labeling for progestin-only pills suggests that fully breastfeeding women begin tablets 6 weeks postpartum and advise partially breastfeeding women to begin at 3 weeks.

When initiated immediately postpartum, use of DMPA does not adversely affect lactation (79, 81) or infant development (84, 85). Given the lack of procoagulation effect and the safety in breastfeeding women with DMPA and progestin-only pills, their use at 6 weeks postpartum in lactating women and immediately postpartum in nonlactating women appears reasonable.

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

Anticonvulsants

Anticonvulsants that induce hepatic enzymes can decrease serum concentrations of the estrogen or progestin component of oral contraceptives, or both (86) (see the box). This effect has been observed with phenobarbital (87), phenytoin (48), carbamazepine (88), oxcarbazepine (89, 90), felbamate (91), and, to a lesser extent, topiramate (92). Therapeutic doses of vigabatrin do not induce hepatic enzymes. Nonetheless, a small randomized crossover clinical trial found ethinyl estradiol levels lower than during placebo use in two of 13 volunteers taking this anticonvulsant (93). Although each of these studies demonstrated reduced serum levels of oral contraceptive steroids during anticonvulsant use, and many of them demonstrated associated breakthrough bleeding, investigators did not observe ovulation or accidental pregnancy during anticonvulsant use.

Interaction of Anticonvulsants and Combination Oral Contraceptives

Anticonvulsants that decrease steroid levels in women taking combination oral contraceptives

- Barbiturates (including phenobarbital and primidone)
- Carbamazepine and oxcarbazepine
- Felbamate
- Phenytoin
- Topiramate
- Vigabatrin

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

- Ethosuximide*
- Gabapentin†
- Lamotrigine†
- Levetiracetam
- Tiagabine†
- Valproic acid
- Zonisamide

*No pharmacokinetic data are available.

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

In contrast to the above anticonvulsants, use of valproic acid (94), gabapentin (95), tiagabine (96), levetiracetam (97), and zonisamide (98) does not appear to decrease serum levels of contraceptive steroids in women using combination oral contraceptives. Although no formal pharmacokinetic data are available, use of ethosuximide, which does not have enzyme-inducing properties, is not thought to have an impact on steroid levels in oral contraceptive users (99). Practitioners should be aware, however, that studies of gabapentin, lamotrigine, and tiagabine were done using anticonvulsant doses lower than those used in clinical practice (100).

Some clinicians prescribe oral contraceptives containing 50 mcg of ethinyl estradiol to women taking liver enzyme-inducing anticonvulsants and other medications that reduce steroid levels in oral contraceptive users; no published data support the enhanced contraceptive effi-

cacy of this practice. Although it would appear prudent to use 30–35-mcg rather than 20–25-mcg estrogen oral contraceptives in women taking medications that reduce oral contraceptive steroid levels, no published data support this recommendation. Use of condoms in conjunction with oral contraceptives or use of an IUD may be considered for such women (see the box on the previous page).

Antibiotics

Although there have been many anecdotal reports of oral contraceptive failure in women taking concomitant antibiotics, pharmacokinetic evidence of lower serum steroid levels exists only for rifampin (101) (see the box below). Because oral contraceptive steroids are strikingly reduced in women concomitantly taking rifampin, such women should not rely on combination oral contraceptives, progestin-only oral contraceptives, or implants for contraceptive protection. Pharmacokinetic studies have not demonstrated decreased oral contraceptive steroid levels with concomitant use of tetracycline (102), doxycycline (103), ampicillin or metronidazole (104), or quinolone antibiotics (105–107). A pharmacokinetic study noted that concomitant use of fluconazole does not decrease steroid levels (and, in fact, slightly increases ethinyl estradiol levels) in women using combination oral contraceptives (108). A pharmacokinetic trial of women using the contraceptive vaginal ring noted that contraceptive steroid levels were not reduced by single or multiple administration of nonprescription vaginal miconazole suppositories or cream (109, 110).

Interaction of Antiinfective Agents and Combination Oral Contraceptives

Antiinfective agent that decreases steroid levels in women taking combination oral contraceptives

- Rifampin

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

- Ampicillin
- Doxycycline
- Fluconazole
- Metronidazole
- Miconazole*
- Quinolone antibiotics
- Tetracycline

*Vaginal administration does not lower steroid levels in women using the contraceptive vaginal ring.

Antiretrovirals

Data from a number of small studies suggest that the steroid levels in oral contraceptive users may be altered by the use of various antiretroviral medications (Table 1). In the absence of clinical outcome studies, the practical implications of these pharmacokinetic observations are unknown.

Serum progestin levels during use of progestin-only oral contraceptives and implants are lower than during combined oral contraceptive use. Accordingly, these low-dose progestin-only contraceptives are not appropriate choices for women using concomitant liver enzyme inducers (83, 111). The contraceptive efficacy of the levonorgestrel intrauterine system has been observed to remain high with concomitant use of antiepileptic and other liver enzyme-inducing medications (112). 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 (48).

Other Medications

An aggregate analysis of randomized clinical trials of fluoxetine for the treatment of depression found that use of medication did not increase pregnancy rates in women using oral contraceptives. Likewise, efficacy of fluoxetine in treating depression was not affected by oral contraceptive use (113). In contrast, a clinical trial observed that use of the herbal remedy St. John's wort, a hepatic enzyme inducer, increased progestin and estrogen metabolism as

Table 1. Pharmacokinetic Combination Oral Contraceptive–Antiretroviral Drug Interactions

Antiretroviral Levels	Contraceptive Steroid Levels	Antiretroviral
Protease inhibitors		
Nelfinavir	⇓	No data
Ritonavir	⇓	No data
Lopinavir/ritonavir	⇓	No data
Atazanavir	⇑	No data
Amprenavir	⇑	⇓
Indinavir	⇑	No data
Saquinavir	No data	No change
Nonnucleoside reverse transcriptase inhibitors		
Nevirapine	⇓	No change
Efavirenz	⇑	No change
Delavirdine	?⇑	No data

World Health Organization. Medical eligibility criteria for contraceptive use. Annex 1. COCs and antiretroviral therapies. 3rd ed. Geneva: WHO; 2004.

well as breakthrough bleeding and the likelihood of ovulation in women using combination oral contraceptives (114). Pharmacokinetic studies of the following additional medications indicate that concomitant administration should not impair the efficacy of combination oral contraceptives: rizatriptan (115), isotretinoin (116), alosetron (117), rosuvastatin (118), and rosiglitazone (119).

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

The estrogenic component of combination oral contraceptives increases hepatic production of serum globulins involved in coagulation (including factor VII, factor X, and fibrinogen) and increases the risk of venous thromboembolism in users. A U.S. case–control study based on participants in a large health maintenance organization who used oral contraceptive formulations containing less than 50 mcg of ethinyl estradiol combined with norethindrone or levonorgestrel found that, compared with nonusers, current users of oral contraceptives experience a fourfold increased risk of venous thromboembolism (120). This risk, in absolute terms, remains lower than the increased risk of venous thromboembolism during pregnancy (121). The use of combination oral contraceptives formulated with the progestin desogestrel is associated with a venous thromboembolism risk 1.7–19 times higher than that associated with levonorgestrel oral contraceptives (121–123).

In addition to current use of exogenous estrogens, risk factors for venous thromboembolism include age (8), personal history of venous thromboembolism, pregnancy and the puerperium (121), obesity (8, 120), surgery, air travel (124), and certain familial coagulation disorders (125, 126). Although cigarette smoking, hypertension, and diabetes represent risk factors for arterial disease, including myocardial infarction and stroke, they do not increase venous thromboembolism risk (25). Likewise, the presence of superficial varicose veins does not increase venous thromboembolism risk (25). Health risks (including venous thromboembolism) associated with pregnancy, noncontraceptive oral contraceptive benefits, and the potential for effective use of contraceptives that do not increase venous thromboembolism risk (eg, progestin-only oral contraceptives and intrauterine and barrier methods) should all be factored into risk–benefit considerations. Although pharmacologic data for the contraceptive patch indicate that estrogen exposure is higher for the patch than oral contraceptives or the vaginal ring, it is unclear whether this results in an absolute increased venous thromboembolism risk with the patch as compared with combined oral contraceptives.

Women with a documented history of unexplained venous thromboembolism or venous thromboembolism associated with pregnancy or exogenous estrogen use should not use combination hormonal contraceptives unless they are currently taking anticoagulants. An oral contraceptive candidate who had experienced a single episode of venous thromboembolism years earlier associated with a nonrecurring risk factor (eg, venous thromboembolism occurring after immobilization following a motor vehicle accident) may not currently be at increased risk for venous thromboembolism. Accordingly, the decision to initiate combination oral contraceptives in such a candidate can be individualized.

Should women awaiting surgery discontinue combination contraceptive 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 venous thromboembolism was approximately twice as high ($P > .05$) in oral contraceptive users as in nonusers (127). A prospective study found that, among women taking oral contraceptives formulated with 30 mcg of estrogen, oral contraceptive-induced procoagulant changes did not substantially resolve until 6 or more weeks after oral contraceptive discontinuation (128). Accordingly, the benefits associated with stopping combination contraceptives 1 month or more before major surgery should be balanced against the risks of an unintended pregnancy (129). If oral contraceptives are continued before major surgical procedures, heparin prophylaxis should be considered (129). Use of oral contraceptives at the time of arthroscopic surgery has been observed to increase venous thromboembolism risk (130, 131). Because of the low perioperative risk of venous thromboembolism, it currently is not considered necessary to discontinue combination contraceptives before laparoscopic tubal sterilization or other brief surgical procedures not known to be associated with an elevated venous thromboembolism risk.

Is hormonal contraceptive use safe in women with hypercoagulable states?

Women with familial thrombophilic syndromes, including factor V Leiden mutation, prothrombin G2010 A mutation, and protein C, protein S, or antithrombin deficiency have an increased risk of venous thromboembolism during oral contraceptive use and also develop venous thromboembolism earlier during use than lower risk users (126). An initial study concluded that women with factor V Leiden mutation had an eightfold increased risk of venous thromboembolism than did women without the mutation. The risk was more than 30 times higher in carriers who

used oral contraceptives than in nonoral contraceptive users who were not carriers of the mutation (125). A more recent report estimated this odds ratio at 10 (132); variations in the respective study populations may account for these differences. Screening would identify approximately 5% of U.S. oral contraceptive candidates as having factor V Leiden mutation; however, most of these women will never experience venous thromboembolism, even if they used combination oral contraceptives (133). Given the rarity of fatal venous thromboembolism, one group of investigators concluded that screening more than 1 million combination oral contraceptive candidates for thrombophilic markers would, at best, prevent two oral contraceptive-associated deaths (134).

▶ *Which hormonal contraceptives are appropriate for women being treated with anticoagulation therapy?*

Women using warfarin for chronic anticoagulation may experience menorrhagia and, rarely, hemoperitoneum after rupture of ovarian cysts. In addition, warfarin is a teratogen. Because use of combination oral contraceptives can reduce menstrual blood loss (68) and does not increase the risk of recurrent thrombosis in well anticoagulated women (133, 135), some authorities recommend their use in such patients.

Because intramuscular injection of DMPA consistently suppresses ovulation (136) and anecdotal experience has not revealed injection site problems, such as hematoma in anticoagulated women, DMPA represents another potential contraceptive choice in this patient population. In a small prospective study (137) of 13 women receiving chronic anticoagulation for prosthetic heart valves with ovarian bleeding, DMPA given after the initial bleeding episode prevented recurrent hemorrhagic corpora lutea and did not affect anticoagulation. Because use of the levonorgestrel intrauterine system provides effective contraception and reduces menstrual blood loss, it is another appropriate method for anticoagulated patients.

▶ *Which hormonal contraceptives are appropriate for obese women?*

The proportion of Americans who are obese (body mass index [BMI] of 30 or higher) has increased to 30% (138). Obesity may impair efficacy of combination oral and transdermal contraceptives. A case–control study performed in a West Coast health maintenance organization observed a higher risk of oral contraceptive failure in obese women than in women with a normal BMI (odds ratio [OR], 1.72; 95% confidence interval [CI], 1.04–2.82) (139). In clinical trials of the transdermal patch, women in the highest weight decile (90 kg or more) had a substantially higher failure rate (140). The incrementally higher contraceptive failure rates in this setting with oral and transdermal methods should not exclude their use in overweight women motivated to use these methods in preference to other less effective methods. Among overweight women, higher pregnancy rates have not been observed with use of the 150-mg intramuscular or 106-mg subcutaneous formulations of DMPA (141, 23).

Use of combination oral contraceptives and obesity represent independent risk factors for venous thromboembolism. A Dutch case–control study found that in women with a BMI greater than 25 who also use oral contraceptives, the venous thromboembolism risk is 10-fold higher than in lean women not using oral contraceptives (142). A British case–control study also observed a substantially higher risk of venous thromboembolism in obese women using oral contraceptives than in lean oral contraceptive users (8). Accordingly, consideration should be given to progestin-only and intrauterine methods when counseling obese women regarding contraceptive choices. In helping overweight women make sound contraceptive choices, practitioners should incorporate the above observations into discussions with patients. Because obese women experience an elevated risk for dysfunctional uterine bleeding and endometrial neoplasia, use of the levonorgestrel intrauterine system may represent a particularly sound choice for obese women (34).

▶ *Does the use of emergency contraception increase the risk of venous thromboembolism?*

The only dedicated formulation for postcoital (emergency) contraception available in the United States is the progestin-only levonorgestrel formulation. Use of progestin-only contraceptives has not been linked with an increased risk of venous thromboembolism (25). A retrospective cohort analysis from Britain found no cases of venous thromboembolism in more than 100,000 episodes of use of the estrogen–progestin Yuzpe regimen (143).

▶ *Are hormonal contraceptives safe for women with systemic lupus erythematosus?*

Although effective contraception is important for women with lupus, concerns about increasing disease activity and thrombosis have resulted in clinicians rarely prescribing combination estrogen–progestin oral contraceptives to women with this disease. Two 1-year clinical trials, both of which used the same detailed index to measure lupus activity, shed new light on this issue.

In a multicenter double-blind trial, 183 ethnically diverse U.S. women (mean age, 30 years) with inactive or stable lupus without moderate or high levels of anti-

cardiolipin antibodies were randomized to a combination oral contraceptive or placebo. Based on their disease activity scores, most participants had mild lupus at baseline. Rates of severe as well as mild–moderate disease flare were almost identical in both treatment groups. Two thrombotic events occurred in those taking oral contraceptives while three such events occurred in the placebo group. One death in the placebo group occurred a year after study drug discontinuation (144).

In a single-blind study, 162 Mexican women (mean age, 27 years) with lupus were randomized to combination oral contraceptives, a progestin-only pill, or a copper IUD (145). Although baseline disease activity scores were somewhat higher than in the U.S. study, most Mexican participants had mild disease. Rates of flare overall during this study were similar in the three treatment groups; likewise, severe disease flares were uncommon and occurred at similar rates in the three groups. Two thrombotic events occurred in the combination oral contraceptives group and two in the progestin-only oral contraceptive group; all four of these women had low titers of antiphospholipid antibodies at baseline (between 26% and 33% of participants were antibody positive at baseline). Severe infections were diagnosed in 3, 2, and 5 participants in the combination oral contraceptive, progestin-only oral contraceptive, and IUD groups, respectively. Hospitalizations occurred in 11, 7, and 9 participants, respectively. One participant (combination oral contraceptive group) died from antibiotic-related neutropenia during the trial.

Almost one quarter of women with lupus who conceive choose to terminate their pregnancies, underscoring the importance of effective birth control for patients with this autoimmune disease (146). In the findings that combination oral contraceptives are safe for women with mild lupus who do not have antiphospholipid antibodies, these two trials break important new ground. However, data from observational studies suggest that combination oral contraceptive use should be avoided in women with systemic lupus erythematosus and a history of vascular disease, nephritis, or antiphospholipid antibodies, although progestin-only methods are safe alternatives. There are few data regarding the safety of IUDs in women with lupus; however, in general these devices provide highly effective birth control and may provide a sensible option for patients with lupus.

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

In individuals 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 (147).

Two controlled studies have assessed the use of DMPA in women with sickle cell disease (148, 149). 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.

No well-controlled study has assessed whether venous thromboembolism risk in oral contraceptive users with sickle cell disease is higher than in other combination oral contraceptive users. Cross-sectional studies in women with sickle cell disease have observed no differences in markers of platelet activation, thrombin generation, fibrinolysis, or red cell deformability between users of combination oral contraceptives, progestin-only methods, and nonusers of hormonal contraception (150, 151). On the basis of these observations as well as studies of pregnant women with sickle cell disease, small observational studies of women with sickle cell disease who use combination oral contraceptives, and theoretical considerations, the consensus is that pregnancy carries a greater risk than does combination oral contraceptive use.

▶ *What are the effects of hormonal contraception in women with depressed mood?*

A cohort from the fluoxetine clinical trials database of 1,698 combined oral contraceptive users and nonusers from 17 randomized double-blind, placebo-controlled clinical trials was evaluated (111). There was no significant effect of oral contraceptive use on depression, and oral contraceptive use did not modify the effectiveness of fluoxetine. In another small study (152), adolescents starting Norplant or DMPA were compared with those using oral contraceptives. Approximately 50% were depressed at baseline, but there was no significant change from baseline in depression symptoms at 6 months in oral contraceptive or DMPA users returning for follow-up.

A large prospective multicenter U.S. study evaluated depressive symptoms before starting and during use of DMPA contraception. Among the 495 women choosing DMPA, 391 completed 12 months of follow-up; 44% were still using DMPA and 56% had discontinued. Ongoing use of DMPA was associated with slight improvement in depressive symptoms. Women who continued the method at one year had fewer depressive symptoms at baseline than did those who discontinued DMPA (153). Among those in the quintile with the highest scores at baseline who returned for follow-up, mean scores decreased during the study for both continuers and discontinuers. Another cohort study of DMPA and

depressive symptoms in adolescents compared 39 first-time DMPA users with a group of 24 adolescents not using hormonal contraception (154). In the 19 DMPA users completing 1 year of follow-up, mean depression scores decreased from a baseline of 10.8 to 6.9, while scores in the control group remained stable.

Data on use of hormonal contraceptives in women with depression are limited, but generally show no effect. Women with depressive disorders do not appear to experience worsening of symptoms with use of hormonal methods of contraception.

▶ *Does use of hormonal contraception affect acquisition or transmission of human immunodeficiency virus infection?*

Four cohort studies have evaluated risk of acquiring HIV infection with oral contraceptive or DMPA use in lower risk women, but data are inconclusive (155–158). Among higher risk women, two studies showed increased risk of HIV acquisition with oral contraceptives (159) (OR, 4.5; 95% CI, 1.4–13.8) (160) (hazard rate [HR], 1.5; 95% CI, 1.0–2.1), whereas five studies showed no increased risk (161–165). Two studies examining the DMPA–HIV association reported increased risks (164) (RR, 3.83; 95% CI, 1.02–14.43) (160) (HR, 2.0; 95% CI, 1.3–3.1), and one showed no increase in risk (162). Many of these studies were flawed, making generalizability of study results difficult (166).

Genital shedding of HIV virus may increase risk of transmission. One prospective study evaluated risk of genital shedding of HIV in infected women using hormonal contraception (167). In this study of Kenyan sex workers, there was a significant increase in shedding of HIV-1 DNA but not of HIV-1 RNA after women began hormonal contraception. The results were not significant when comparing methods (oral contraceptive or DMPA). There are conflicting data on the effect of hormonal contraception on the risk of HIV acquisition. Data on transmission are too limited to draw firm conclusions.

▶ *What are the effects of DMPA on skeletal health?*

Use of DMPA in contraceptive doses suppresses ovarian production of estradiol (168). Thus, there has been concern that women using DMPA for contraception might increase their future risk of developing osteoporosis. In 2004, the FDA added a black box warning to DMPA regarding loss of bone mineral density, indicating that injectable contraception should be continued for more than 2 years only if other birth control methods are inadequate. A letter from the manufacturer suggested that dual-energy X-ray absorptiometry (DXA) studies might be used to monitor bone mineral density in DMPA users.

Many studies have observed bone mineral density declines in current users of DMPA, which is seen as a surrogate marker for future osteoporosis and fracture (169–171). None of these found evidence of osteoporosis or fractures in DMPA users. Two cross-sectional studies found that years after DMPA discontinuation, bone mineral density was similar in former and never users of DMPA (172, 173). A large U.S. prospective study of adult DMPA users found that within 30 months following DMPA discontinuation, bone mineral density of the spine and hip was similar to that of nonusers (171).

As in adults, DMPA use in adolescents is associated with declines in bone mineral density (171, 174). A U.S. prospective study of 61 teens discontinuing DMPA noted that within 12 months after discontinuation, bone mineral density was at least as high in former DMPA users as in nonusers (171).

In adult women, supplementation with daily 0.625-mg oral conjugated equine estrogen has been observed to prevent loss of bone mineral density associated with use of DMPA (175). Likewise, supplementation with monthly 5-mg intramuscular estradiol cypionate injections prevented loss of bone mineral density in teens using DMPA (176). The bone mineral density trends seen with DMPA seem to be similar to those noted during lactation in that no long-term decrease occurs (177, 178).

Given the above observations, skeletal health concerns should not restrict use of DMPA in adult women. In adolescents, the advantages of DMPA likely outweigh the theoretical safety concerns regarding bone mineral density and fractures. However, in the absence of long-term data in this population, consideration of long-term use should be individualized. Regardless of age, short or long-term use of DMPA in healthy women likewise should not be considered an indication for DXA or other tests that assess bone mineral density (179).

Summary of Recommendations and Conclusions

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

- A history of benign breast disease or a positive family history of breast cancer should not be regarded as contraindications to oral contraceptive use.

- Combination oral contraceptives are safe for women with mild lupus who do not have antiphospholipid antibodies.
- Combination contraceptives are not recommended for women with a documented history of unexplained venous thromboembolism or venous thromboembolism associated with pregnancy or exogenous estrogen use, unless they are taking anticoagulants.
- Combination oral contraceptives should be prescribed with caution, if ever, to women who are older than 35 years and are smokers.
- Use of the levonorgestrel intrauterine system is appropriate for women with diabetes without retinopathy, nephropathy, or other vascular complications.

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

- Healthy, nonsmoking women doing well on a combination contraceptive can continue their method until the ages of 50–55 years, after weighing the risks and benefits.
- Progestin-only oral contraceptives and DMPA can be initiated safely at 6 weeks postpartum in lactating women and immediately postpartum in nonbreastfeeding women.
- Combination contraceptives are not recommended as the first choice for breastfeeding women because of the possible negative impact of contraceptive doses of estrogen on lactation. However, use of combination contraceptives 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.
- Women with well-controlled and monitored hypertension who are aged 35 years or younger are appropriate candidates for a trial of combination contraceptives, provided they are otherwise healthy, show no evidence of end-organ vascular disease, and do not smoke.
- The use of combination contraceptives 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.
- The use of combination contraceptives 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. Although cerebrovascular events rarely occur among women with migraines who use combination oral contraceptives, the impact of a stroke is so devastating that clinicians should consider the use of progestin-only, intrauterine, or barrier contraceptives in this setting.
- Because of the increased risk of venous thrombotic embolism, combination contraceptives should be used with caution in women older than 35 years who are obese.
- In women with depressive disorders, symptoms do not appear to worsen with use of hormonal methods of contraception.
- If oral contraceptives are continued before major surgery, heparin prophylaxis should be considered.

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

- Most women with controlled dyslipidemia can use combination oral contraceptives formulated with 35 mcg 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.
- Depot medroxyprogesterone acetate has noncontraceptive benefits and is appropriate for 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 contraceptives are contraindicated in these women.
- Short- or long-term use of DMPA in healthy women should not be considered an indication for DXA or other tests that assess bone mineral density. In adolescents, the advantages of DMPA likely outweigh the theoretical safety concerns regarding bone mineral density and fractures. However, in the absence of long-term data in this population, consideration of long-term use should be individualized.

Proposed Performance Measure

Percentage of women taking combination contraceptives with a documented history of unexplained venous thromboembolism or venous thromboembolism associated with pregnancy or exogenous estrogen use who are also taking anticoagulants

References

1. van den Heuvel MW, van Bragt AJ, Alnabawy AK, Kaptein MC. Comparison of ethinylestradiol pharmacokinetics in three hormonal contraceptive formulations: the vaginal ring, the transdermal patch and an oral contraceptive. Contraception 2005;72:168–74. (Level II-1)
2. World Health Organization. Medical eligibility criteria for contraceptive use. 3rd ed. Geneva: WHO; 2004. Available at: http://www.who.int/reproductive-health/publications/mec/index.htm. Retrieved April 4, 2006. (Level III)
3. Corfman P. Labeling guidance text for progestin-only oral contraceptives. Contraception 1995;52:71–6. (Level III)
4. Sidney S, Siscovick DS, Petitti DB, Schwartz SM, Quesenberry CP, Psaty BM, et al. Myocardial infarction and use of low-dose oral contraceptives: a pooled analysis of 2 US studies. Circulation 1998;98:1058–63. (Level II-2)
5. Schwartz SM, Petitti DB, Siscovick DS, Longstreth WT Jr, Sidney S, Raghunathan TE, et al. Stroke and use of low-dose oral contraceptives in young women: a pooled analysis of two US studies. Stroke 1998;29:2277–84. (Level II-2)
6. Gambacciani M, Spinetti A, Taponeco F, Cappagli B, Piaggesi L, Fioretti P. Longitudinal evaluation of perimenopausal vertebral bone loss: effects of a low-dose oral contraceptive preparation on bone mineral density and metabolism. Obstet Gynecol 1994;83:392–6. (Level I)
7. Casper RF, Dodin S, Reid RL. The effect of 20 µg ethinyl estradiol/1 mg norethindrone acetate (Minestrin™), a low-dose oral contraceptive, on vaginal bleeding patterns, hot flashes, and quality of life in symptomatic perimenopausal women. Menopause 1997;4:139–47. (Level I)
8. Nightingale AL, Lawrenson RA, Simpson EL, Williams TJ, MacRae KD, Farmer RD. The effects of age, body mass index, smoking and general health on the risk of venous thromboembolism in users of combined oral contraceptives. Eur J Contracept Reprod Health Care 2000;4:265–74. (Level II-3)
9. Marchbanks PA, McDonald JA, Wilson HG, Folger SG, Mandel MG, Daling JR, et al. Oral contraceptives and the risk of breast cancer. N Engl J Med 2002;346:2025–32. (Level II-2)
10. Gebbie AE, Glasier A, Sweeting V. Incidence of ovulation in perimenopausal women before and during hormone replacement therapy. Contraception 1995;52:221–2. (Level II-3)
11. Burger HG. Diagnostic role of follicle-stimulating hormone (FSH) measurements during the menopausal transition—an analysis of FSH, oestradiol and inhibin. Eur J Endocrinol 1994;130:38–42. (Level III)
12. Castracane VD, Gimpel T, Goldzieher JW. When is it safe to switch from oral contraceptives to hormonal replacement therapy? Contraception 1995;52:371–6. (Level II-2)
13. Creinin MD. Laboratory criteria for menopause in women using oral contraceptives. Fertil Steril 1996;66:101–4. (Level II-3)
14. Croft P, Hannaford PC. Risk factors for acute myocardial infarction in women: evidence from the Royal College of General Practitioners' oral contraception study. BMJ 1989;298:165–8. (Level II-2)
15. Tanis BC, van den Bosch MA, Kemmeren JM, Cats VM, Helmerhorst FM, Algra A, et al. Oral contraceptives and the risk of myocardial infarction. N Engl J Med 2001;345:1787–93. (Level II-2)
16. Cardoso F, Polonia J, Santos A, Silva-Carvalho J, Ferreira-de-Almeida J. Low-dose oral contraceptives and 24-hour ambulatory blood pressure. Int J Gynaecol Obstet 1997;59:237–43. (Level II-3)
17. Narkiewicz K, Graniero GR, D'Este D, Mattarei M, Zonzin P, Palatini P. Ambulatory blood pressure in mild hypertensive women taking oral contraceptives. A case-control study. Am J Hypertens 1995;8:249–53. (Level II-2)
18. Lidegaard O. Oral contraceptives, pregnancy and the risk of cerebral thromboembolism: the influence of diabetes, hypertension, migraine and previous thrombotic disease. Br J Obstet Gynaecol 1995;102:153–9. (Level II-2)
19. Ischemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet 1996;348:498–505. (Level II-2)
20. Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Lancet 1997;349:1202–9. (Level II-2)
21. Black HR, Leppert P, DeCherney A. The effect of medroxyprogesterone acetate on blood pressure. Int J Gynaecol Obstet 1978;17:83–7. (Level II-3)
22. Taneepanichskul S, Reinprayoon D, Jaisamrarn U. Effects of DMPA on weight and blood pressure in long-term acceptors. Contraception 1999;59:301–3. (Level II-3)
23. Jain J, Jakimiuk AJ, Bode FR, Ross D, Kaunitz AM. Contraceptive efficacy and safety of DMPA-SC. Contraception 2004;70:269–75. (Level II-3)
24. Hussain SF. Progestogen-only pills and high blood pressure: is there an association? A literature review. Contraception 2004;69:89–97. (Level III)
25. Cardiovascular disease and steroid hormone contraception. Report of a WHO Scientific Group. World Health Organ Tech Rep Ser 1998;877:i–vii,1–89. (Level III)
26. Heinemann LA, Assmann A, DoMinh T, Garbe E. Oral progestogen-only contraceptives and cardiovascular risk: results from the Transnational Study on Oral Contraceptives and the Health of Young Women. Eur J Contracept Reprod Health Care 1999;4:67–73. (Level II-2)
27. Walsh BW, Schiff I, Rosner B, Greenberg L, Ravnikar V, Sacks FM. Effects of postmenopausal estrogen replacement on the concentrations and metabolism of plasma lipoproteins. N Engl J Med 1991;325:1196–204. (Level II-1)

28. Walsh BW, Sacks FM. Effects of low dose oral contraceptives on very low density and low density lipoprotein metabolism. J Clin Invest 1993;91:2126–32. (Level II-2)

29. van Rooijen M, von Schoultz B, Silveira A, Hamsten A, Bremme K. Different effects of oral contraceptives containing levonorgestrel or desogestrel on plasma lipoproteins and coagulation factor VII. Am J Obstet Gynecol 2002;186:44–8. (Level II-1)

30. Creasy GW, Fisher AC, Hall N, Shangold GA. Transdermal contraceptive patch delivering norelgestromin and ethinyl estradiol. Effects on the lipid profile. J Reprod Med 2003;48:179–86. (Level I)

31. Tuppurainen M, Klimscheffskij R, Venhola M, Dieben TO. The combined contraceptive vaginal ring (NuvaRing) and lipid metabolism: a comparative study. Contraception 2004;69:389–94. (Level II-2)

32. Kongsayreepong R, Chutivongse S, George P, Joyce S, McCone JM, Garza-Flores J, et al. A multicentre comparative study of serum lipids and apolipoproteins in long-term users of DMPA and a control group of IUD users. WHO Task Force on Long-Acting Systemic Agents for Fertility Regulation Special Programme of Research, Development, and Research Training in Human Reproduction. Contraception 1993;47:177–91. (Level II-2)

33. Westhoff C. Depot medroxyprogesterone acetate contraception. Metabolic parameters and mood changes. J Reprod Med 1996;41(5 suppl):401–6. (Level III)

34. Grimes DA, Shields WC. Family planning for obese women: challenges and opportunities. Contraception 2005;72:1–4. (Level III)

35. Khader YS, Rice J, John L, Abueita O. Oral contraceptives use and the risk of myocardial infarction: a meta-analysis. Contraception 2003;68:11–7. (Meta-analysis)

36. Chasan-Taber L, Stampfer MJ. Epidemiology of oral contraceptives and cardiovascular disease. Ann Intern Med 1998;128:467–77. (Level III)

37. Knopp RH, LaRosa JC, Burkman RT Jr. Contraception and dyslipidemia. Am J Obstet Gynecol 1993;168: 1994–2005. (Level III)

38. Ahmed SB, Hovind P, Parving HH, Rossing P, Price DA, Laffel LM, et al. Oral contraceptives, angiotensin-dependent renal vasoconstricton, and risk of diabetic nephropathy. Diabetes Care 2005;28:1988–94. (Level II-2)

39. Garg SK, Chase HP, Marshall G, Hoops SL, Holmes DL, Jackson WE. Oral contraceptives and renal and retinal complications in young women with insulin-dependent diabetes mellitus. JAMA 1994;271:1099–102. (Level II-2)

40. Petersen KR, Skouby SO, Vedel P, Haaber AB. Hormonal contraception in women with IDDM. Influence on glycometabolic control and lipoprotein metabolism. Diabetes Care 1995;18:800–6. (Level III)

41. Petersen KR. Pharmacodynamic effects of oral contraceptive steroids on biochemical markers for arterial thrombosis. Studies in non-diabetic women and in women with insulin-dependent diabetes mellitus. Dan Med Bull 2002;49:43–60. (Level III)

42. Diab KM, Zaki MM. Contraception in diabetic women: comparative metabolic study of Norplant, depot medroxyprogesterone acetate, low dose oral contraceptive pill and CuT380A. J Obstet Gynaecol Res 2000;26:17–26. (Level II-3)

43. Rogovskaya S, Rivera R, Grimes DA, Chen PL, Pierre-Louis B, Prilepskaya V. Effect of a levonorgestrel intrauterine system on women with type 1 diabetes: a randomized trial. Obstet Gynecol 2005;105:811–5. (Level I)

44. Chasan-Taber L, Willett WC, Stampfer MJ, Hunter DJ, Colditz GA, Spiegelman D, et al. A prospective study of oral contraceptives and NIDDM among U.S. women. Diabetes Care 1997;20:330–5. (Level II-2)

45. Kim C, Siscovick DS, Sidney S, Lewis CE, Kiefe CI, Koepsell TD. Oral contraceptive use and association with glucose, insulin, and diabetes in young adult women: the CARDIA Study. Coronary Artery Risk Development in Young Adults. Diabetes Care 2002;25:1027–32. (Level II-2)

46. Kjos SL, Peters RK, Xiang A, Thomas D, Schaefer U, Buchanan TA. Contraception and the risk of type 2 diabetes mellitus in Latina women with prior gestational diabetes mellitus. JAMA 1998;280:533–8. (Level II-3)

47. Kim C, Seidel KW, Begier EA, Kwok YS. Diabetes and depot medroxyprogesterone contraception in Navajo women. Arch Intern Med 2001;161:1766–71. (Level II-2)

48. Mattson RH, Rebar RW. Contraceptive methods for women with neurologic disorders. Am J Obstet Gynecol 1993;168:2027–32. (Level II-3)

49. British Association for the Study of Headache. Guidelines for all doctors in the diagnosis and management of migraine and tension-type headache. 2nd ed. Available at: http://64.227.208.149/NS_BASH/BASH_guideline31Aug05.pdf. Retrieved November 29, 2005. (Level II)

50. Etminan M, Takkouche B, Isorna FC, Samii A. Risk of ischaemic stroke in people with migraine: systematic review and meta-analysis of observational studies [published errata appears in BMJ 2005;330:345. BMJ 2005; 330:596]. BMJ 2005;330:63–5. (Meta-analysis)

51. Donaghy M, Chang CL, Poulter N. Duration, frequency, recency, and type of migraine and the risk of ischaemic stroke of women of childbearing age. European Collaborators of The World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. J Neurol Neurosurg Psychiatry 2002;73: 747–50. (Level II-2)

52. Tzourio C, Tehindrazanarivelo A, Iglesias S, Alperovitch A, Chedru F, d'Anglejan-Chatillon J, et al. Case-control study of migraine and risk of ischaemic stroke in young women. BMJ 1995;310:830–3. (Level II-2)

53. Carolei A, Marini C, De Matteis G. History of migraine and risk of cerebral ischaemia in young adults. The Italian Research Council Study Group on Stroke in Young. Lancet 1996;347:1503–6. (Level II-2)

54. Kurth T, Slomke MA, Kase CS, Cook NR, Lee IM, Gaziano JM, et al. Migraine, headache and the risk of stroke in women: a prospective study. Neurology 2005; 64:1020–6. (Level II-2)

55. Stang PE, Carson AP, Rose KM, Mo J, Ephross SA, Shahar E, et al. Headache, cerebrovascular symptoms, and stroke: the Atherosclerosis Risk in Communities Study. Neurology 2005;64:1573–7. (Level II-3)

56. MacGregor EA, Guillebaud J. Combined oral contraceptives, migraine and ischaemic stroke. Clinical and Scientific Committee of the Faculty of Family Planning and Reproductive Health Care and the Family Planning Association. Br J Fam Plann 1998;24:55–60. (Level III)

57. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med 1985;312:146–51. (Level II-2)

58. Hartmann LC, Sellers TA, Frost MH, Lingle WL, Degnim AC, Ghosh K, et al. Benign breast disease and the risk of breast cancer. N Engl J Med 2005;353: 229–37. (Level II-2)

59. Rohan TE, Miller AB. A cohort study of oral contraceptive use and risk of benign breast disease. Int J Cancer 1999;82:191–6. (Level II-2)

60. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53 297 women with breast cancer and 100 239 women without breast cancer from 54 epidemiological studies. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet 1996;347: 1713–27. (Level III)

61. Breast cancer and hormonal contraceptives: further results. Collaborative Group on Hormonal Factors in Breast Cancer. Contraception 1996;54:(3 suppl):1S–106S. (Level III)

62. Silvera SA, Miller AB, Rohan TE. Oral contraceptive use and risk of breast cancer among women with a family history of breast cancer: a prospective cohort study. Cancer Causes Control 2005;16:1059–63. (Level II-2)

63. Strom BL, Berlin JA, Weber AL, Norman SA, Bernstein L, Burkman RT. Absence of an effect of injectable and implantable progestin-only contraceptives on subsequent risk of breast cancer. Contraception 2004;69:353–60. (Level II-2)

64. Narod SA, Dube MP, Klijn J, Lubinski J, Lynch HT, Ghadirian P, et al. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 2002;94:1773–9. (Level II-2)

65. Milne RL, Knight JA, John EM, Dite GS, Balbuena R, Ziogas A, et al. Oral contraceptive use and risk of early-onset breast cancer in carriers and noncarriers of BRCA1 and BRCA2 mutations. Cancer Epidemiol Biomarkers Prev 2005;14:350–6. (Level II-2)

66. Narod SA, Risch H, Moslehi R, Dorum A, Neuhausen S, Olsson H. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. N Engl J Med 1998;339:424–8. (Level II-2)

67. Whittemore AS, Balise RR, Pharoah PD, DiCiccio RA, Oakley-Girvan I, Ramus SJ, et al. Oral contraceptive use and ovarian cancer risk among carriers of BRCA1 or BRCA2 mutations. Br J Cancer 2004; 91:1911–5. (Level II-2)

68. Larsson G, Milsom I, Lindstedt G, Rybo G. The influence of a low-dose combined oral contraceptive on menstrual blood loss and iron status. Contraception 1992; 46:327–34. (Level III)

69. Nilsson L, Rybo G. Treatment of menorrhagia. Am J Obstet Gynecol 1971;110:713–20. (Level II-2)

70. Ross RK, Pike MC, Vessey MP, Bull D, Yeates D, Casagrande JT. Risk factors for uterine fibroids: reduced risk associated with oral contraceptives [published erratum appears in Br Med J (Clin Res Ed) 1986;293:1027]. Br Med J (Clin Res Ed) 1986;293:359–62. (Level II-2)

71. Marshall LM, Spiegelman D, Goldman MB, Manson JE, Colditz GA, Barbieri RL, et al. A prospective study of reproductive factors and oral contraceptive use in relation to the risk of uterine leiomyomata. Fertil Steril 1998; 70:432–9. (Level II-2)

72. Parazzini F, Negri E, LaVecchia C, Fedele L, Rabaiotti M, Luchini L. Oral contraceptive use and risk of uterine fibroids. Obstet Gynecol 1992;79:430–3. (Level II-2)

73. Lumbiganon P, Rugpao S, Pandhu-fung S, Laopaiboon M, Vudhikamraksa N, Werawatakul Y. Protective effect of depot-medroxyprogesterone acetate on surgically treated uterine leiomyomas: a multicentre case-control study. Br J Obstet Gynaecol 1996;103:909–14. (Level II-2)

74. Wise LA, Palmer JR, Harlow BL, Spiegelman D, Stewart EA, Adams-Campbell LL, et al. Reproductive factors, hormonal contraception, and risk of uterine leiomyomata in African-American women: a prospective study. Am J Epidemiol 2004;159:113–23. (Level II-2)

75. Venkatachalam S, Bagratee JS, Moodley J. Medical management of uterine fibroids with medroxyprogesterone acetate (Depo Provera): a pilot study. J Obstet Gynaecol 2004;24:798–800. (Level III)

76. Grigorieva V, Chen-Mok M, Tarasova M, Mikhailov A. Use of a levonorgestrel-releasing intrauterine system to treat bleeding related to uterine leiomyomas. Fertil Steril 2003;79:1194–8. (Level II-3)

77. Mercorio R, De Simone R, Di Spiezio Sardo A, Cerrota G, Bifulco G, Vanacore F, et al. The effect of a levonorgestrel-releasing intrauterine device in the treatment of myoma-related menorrhagia. Contraception 2003;67: 277–80. (Level III)

78. Soysal S, Soysal ME. The efficacy of levonorgestrel-releasing intrauterine device in selected cases of myoma-related menorrhagia: a prospective controlled trial. Gynecol Obstet Invest 2005;59:29–35. (Level II-2)

79. Effects of hormonal contraceptives on breast milk composition and infant growth. World Health Organization (WHO) Task Force on Oral Contraceptives. Stud Fam Plann 1988;19:361–9. (Level II-2)

80. Truitt ST, Fraser AB, Grimes DA, Gallo MF, Schulz KF. Hormonal contraception during lactation: systematic review of randomized controlled trials. Contraception 2003;68:233–8. (Level III)

81. Halderman LD, Nelson AL. Impact of early postpartum administration of progestin-only hormonal contraceptives compared with nonhormonal contraceptives on short-term breast-feeding patterns. Am J Obstet Gynecol 2002;186:1250–6; discussion 1256–8. (Level II-2)

82. Koetsawang S. The effects of contraceptive methods on the quality and quantity of breast milk. Int J Gynaecol Obstet 1987;25 suppl:115–27. (Level III)

83. McCann MF, Potter LS. Progestin-only oral contraception: a comprehensive review. Contraception 1994;50(6 suppl 1):S1–S195. (Level III)

84. Progestogen-only contraceptives during lactation: I. Infant growth. World Health Organization Task Force for Epidemiological Research on Reproductive Health; Special Programme of Research, Development, and Research Training in Human Reproduction. Contraception 1994;50:35–53. (Level II-3)

85. Progestogen-only contraceptives during lactation: II. Infant development. World Health Organization, Task Force for Epidemiological Research on Reproductive Health; Special Programme of Research, Development, and Research Training in Human Reproduction. Contraception 1994;50:55–68. (Level II-3)

86. Back DJ, Orme ML. Pharmacokinetic drug interactions with oral contraceptives. Clin Pharmacokinet 1990;18: 472–84. (Level III)

87. Back DJ, Bates M, Bowden A, Breckenridge AM, Hall MJ, Jones H, et al. The interaction of phenobarbital and other anticonvulsants with oral contraceptive steroid therapy. Contraception 1980;22:495–503. (Level II-3)

88. Crawford P, Chadwick DJ, Martin C, Tjia J, Back DJ, Orme M. The interaction of phenytoin and carbamazepine with combined oral contraceptive steroids. Br J Clin Pharmacol 1990;30:892–6. (Level II-3)

89. Klosterskov Jensen P, Saano V, Haring P, Svenstrup B, Menge GP. Possible interaction between oxcarbazepine and an oral contraceptive. Epilepsia 1992;33:1149–52. (Level III)

90. Fattore C, Cipolla G, Gatti G, Limido GL, Sturm Y, Bernasconi C, et al. Induction of ethinylestradiol and levonorgestrel metabolism by oxcarbazepine in healthy women. Epilepsia 1999;40:783–7. (Level II-3)

91. Saano V, Glue P, Banfield CR, Reidenberg P, Colucci RD, Meehan JW, et al. Effects of felbamate on the pharmacokinetics of a low-dose combination oral contraceptive. Clin Pharmacol Ther 1995;58:523–31. (Level I)

92. Rosenfeld WE, Doose DR, Walker SA, Nayak RK. Effect of topiramate on the pharmacokinetics of an oral contraceptive containing norethindrone and ethinyl estradiol in patients with epilepsy. Epilepsia 1997;38:317–23. (Level II-3)

93. Bartoli A, Gatti G, Cipolla G, Barzaghi N, Veliz G, Fattore C, et al. A double-blind, placebo-controlled study on the effect of vigabatrin on in vivo parameters of hepatic microsomal enzyme induction and on the kinetics of steroid oral contraceptives in healthy female volunteers. Epilepsia 1997;38:702–7. (Level I)

94. Crawford P, Chadwick D, Cleland P, Tjia J, Cowie A, Back DJ, et al. The lack of effect of sodium valproate on the pharmacokinetics of oral contraceptive steroids. Contraception 1986;33:23–9. (Level II-3)

95. Eldon MA, Underwood BA, Randinitis EJ, Sedman AJ. Gabapentin does not interact with a contraceptive regimen of norethindrone acetate and ethinyl estradiol. Neurology 1998;50:1146–8. (Level II-3)

96. Mengel HB, Houston A, Back DJ. An evaluation of the interaction between tiagabine and oral contraceptives in female volunteers. J Pharm Med 1994;4:141–50. (Level II-3)

97. Ragueneau-Majlessi I, Levy RH, Janik F. Levetiracetam does not alter the pharmacokinetics of an oral contraceptive in healthy women. Epilepsia 2002;43:697–702. (Level II-3)

98. Griffith SG, Dai Y. Effect of zonisamide on the pharmacokinetics and pharmacodynamics of a combination ethinyl estradiol-norethindrone oral contraceptive in healthy women. Clin Ther 2004;26:2056–65. (Level II-2)

99. Crawford P. Interactions between antiepileptic drugs and hormonal contraception. CNS Drugs 2002;16:263–72. (Level III)

100. Natsch S, Hekster YA, Keyser A, Deckers CL, Meinardi H, Renier WO. Newer anticonvulsant drugs: role of pharmacology, drug interactions and adverse reactions in drug choice. Drug Saf 1997;17:228–40. (Level III)

101. Back DJ, Breckenridge AM, Crawford F, MacIver M, Orme ML, Park BK, et al. The effect of rifampicin on norethisterone pharmacokinetics. Eur J Clin Pharmacol 1979;15:193–7. (Level III)

102. Murphy AA, Zacur HA, Charache P, Burkman RT. The effect of tetracycline on levels of oral contraceptives. Am J Obstet Gynecol 1991;164:28–33. (Level II-3)

103. Neely JL, Abate M, Swinker M, D'Angio R. The effect of doxycycline on serum levels of ethinyl estradiol, norethindrone, and endogenous progesterone. Obstet Gynecol 1991;77:416–20. (Level II-2)

104. Joshi JV, Joshi UM, Sankholi GM, Krishna U, Mandlekar A, Chowdhury V, et al. A study of interaction of low-dose combination oral contraceptive with ampicillin and metronidazole. Contraception 1980;22: 643–52. (Level II-2)

105. Maggiolo F, Puricelli G, Dottorini M, Caprioli S, Bianchi W, Suter F. The effect of ciprofloxacin on oral contraceptive steroid treatments. Drugs Exp Clin Res 1991; 17:451–4. (Level II-3)

106. Back DJ, Tjia J, Martin C, Millar E, Mant T, Morrison P, et al. The lack of interaction between temafloxacin and combined oral contraceptive steroids. Contraception 1991;43:317–23. (Level II-2)

107. Csemiczky G, Alvendal C, Landgren BM. Risk for ovulation in women taking a low-dose oral contraceptive (Microgynon) when receiving antibacterial treatment with a fluoroquinolone (ofloxacin). Adv Contracept 1996;12:101–9. (Level II-1)

108. Hilbert J, Messig M, Kuye O, Friedman H. Evaluation of interaction between fluconazole and an oral contraceptive in healthy women. Obstet Gynecol 2001;98:218–23. (Level II-3)

109. Verhoeven CH, van den Heuvel MW, Mulders TM, Dieben TO. The contraceptive vaginal ring, NuvaRing, and antimycotic co-medication. Contraception 2004;69; 129–32. (Level II-1)

110. Dogterom P, van den Heuvel MW, Thomsen T. Absence of pharmacokinetic interactions of the combined contraceptive vaginal ring NuvaRing with oral amoxicillin or doxycycline in two randomised trials. Clin Pharmacokinet 2005;44:429–38. (Level II-1)

111. Haukkamaa M. Contraception by Norplant subdermal capsules is not reliable in epileptic patients on anticonvulsant treatment. Contraception 1986;33:559–65. (Level II-3)

112. Bounds W, Guillebaud J. Observational series on women using the contraceptive Mirena concurrently with antiepileptic and other enzyme-inducing drugs. J Fam Plann Reprod Health Care 2002;28:78–80. (Level III)

113. Koke SC, Brown EB, Miner CM. Safety and efficacy of fluoxetine in patients who receive oral contraceptive therapy. Am J Obstet Gynecol 2002;187:551–5. (Level II-3)

114. Murphy PA, Kern SE, Stanczyk FZ, Westhoff CL. Interaction of St. John's Wort with oral contraceptives: effects on the pharmacokinetics of norethindrone and ethinyl estradiol, ovarian activity and breakthrough bleeding. Contraception 2005;71:402–8. (Level II-3)

115. Shadle CR, Liu G, Goldberg MR. A double-blind, placebo-controlled evaluation of the effect of oral doses of rizatriptan 10 mg on oral contraceptive pharmacokinetics in healthy female volunteers. J Clin Pharmacol 2000; 40:309–15. (Level II-3)

116. Hendrix CW, Jackson KA, Whitmore E, Guidos A, Kretzer R, Liss CM, et al. The effect of isotretinoin on the pharmacokinetics and pharmacodynamics of ethinyl estradiol and norethindrone. Clin Pharmacol Ther 2004; 75:464–75. (Level II-3)

117. Koch K, Campanella CA, Baidoo C, Manzo JA, Ameen VZ, Kersey KE. Pharmacodynamics and pharmacokinetics of oral contraceptives co-administered with alosetron (Lotronex). Dig Dis Sci 2004;49:1244–9. (Level II-3)

118. Simonson SG, Martin PD, Warwick MJ, Mitchell PD, Schneck DW. The effect of rosuvastatin on oestrogen & progestin pharmacokinetics in healthy women taking an oral contraceptive. Br J Clin Pharmacol 2004;57:279–86. (Level II-3)

119. Inglis AM, Miller AK, Culkin KT, Finnerty D, Patterson SD, Jorkasky DK, et al. Lack of effect of rosiglitazone on the pharmacokinetics of oral contraceptives in healthy female volunteers. J Clin Pharmacol 2001;41:683–90. (Level II-3)

120. Sidney S, Petitti DB, Soff GA, Cundiff DL, Tolan KK, Quesenberry CP Jr. Venous thromboembolic disease in users of low-estrogen combined estrogen-progestin oral contraceptives. Contraception 2004;70:3–10. (Level II-2)

121. Samuelsson E, Hagg S. Incidence of venous thromboembolism in young Swedish women and possibly preventable cases among combined oral contraceptive users. Acta Obstet Gynecol Scand 2004;83:674–81. (Level II-2)

122. Jick H, Kaye JA, Vasilakis-Scaramozza C, Jick SS. Risk of venous thromboembolism among users of third generation oral contraceptives compared with users of oral contraceptives with levonorgestrel before and after 1995: cohort and case-control analysis. BMJ 2000;321: 1190–95. (Level II-2)

123. Kemmeren JM, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. BMJ 2001;323:131–4. (Meta-analysis)

124. Martinelli I, Taioli E, Battaglioli T, Podda GM, Passamonti SM, Pedotti P, et al. Risk of venous thromboembolism after air travel: interaction with thrombophilia and oral contraceptives. Arch Intern Med 2003; 163:2771–4. (Level II-2)

125. Vandenbroucke JP, Koster T, Briet E, Reitsma PH, Bertina RM, Rosendaal FR. Increased risk of venous thrombosis in oral-contraceptive users who are carriers of factor V Leiden mutation. Lancet 1994;344:1453–7. (Level II-2)

126. Bloemenkamp KW, Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Higher risk of venous thrombosis during early use of oral contraceptives in women with inherited clotting defects. Arch Intern Med 2000;160: 49–52. (Level II-2)

127. Vessey M, Mant D, Smith A, Yeates D. Oral contraceptives and venous thromboembolism: findings in a large prospective study. Br Med J 1986;292:526. (Level II-2)

128. Robinson GE, Burren T, Mackie IJ, Bounds W, Walshe K, Faint R, et al. Changes in haemostasis after stopping the combined contraceptive pill: implications for major surgery. BMJ 1991;302:269–71. (Level II-3)

129. Bonnar J. Can more be done in obstetric and gynecologic practice to reduce morbidity and mortality associated with venous thromboembolism? Am J Obstet Gynecol 1999;180:784–91. (Level III)

130. Delis KT, Hunt N, Strachan RK, Nicolaides AN. Incidence, natural history and risk factors of deep vein thrombosis in elective knee arthroscopy. Thromb Haemost 2001;86:817–21. (Level II-2)

131. Black C, Kaye JA, Jick H. Clinical risk factors for venous thromboembolus in users of the combined oral contraceptive pill. Br J Clin Pharmacol 2002;53:637–40. (Level II-2)

132. Spannagl M, Heinemann LA, Schramm W. Are factor V Leiden carriers who use oral contraceptives at extreme risk for venous thromboembolism? Eur J Contracept Reprod Health Care 2000;5:105–12. (Level II-2)

133. Comp PC. Thrombophilic mechanisms of OCs. Int J Fertil Womens Med 1997;42 (suppl 1):170–6. (Level III)

134. Price DT, Ridker PM. Factor V Leiden mutation and the risks for thromboembolic disease: a clinical perspective. Ann Intern Med 1997;127:895–903. (Level III)

135. Comp PC, Zacur HA. Contraceptive choices in women with coagulation disorders. Am J Obtset Gynecol 1993; 168:1990–3. (Level III)

136. Mishell DR Jr. Pharmacokinetics of depot medroxyprogesterone acetate contraception. J Reprod Med 1996; 41(5 suppl):381–90. (Level III)

137. Sonmezer M, Atabekoglu C, Cengiz B, Dokmeci F, Cengiz SD. Depot-medroxyprogesterone acetate in anticoagulated patients with previous hemorrhagic corpus luteum. Eur J Contracept Reprod Health Care 2005; 10:9–14. (Level III)

138. National Center for Health Statistics: Prevalence of overweight and obesity among adults: United Sates, 1999-2002. Available at: http://www.cdc.gov/nchs/products/pubs/pubd/hestats/obese/obse99.htm#Table%201. Retrieved December 8, 2005. (Level II-3)

139. Holt VL, Scholes D, Wicklund KG, Cushing-Haugen KL, Daling JR. Body mass index, weight, and oral contraceptive failure risk. Obstet Gynecol 2005;105:46–52. (Level II-2)

140. Zieman M, Guillebaud J, Weisberg E, Shangold GA, Fisher AC, Creasy GW. Contraceptive efficacy and cycle control with Ortho Evra/Evra transdermal system: the analysis of pooled data. Fertil Steril 2002;77:S13–8. (Level III)

141. Leiman G. Depo-medroxyprogesterone acetate as a contraceptive agent: its effect on weight and blood pressure. Am J Obstet Gynecol 1972;114:97–102. (Level III)

142. Abdollahi M, Cushman M, Rosendaal F. Obesity: risk of venous thrombosis and the interaction with coagulation factor levels and oral contraceptive use. Thromb Haemost 2003;89:493–8. (Level II-2)

143. Vasilakis C, Jick SS, Jick H. The risk of venous thromboembolism in users of postcoital contraceptive pills. Contraception 1999;59:79–83. (Level II-2)

144. Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, et al. Combined oral contraceptives in women with systemic lupus erythematosus. OC-SELENA Trial. N Engl J Med 2005;353:2550–8. (Level I)

145. Sanchez-Guerrero J, Urive AG, Jimenez-Santana L, Mestanza-Peralta M, Lara-Reyes P, Seuc AH, et al. A trial of contraceptive methods in women with systemic lupus erythematosus. N Engl J Med 2005;353:2539–49. (Level I)

146. Bermas BL. Oral contraceptives in systemic lupus erythematosus—a tough pill to swallow? N Engl J Med 2005;353:2602–4. (Level III)

147. Charache S, Niebyl JR. Pregnancy in sickle cell disease. Clin Haematol 1985;14:729–46. (Level III)

148. De Ceulaer K, Gruber C, Hayes R, Serjeant GR. Medroxyprogesterone acetate and homozygous sickle-cell disease. Lancet 1982;2:229–31. (Level II-2)

149. de Abood M, de Castillo Z, Guerrero F, Espino M, Austin KL. Effect of Depo-Provera or Microgynon on the painful crises of sickle cell anemia patients. Contraception 1997;56:313–6. (Level I)

150. Yoong WC, Tuck SM, Pasi KJ, Owens D, Perry DJ. Markers of platelet activation, thrombin generation and fibrinolysis in women with sickle cell disease: effects of differing forms of hormonal contraception. Eur J Haematol 2003;70:310–4. (Level II-3)

151. Yoong WC, Tuck SM, Yardumian A. Red cell deformability in oral contraceptive pill users with sickle cell anaemia. Br J Haematol 1999;104:868–70. (Level II-3)

152. Cromer BA, Smith RD, Blair JM, Dwyer J, Brown RT. A prospective study of adolescents who choose among levonorgestrel implant (Norplant), medroxyprogesterone acetate (Depo-Provera), or the combined oral contraceptive pill as contraception. Pediatrics 1994;94:687–94. (Level II-3)

153. Westhoff C, Truman C, Kalmuss D, Cushman L, Davidson A, Rulin M, et al. Depressive symptoms and Depo-Provera. Contraception 1998;57:237–40. (Level II-2)

154. Gupta N, O'Brien R, Jacobsen LJ, Davis A, Zuckerman A, Supran S, et al. Mood changes in adolescents using depot-medroxyprogesterone acetate for contraception: a prospective study. J Pediatr Adolesc Gynecol 2001;14: 71–6. (Level II-2)

155. Sinei SK, Fortney JA, Kigondu CS, Feldblum PJ, Kuyoh M, Allen MY, et al. Contraceptive use and HIV infection in Kenyan family planning clinic attenders. Int J STD AIDS 1996;7:65–70. (Level II-2)

156. Kapiga SH, Lyamuya EF, Lwihula GK, Hunter DJ. The incidence of HIV infection among women using family planning methods in Dar es Salaam, Tanzania. AIDS 1998;12:75–84. (Level II-2)

157. Kiddugavu M, Makumbi F, Wawer MJ, Serwadda D, Sewankambo NK, Wabwire-Mangen F, et al. Hormonal contraceptive use and HIV-1 infection in a population-based cohort in Rakai, Uganda. Rakai Project Study Group. AIDS 2003;17:233–240. (Level II-2)

158. Bulterys M, Chao A, Habimana P, Dushimimana A, Nawrocki P, Saah A. Incident HIV-1 infection in a cohort of young women in Butare, Rwanda. AIDS 1994;8: 1585–91. (Level II-2)

159. Plummer FA, Simonsen JN, Cameron DW, Ndinya-Achola JO, Kreiss JK, Gakinya MN, et al. Cofactors in male-female sexual transmission of human immunodeficiency virus type 1. J Infect Dis 1991;163:233–9. (Level II-2)

160. Lavreys L, Baeten JM, Martin HL Jr, Overbaugh J, Mandaliya K, Ndinya-Achola JV, et al. Hormonal contraception and risk of HIV-1 acquisition: results of a 10-year prospective study. AIDS 2004;18:695–7. (Level II-2)

161. Plourde PJ, Pepin J, Agoki E, Ronald AR, Ombette J, Tyndall M, et al. Human immunodeficiency virus type 1 seroconversion in women with genital ulcers. J Infect Dis 1994;170:313–7. (Level III)

162. Kilmarx PH, Limpakarnjanarat K, Mastro TD, Saisorn S, Kaewkungwal J, Korattana S, et al. HIV-1 seroconversion in a prospective study of female sex workers in northern Thailand: continued high incidence among brothel-based women. AIDS 1998;12:1889–98. (Level III)

163. de Vincenzi I. A longitudinal study of human immunodeficiency virus transmission by heterosexual partners. European Study Group on Heterosexual Transmission of HIV. N Engl J Med 1994;331:341–6. (Level II-2)

164. Ungchusak K, Rehle T, Thammapornpilap P, Spiegelman D, Brinkmann U, Siraprapasiri T. Determinants of HIV infection among female commercial sex workers in northeastern Thailand: results from a longitudinal study [published erratum appears in J Acquir Immune Defic Syndr Hum Retrovirol 1998;18:192]. J Acquir Immune Defic Syndr Hum Retrovirol 1996;12:500–7. (Level II-2)

165. Saracco A, Musicco M, Nicolosi A, Angarano G, Arici C, Gavazzeni G, et al. Man-to-woman sexual transmission of HIV: longitudinal study of 343 steady partners of infected men. J Acquir Immune Defic Syndr 1993;6: 497–502. (Level II-2)

166. Morrison CS, Richardson BA, Celentano DD, Chipato T, Mmiro F, Mugerwa R, et al. Prospective clinical trials designed to assess the use of hormonal contraceptives

and risk of HIV acquisition. J Acquir Immune Defic Syndr 2005;38(suppl 1):S17–8. (Level II-2)

167. Wang CC, McClelland RS, Overbaugh J, Reilly M, Panteleeff DD, Mandaliya K, et al. The effect of hormonal contraception on genital tract shedding of HIV-1. AIDS 2004;18:205–9. (Level II-2)
168. Clark MK, Sowers M, Levy BT, Tenhundfeld P. Magnitude and variability of sequential estradiol and progesterone concentrations in women using depot medroxyprogesterone acetate for contraception. Fertil Steril 2001;75:871–7. (Level III)
169. Banks E, Berrington A, Casabonne D. Overview of the relationship between use of progestogen-only contraceptives and bone mineral density. BJOG 2001;108: 1214–21. (Level III)
170. Clark MK, Sowers MR, Nichols S, Levy B. Bone mineral density changes over two years in first-time users of depot medroxyprogesterone acetate. Fertil Steril 2004; 82:1580–6. (Level II-2)
171. Scholes D, LaCroix AZ, Ichikawa LE, Barlow WE, Ott SM. Injectable hormone contraception and bone density: results from a prospective study [Published erratum appears in Epidemiology 2002;13:749]. Epidemiology 2002;13:581–7. (Level II-2)
172. Orr-Walker BJ, Evans MC, Ames RW, Clearwater JM, Cundy T, Reid IR. The effect of past use of the injectable contraceptive depot medroxyprogesterone acetate on bone mineral density in normal post-menopausal women. Clin Endocrinol (Oxf) 1998;49:615–8. (Level II-3)
173. Petitti DB, Piaggio G, Mehta S, Cravioto MC, Meirik O. Steroid hormone contraception and bone mineral density: a cross sectional study in an international population. The WHO Study of Hormonal Contraception and Bone Health. Obstet Gynecol 2000;95:736–44. (Level II-3)
174. Cromer BA, Blair JM, Mahan JD, Zibners L, Naumovski Z. A prospective comparison of bone density in adolescent girls receiving depot medroxyprogesterone acetate (Depo-Provera), levonorgestrel (Norplant), or oral contraceptives. J Pediatr 1996;129:671–6. (Level II-2)
175. Cundy T, Ames R, Horne A, Clearwater J, Roberts H, Gamble G, et al. A randomized controlled trial of estrogen replacement therapy in long-term users of depot medroxyprogesterone acetate. J Clin Endocrinol Metab 2003;88:78–81. (Level I)
176. Cromer BA, Lazebnik R, Rome E, Stager M, Bonny A, Ziegler J, et al. Double-blinded randomized controlled trial of estrogen supplementation in adolescent girls who receive depot medroxyprogesterone acetate for contraception. Am J Obstet Gynecol 2005;192:42–7. (Level I)
177. Kolthoff N, Eiken P, Kristensen B, Nielsen SP. Bone mineral changes during pregnancy and lactation: a longitudinal cohort study. Clin Sci (Lond) 1998;94:405–12. (Level II-3)
178. Kalkwarf HJ, Specker BL, Bianchi DC, Ranz J, Ho M. The effect of calcium supplementation on bone density during lactation and after weaning. N Engl J Med 1997; 337:523–8. (Level I)
179. Kaunitz AM. Depo-Provera's black box: time to reconsider? Contraception 2005;72:165–7. (Level III)

The MEDLINE database, the Cochrane Library, and the American College of Obstetricians and Gynecologists' own internal resources and documents were used to conduct a literature search to locate relevant articles published between July 1971 and February 2006. 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 ACOG 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.

ISSN 1099-3630

The American College of Obstetricians and Gynecologists
409 12th Street, SW, PO Box 96920, Washington, DC 20090-6920

Use of hormonal contraception in women with coexisting medical conditions. ACOG Practice Bulletin No. 73. American College of Obstetricians and Gynecologists. Obstet Gynecol 2006:107:1453–72.