CLINICAL PRACTICE

Combination Estrogen–Progestin Oral Contraceptives

Diana B. Petitti, M.D., M.P.H.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.

A healthy, sexually active, 35-year-old woman presents for advice about the use of oral contraceptives. She does not smoke cigarettes and has no personal or family history of venous thromboembolism, myocardial infarction, or stroke. Her blood pressure is 120/80 mm Hg. Should an oral contraceptive be prescribed, and if so, how should a formulation be chosen?

THE CLINICAL PROBLEM

Most oral contraceptives now in widespread use are combinations of an estrogen and a progestin. At least 10 million women in the United States and 100 million women worldwide use combination oral contraceptives. They are highly effective in preventing pregnancy: about 5 women per 100 typical users[1] and fewer than 1 per 100 women with perfect use become pregnant per year.

The first oral-contraceptive formulations marketed in the United States, in 1960 and 1961, contained 2 to 5 times as much estrogen and 5 to 10 times as much progestin as the oral contraceptives now in use. The use of these high-dose formulations was linked to increased risks of ischemic stroke, myocardial infarction, and pulmonary embolism in healthy young women. The doses of estrogen and progestin were reduced rapidly during the 1960s and 1970s because of concern about safety and because the reduction of the doses did not reduce the contraceptive effectiveness.

The reductions in the dose of estrogen are believed to have decreased the risk of venous thrombosis. Because the effects of combination oral contraceptives on cardiovascular risk factors such as lipid levels and glucose tolerance vary with the type of progestin used in conjunction with the same dose of estrogen, oral-contraceptive formulations with fewer adverse effects on these metabolic variables were developed.

The combination estrogen–progestin oral contraceptives that are now on the market contain estrogen at doses ranging from 20 to 50 μg of ethinyl estradiol or, uncommonly, mestranol. These estrogens are combined with any of several different progestins, which may be given at the same dose every day ("monophasic") or at varying doses according to the phase of the cycle ("biphasic" or "triphasic") to mimic more closely the production of progesterone during the normal menstrual cycle. Details of formulations and doses are provided in Supplementary Appendix 1 (available with the full text of this article at http://www.nejm.org).

Recently, oral contraceptives have been classified by some according to "generation" (first, second, third, and most recently, fourth generation). These terms sometimes refer to the timing of the introduction of a product (given both the dose of estrogen and the type of progestin), sometimes refer to the timing of the market introduction of the progestin, sometimes refer to the structure of the carbon ring from which the progestin is derived (estrane or gonane), and sometimes lack a clear definition. Thus, the same

From the Research and Evaluation Department, Kaiser Permanente Southern California, Pasadena. Address reprint requests to Dr. Petitti at Research and Evaluation, Kaiser Permanente Southern California, 100 S. Los Robles, 2nd Fl., Pasadena, CA 91188, or at diana.b.petitti@kp.org.

N Engl J Med 2003;349:1443-50.

formulation may be classified as being of different generations in different studies (Table 1). Because of this confusion, I avoid the use of such terms in this article.

The use of combined oral contraceptives has many noncontraceptive benefits, but there are also risks, including risks of venous thromboembolism and arterial vascular disease, which may vary according to the formulation. The challenge for the clinician is to identify women in whom the risks associated with oral-contraceptive use outweigh the benefits and to select formulations for other women that minimize the risks and maximize the benefits.

Table 1. Types of Progestin in Combination Estrogen–Progestin Oral Contraceptives Marketed in the United States or Mentioned in Studies of Types of Progestin and Cardiovascular Disease.

Type of Progestin	Generation		Brand Names of Selected Products*
	According to Time of Market Introduction†	According to Published Studies of Vascular Disease	
Ever marketed in the United States			
Chlormadinone acetate‡§	First	Other	C-Quens
Desogestrel	Third	Third	Desogen, Ortho-Cept, Apri (monophasic) Cyclessa (triphasic)
Dimethisterone‡§	First	Not mentioned	Oracon
Drospirenone	Fourth	Not studied	Yasmin (monophasic)
Ethynodiol diacetate	First	First or second	Demulen 1/35, Zovia 1/35E (monophasic)
Levonorgestrel	Second	Second	Levlen, Levora, Nordette, Portia (monophasic) Alesse, Aviane, Lessina, Levlite (monophasic) Enpresse, Tri-Levlen, Triphasil, Trivora (triphasic)
Medroxyprogesterone acetate‡	First	Not mentioned	Provest
Norethindrone	First	First or second	Necon 1/35, Norinyl 1+35, Nortrel 1/35, Ortho-Novum 1/35 (monophasic) Brevicon, Modicon, Neocon 0.5/35, Nortrel 0.5/35 (monophasic) Ovcon-35 (monophasic) Necon 7/7/7, Ortho-Novum 7/7/7, Nortrel 7/7/7, Tri-Norinyl (triphasic)
Norethindrone acetate‡	First	First or second	Loestrin 21 1.5/30, Loestrin Fe 1.5/30, Microgestin Fe 1.5/30 (monophasic) Loestrin 21 1/20, Loestrin Fe 1/20, Microgestin Fe 1/20 (monophasic) Estrostep 21, Estrostep Fe (triphasic)
Norethynodrel‡	First	First	Enovid
Norgestimate‡	Third	Second, third, or other	Mononessa, Ortho-Cyclen, Sprintec (monophasic) Ortho Tri-Cyclen, Ortho Tri-Cyclen Lo (triphasic)
Norgestrel	First	First or second	Cryselle, Lo/Ovral, Low-Ogestrel (monophasic)
Never marketed in the United States			
Gestodene	Third	Third	—
Lynestrenol	First	First or second	—

* Among products currently marketed in the United States, the lists include only monophasic and triphasic formulations containing less than 50 μg of ethinyl estradiol; each list of monophasic formulations containing a given type of progestin includes products containing the same amount of estrogen and progestin; separate lists of monophasic preparations containing a given type of progestin appear in order of decreasing dose of ethinyl estradiol or progestin. The listed products are provided as examples and were not selected on the basis of cost or market share.

† According to this classification, the first generation includes contraceptives approved for marketing in the United States before 1973, the second generation those approved for marketing in the United States between 1973 and 1989, the third generation those approved for marketing in the United States or Europe between 1990 and 2000, and the fourth generation those approved for marketing in the United States after 2000.

‡ This type of progestin is not contained in any combination estrogen–progestin oral contraceptives currently marketed in the United States.

§ In the United States, this type of progestin has been marketed only in combination oral contraceptives involving the sequential administration of estrogen and progestin.

STRATEGIES AND EVIDENCE

BENEFITS OF ORAL-CONTRACEPTIVE USE

Ovarian Cancer

The risk of ovarian cancer is reduced by at least half among women who use oral contraceptives, including those who use low-estrogen formulations.[2,3] The reduction in risk occurs after relatively short-term use (5 years) and persists for 10 to 20 years after use has been discontinued. This benefit extends to women with a family history of ovarian cancer[4] and women with a mutation in the *BRCA1* or *BRCA2* gene.[5,6] The suggested mechanism for this effect is the suppression of ovulation.

Endometrial Cancer

Older formulations of oral contraceptives, which contained higher doses of estrogen, reduce the risk of endometrial cancer, presumably by progestin-mediated suppression of estrogen-induced proliferation of endometrial cells. The reduction in risk occurs after a relatively short period of use (five years) and persists long after discontinuation. Newer formulations have not been studied, but the presumed mechanism suggests that these formulations would also reduce the risk of endometrial cancer.[7]

Acne

Randomized, double-blind, placebo-controlled trials show substantial reductions in the severity of acne among both patients given oral contraceptives and patients given placebo, but the patients who received oral contraceptives had greater improvement.[8] Randomized trials comparing low-estrogen oral contraceptives including different progestins do not show consistent differences among formulations.[9] Some formulations have been approved for a marketing claim regarding their beneficial effect on acne, but all low-dose combination oral contraceptives cause a similar decrease in the concentration of free testosterone, the presumed mechanism for the improvement of acne.[10]

Menstrual Disorders, Loss of Blood, and Anemia

One randomized, double-blind, placebo-controlled trial of low-dose oral contraceptives showed that their use reduces the severity of dysfunctional uterine bleeding.[11] Oral-contraceptive use decreases menstrual blood flow and is associated with a reduced prevalence of anemia and increased hemoglobin concentrations in anemic women.[12-14]

RISKS ASSOCIATED WITH ORAL-CONTRACEPTIVE USE

Myocardial Infarction and Ischemic Stroke

Whereas older oral-contraceptive preparations increased the risk of myocardial infarction and ischemic stroke, studies reported in the past seven years have yielded conflicting results.[15-23] The relative risks of myocardial infarction and ischemic stroke among current users of oral contraceptives, as compared with nonusers, were 1.0 and 1.1, respectively, according to a pooled analysis of data from two case–control studies in the United States.[18-22] The Myocardial Infarction and Oral Contraceptives (MICA) study[15] reported a relative risk of myocardial infarction among current users of oral contraceptives of 1.4, which was not statistically significant. Other studies reported statistically significant increases by a factor of two to five in the relative risks of myocardial infarction[17,19] and ischemic stroke[20,21,23] among current users of oral contraceptives. The differences are probably due to the higher prevalence of smoking and of untreated and undiagnosed hypertension in the populations of the latter studies.

In keeping with these findings, large increases (by a factor ranging from 7 to more than 100) have been observed in the relative risks of myocardial infarction and ischemic stroke among users of oral contraceptives who smoke or have hypertension.[16,19,20,23] Table 2 shows the estimated number of excess cases of ischemic stroke or myocardial infarction attributable to oral-contraceptive use among nonsmokers, smokers, and women with hypertension according to age.[24] For comparison, the pregnancy-related rate of death per 100,000 live births in 1999[25] is also shown.

It has been proposed that the type of progestin used may modify the arterial vascular risk associated with the use of oral contraceptives. However, when the dose of estrogen was less than 50 μg, the risk of ischemic stroke did not differ between women taking oral-contraceptive formulations containing desogestrel or gestodene and women taking formulations containing levonorgestrel or norethindrone.[20]

Venous Thromboembolism and Cerebral Venous Thrombosis

The risk of venous thromboembolism (pulmonary embolism and deep venous thrombosis) is increased by a factor of three to four among current users of low-estrogen oral contraceptives[26-32] containing norethindrone, norethindrone acetate, lynestrenol,

Table 2. Age-Specific Estimates of the Excess Rates of Myocardial Infarction, Ischemic Stroke, and Venous Thromboembolism Attributable to the Use of Low-Estrogen Oral Contraceptives and Pregnancy-Related Mortality.*

Variable	Age		
	20–24 Yr	30–34 Yr	40–44 Yr
No. of excess cases of myocardial infarction and ischemic stroke attributable to oral-contraceptive use (per 100,000 woman-yr of use)†			
Among nonsmokers	0.4	0.6	2
Among smokers	1	2	20
Among women with hypertension	4	7	29
No. of pregnancy-related deaths (per 100,000 live births)	10	12	45
No. of excess cases of venous thromboembolism attributable to oral-contraceptive use (per 100,000 woman-yr of use)			
With norethindrone, norethindrone acetate, levonorgestrel, or ethynodiol diacetate	6	9	12
With desogestrel or gestodene	16	23	30

* Low estrogen was defined as less than 50 μg.
† Data are from Farley et al.[24]

ethynodiol diacetate, levonorgestrel, or norgestrel. Two recent meta-analyses[33,34] both concluded that the use of low-estrogen oral contraceptives containing one of the so-called third-generation progestins, desogestrel or gestodene, increases the risk of venous thromboembolism more than low-estrogen formulations containing levonorgestrel — by a factor of 1.5 to 1.8. These differences in risk appear to be real and cannot be accounted for by methodologic problems in the studies or the analyses.[35] Table 2 shows the number of excess venous thromboembolic events among users of low-estrogen formulations containing desogestrel or gestodene as compared with users of low-estrogen formulations containing levonorgestrel.[24]

The elevation in the risk of venous thromboembolism is greatest in the first year after use is initiated, but an elevated risk persists beyond the first year.[36] Women are not at increased risk for venous thromboembolism, myocardial infarction, or ischemic stroke after they cease taking oral contraceptives.[35,37]

Currently used oral contraceptives also increase the risk of central retinal venous thrombosis.[38,39] Whether this risk is increased more among users of formulations containing gestodene or desogestrel than among users of other formulations is uncertain.[40,41]

The risk of venous thromboembolism among users of oral contraceptives who have thrombophilia — defined as a deficiency in protein C or protein S or the presence of factor V Leiden or the prothrombin G20210A mutation — is much higher (by a factor of 6 to 40) than the risk among nonusers who do not have thrombophilia.[27,29]

EVIDENCE OF NO OR MINIMAL EFFECT

Low-estrogen oral contraceptives do not appear to increase the risk of hemorrhagic stroke among women who do not have hypertension. There is no increase in the risk of hepatocellular carcinoma[42] and only a small increase in the risk of hepatocellular adenoma among users of lower-dose oral contraceptives.[43]

AREAS OF UNCERTAINTY

PARTICULAR PROGESTINS AND VASCULAR DISEASE

Definitive data are lacking regarding the vascular risks associated with the newer progestins, cyproterone and drospirenone. Drospirenone is derived from spirolactone and lacks androgenic activity in cell systems. Although there are theoretical advantages to progestins that have less androgenicity, they have not been proved to have practical implications.

The possibility that low-estrogen oral contraceptives containing desogestrel or gestodene might be associated with a lower risk of myocardial infarction than those containing levonorgestrel cannot be established or ruled out on the basis of current evidence.[15,16,19,44] The risk of venous thromboembolism in formulations containing norgestimate remains uncertain, because in some studies it is considered to be a second-generation progestin, and in others a third-generation progestin.

SCREENING FOR THROMBOPHILIA

Tests for the factor V Leiden and prothrombin-gene mutations, which increase the risk of venous thromboembolism, are not routinely available and are costly where they are available. The role and cost effectiveness of screening for these and other prothrombotic polymorphisms remain uncertain. A family history of venous thromboembolism has a poor positive predictive value for thrombophilic gene defects.[45] Screening is not routinely recommended before the initiation of oral-contraceptive use.

HYPERTENSION AND OTHER CARDIOVASCULAR RISK FACTORS

The risks of myocardial infarction and stroke among users of oral contraceptives who have hypertension and take medications for blood-pressure control are not known. The risks of myocardial infarction and ischemic stroke are 7 to 15 times as high among users of oral contraceptives who have diabetes or hypercholesterolemia as among those who do not have these conditions.[16,20] As with hypertension, whether treatment of these conditions or associated vascular risk factors modifies the risks associated with oral-contraceptive use remains uncertain.

MIGRAINE

Some studies have reported an increased risk of ischemic stroke among oral-contraceptive users who have a history of migraine headache, as compared with women who do not have such a history.[46-48] However, the available studies have had methodologic limitations, including the possibilities that hemiplegic migraines were misdiagnosed as ischemic stroke or that women with ischemic stroke were more likely to report headaches, in retrospect, as having been migraines. Headaches may be classified as migraine without meeting the established criteria for the diagnosis, and self-reported migraine without associated neurologic deficits is not considered to be a contraindication to the use of oral contraceptives.

BREAST CANCER

Despite at least 60 epidemiologic studies of breast cancer and oral-contraceptive use, the effect of oral-contraceptive use on the risk of breast cancer remains controversial. A pooled analysis of data from 54 studies, reported in 1996, showed a small increase in the risk of breast cancer with current use (relative risk, 1.24; 95 percent confidence interval, 1.15 to 1.33); the relative risk decreased to 1.0 within 10 years after use had been discontinued.[49] In contrast, a recent study in the United States that involved 4575 women with breast cancer[50] showed no increase in the risk of breast cancer among women who were using oral contraceptives at the time of the study, women who had ever used oral contraceptives, or women with long-term use. The possibility that women with a strong family history of breast cancer or *BRCA1* or *BRCA2* gene mutations may be at higher risk for breast cancer than other women when using oral contraceptives has not been ruled out.[51-54]

CERVICAL CANCER

Human papillomavirus (HPV) is a causative agent in both squamous-cell and adenomatous cervical cancer,[55] yet until recently, HPV infection was not taken into account in studies of oral-contraceptive use and cervical neoplasia. Because of this and other methodologic problems, there are conflicting data on the association between oral-contraceptive use and the risk of cervical cancer.[56]

Recent studies suggest that oral-contraceptive use, especially long-term use, may increase the risk of cervical cancer in women who are positive for HPV DNA but not in women who are negative for HPV DNA.[57] The data are consistent with a promotional effect of oral contraceptives in women with HPV. Oral-contraceptive use may cause persistence of infection with the particular types of HPV that confer a high risk of cervical cancer[58] and may also affect the acquisition of HPV infection, although these conclusions are still not firm. Any effect of oral-contraceptive use on the risk of cervical neoplasia will be small if neoplasia is detected early and treated.

OTHER NEOPLASIA

The risk of colorectal cancer may be decreased with the use of oral contraceptives,[59] although studies have had conflicting results. A lower risk of benign breast disease among long-term users of oral contraceptives was observed in studies of older formulations, but it is uncertain whether such an association holds true for newer formulations. Whether oral-contraceptive use affects the risk of uterine myoma is also uncertain.[60,61]

OTHER FORMULATION-SPECIFIC EFFECTS

Numerous studies have evaluated contraceptive effectiveness, cycle control, bleeding patterns, or minor side effects such as weight gain with specific formulations; have compared these effects with those of placebo; or have compared the effects of two or three of the dozens of different formulations. There is no evidence of differences in contraceptive effectiveness among different formulations, but the equivalence of all currently marketed products has not been established through rigorous head-to-head comparisons. Studies of cycle control with various formulations have used different measures of bleeding, rendering it impossible to make valid comparisons.[62] The superiority of any specific formulation in reducing the risk of any minor side effect of oral-contraceptive use has not been established.

The cost to the patient of a cycle of oral contraceptives depends on the formulation, insurance coverage, and local pricing practices. It ranges from no cost to the patient to more than $50 per cycle.

GUIDELINES

In 2000, the American College of Obstetricians and Gynecologists (ACOG) issued practice guidelines regarding hormonal contraception.[63] Also in 2000, the World Health Organization (WHO) published guidelines on medical eligibility for contraceptive use.[64] Table 3 summarizes the ACOG and WHO recommendations for the use of combination oral contraceptives in women with characteristics that might put them at particularly high risk for adverse vascular events and according to personal and family history. The two sets of guidelines are similar.

CONCLUSIONS AND RECOMMENDATIONS

For most women who are, like the woman in the vignette, healthy and free of cardiovascular disease and major cardiovascular risk factors, the use of combination estrogen–progestin oral contraceptives is associated with low relative and absolute risks of cardiovascular disease. Even when the health risks are taken into account, the net health benefit of oral-contraceptive use in these women is great, especially given the effect on the risk of ovarian cancer and its effectiveness in preventing pregnancy. The favorable risk–benefit ratio for healthy women applies to all oral contraceptives containing a low dose of estrogen (less than 50 μg). However, among formulations containing less than 50 μg of ethinyl estradiol, those containing desogestrel or gesto-

Table 3. Summary of Guidelines for the Use of Combination Estrogen–Progestin Oral Contraceptives in Women with Characteristics That Might Increase the Risk of Adverse Effects.*

Variable	ACOG Guidelines	WHO Guidelines
Smoker, >35 yr of age		
<15 cigarettes/day	Risk unacceptable	Risk usually outweighs benefit
≥15 cigarettes/day	Risk unacceptable	Risk unacceptable
Hypertension		
Blood pressure controlled	Risk acceptable; no definition of blood-pressure control	Risk usually outweighs benefit if systolic blood pressure is 140–159 mm Hg and diastolic blood pressure is 90–99 mm Hg
Blood pressure uncontrolled	Risk unacceptable; no definition of uncontrolled blood pressure	Risk unacceptable if systolic blood pressure is ≥160 mm Hg or diastolic blood pressure is ≥100 mm Hg
History of stroke, ischemic heart disease, or venous thromboembolism	Risk unacceptable	Risk unacceptable
Diabetes	Risk acceptable if no other cardiovascular risk factors and no end-organ damage	Benefit outweighs risk if no end-organ damage and diabetes is of ≤20 yr duration
Hypercholesterolemia	Risk acceptable if LDL cholesterol <160 mg/dl and no other cardiovascular risk factors	Benefit–risk ratio is dependent on the presence or absence of other cardiovascular risk factors
Multiple cardiovascular risk factors	Not addressed	Risk usually outweighs benefit or risk unacceptable, depending on risk factors
Migraine headache		
Age ≥35 yr	Risk usually outweighs benefit	Risk usually outweighs benefit
Focal symptoms	Risk unacceptable	Risk unacceptable
Breast cancer		
Current disease	Risk unacceptable	Risk unacceptable
Past disease, no active disease for 5 yr	Risk unacceptable	Risk usually outweighs benefit
Family history of breast or ovarian cancer	Risk acceptable	Risk acceptable

* The American College of Obstetricians and Gynecologists (ACOG) guidelines recommend the use of formulations containing less than 50 μg of ethinyl estradiol with the "lowest progestin dose," without mention of the type of progestin. The World Health Organization (WHO) guidelines pertain explicitly to formulations containing 35 μg or less of ethinyl estradiol and do not mention the dose or type of progestin. To convert values for low-density lipoprotein (LDL) cholesterol to millimoles per liter, multiply by 0.02586.

dene are associated with an increase by a factor of 1.5 to 1.8 in the risk of venous thromboembolism as compared with formulations containing norethindrone, norethindrone acetate, ethynodiol diacetate, or levonorgestrel. Initiating oral-contraceptive use with the low-estrogen oral contraceptive that is the least costly for the patient is a reasonable clinical practice.

The risks associated with oral-contraceptive use outweigh the benefits for women with a history of stroke, ischemic heart disease, or venous thromboembolism. Oral contraceptives are contraindicated in women who are known to carry the factor V Leiden gene mutation, although screening for this condition is not recommended. Oral-contraceptive use should be discouraged among women older than 35 years of age who smoke (especially if they smoke more than 15 cigarettes per day) because they clearly have an increased risk of arterial vascular disease when using oral contraceptives. Smoking cessation should be encouraged routinely, and the clinician should document that older women who choose to use oral contraceptives while continuing to smoke have been counseled about the vascular risks associated with oral-contraceptive use. All oral-contraceptive users should have their blood pressure checked before initiating use and periodically thereafter. Women with well-controlled hypertension who elect to use oral contraceptives should be counseled that it is uncertain whether blood-pressure control eliminates the associated increases in the risks of stroke and myocardial infarction. Oral-contraceptive use should be discontinued immediately in any woman with symptoms suggestive of stroke, myocardial infarction, or venous thrombosis. Oral-contraceptive users should be screened regularly for cervical neoplasia but do not require more frequent screening than nonusers.

REFERENCES

1. Fu H, Darroch JE, Haas T, Ranjit N. Contraceptive failure rates: new estimates from the 1995 National Survey of Family Growth. Fam Plann Perspect 1999;31:56-63.
2. Ness RB, Grisso JA, Klapper J, et al. Risk of ovarian cancer in relation to estrogen and progestin dose and use characteristics of oral contraceptives. Am J Epidemiol 2000;152:233-41.
3. Royar J, Becher H, Chang-Claude J. Low-dose oral contraceptives: protective effect on ovarian cancer risk. Int J Cancer 2001;95:370-4.
4. Walker GR, Schlesselman JJ, Ness RB. Family history of cancer, oral contraceptive use, and ovarian cancer risk. Am J Obstet Gynecol 2002;186:8-14.
5. Modan B, Hartge P, Hirsh-Yechezkel G, et al. Parity, oral contraceptives, and the risk of ovarian cancer among carriers and noncarriers of a *BRCA1* or *BRCA2* mutation. N Engl J Med 2001;345:235-40.
6. Narod SA, Risch H, Moslehi R, et al. Oral contraceptives and the risk of hereditary ovarian cancer. N Engl J Med 1998;339:424-8.
7. Burkman RT. Oral contraceptives: current status. Clin Obstet Gynecol 2001;44:62-72.
8. Olson WH, Lippman JS, Robisch DM. The duration of response to norgestimate and ethinyl estradiol in the treatment of acne vulgaris. Int J Fertil Womens Med 1998;43:286-90.
9. Thorneycroft IH, Stanczyk FZ, Bradshaw KD, Ballagh SA, Nichols M, Weber ME. Effect of low-dose oral contraceptives on androgenic markers and acne. Contraception 1999;60:255-62.
10. Koulianos GT. Treatment of acne with oral contraceptives: criteria for pill selection. Cutis 2000;66:281-6.
11. Davis A, Godwin A, Lippman J, Olson W, Kafrissen M. Triphasic norgestimate-ethinyl estradiol for treating dysfunctional uterine bleeding. Obstet Gynecol 2000;96:913-20.
12. Milman N, Clausen J, Byg KE. Iron status in 268 Danish women aged 18-30 years: influence of menstruation, contraceptive method, and iron supplementation. Ann Hematol 1998;77:13-9.
13. Rivera R, Almonte H, Arreola M, et al. The effects of three different regimens of oral contraceptives and three different intrauterine devices on the levels of hemoglobin, serum iron and iron binding capacity in anemic women. Contraception 1983;27:311-27.
14. Effects of contraceptives on hemoglobin and ferritin. Contraception 1998;58:262-73.
15. Dunn N, Thorogood M, Faragher B, et al. Oral contraceptives and myocardial infarction: results of the MICA case-control study. BMJ 1999;318:1579-83.
16. Tanis BC, van den Bosch MAAJ, Kemmeren JM, et al. Oral contraceptives and the risk of myocardial infarction. N Engl J Med 2001;345:1787-93.
17. Lewis MA, Heinemann LA, Spitzer WO, MacRae KD, Bruppacher R. The use of oral contraceptives and the occurrence of acute myocardial infarction in young women: results from the Transnational Study on Oral Contraceptives and the Health of Young Women. Contraception 1997;56:129-40.
18. Sidney S, Siscovick DS, Petitti DB, et al. Myocardial infarction and use of low-dose oral contraceptives: a pooled analysis of 2 US studies. Circulation 1998;98:1058-63.
19. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Acute myocardial infarction and combined oral contraceptives: results of an international multicentre case-control study. Lancet 1997;349:1202-9.
20. Kemmeren JM, Tanis BC, Van Den Bosch MA, et al. Risk of Arterial Thrombosis in Relation to Oral Contraceptives (RATIO) study: oral contraceptives and the risk of ischemic stroke. Stroke 2002;33:1202-8.
21. Heinemann LA, Lewis MA, Spitzer WO, Thorogood M, Guggenmoos-Holzmann I, Bruppacher R. Thromboembolic stroke in young women: a European case-control study on oral contraceptives. Contraception 1998;57:29-37.
22. Schwartz SM, Petitti DB, Siscovick DS, 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.
23. WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Ischaemic stroke and combined oral contraceptives: results of an international, multicentre, case-control study. Lancet 1996;348:498-505.
24. Farley TM, Collins J, Schlesselman JJ. Hormonal contraception and risk of cardiovascular disease: an international perspective. Contraception 1998;57:211-30.
25. Chang J, Elam-Evans LD, Berg CJ, et al. Pregnancy-related mortality surveillance — United States, 1991–1999. MMWR Surveill Summ 2003;52:1-8.
26. Farmer RD, Lawrenson RA, Thompson CR, Kennedy JG, Hambleton IR. Population-based study of risk of venous thromboembolism associated with various oral contraceptives. Lancet 1997;349:83-8.
27. Bloemenkamp KW, Rosendaal FR, Buller

HR, Helmerhorst FM, Colly LP, Vandenbroucke JP. Risk of venous thrombosis with use of current low-dose oral contraceptives is not explained by diagnostic suspicion and referral bias. Arch Intern Med 1999;159:65-70.
28. Lidegaard O, Edstrom B, Kreiner S. Oral contraceptives and venous thromboembolism: a case-control study. Contraception 1998;57:291-301.
29. 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.
30. Parkin L, Skegg DC, Wilson M, Herbison GP, Paul C. Oral contraceptives and fatal pulmonary embolism. Lancet 2000;355:2133-4.
31. Spitzer WO, Lewis MA, Heinemann LA, Thorogood M, MacRae KD. Third generation oral contraceptives and risk of venous thromboembolic disorders: an international case-control study. BMJ 1996;312:83-8.
32. World Health Organization Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. Venous thromboembolic disease and combined oral contraceptives: results of international multicentre case-control study. Lancet 1995;346:1575-82.
33. Hennessy S, Berlin JA, Kinman JL, Margolis DJ, Marcus SM, Strom BL. Risk of venous thromboembolism from oral contraceptives containing gestodene and desogestrel versus levonorgestrel: a meta-analysis and formal sensitivity analysis. Contraception 2001;64:125-33.
34. Kemmeren JM, Algra A, Grobbee DE. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis. BMJ 2001;323:131-4.
35. Hannaford P. Cardiovascular events associated with different combined oral contraceptives: a review of current data. Drug Saf 2000;22:361-71.
36. 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.
37. Stampfer MJ, Willett WC, Colditz GA, Speizer FE, Hennekens CH. Past use of oral contraceptives and cardiovascular disease: a meta-analysis in the context of the Nurses' Health Study. Am J Obstet Gynecol 1990;163:285-91.
38. Martinelli I, Sacchi E, Landi G, Taioli E, Duca F, Mannucci PM. High risk of cerebral-vein thrombosis in carriers of a prothrombin-gene mutation and in users of oral contraceptives. N Engl J Med 1998;338:1793-7.
39. de Bruijn SF, Stam J, Koopman MM, Vandenbroucke JP. Case-control study of risk of cerebral sinus thrombosis in oral contraceptive users and in carriers of hereditary prothrombotic conditions. BMJ 1998;316:589-92. [Erratum, BMJ 1998;316:822.]
40. de Bruijn SF, Stam J, Vandenbroucke JP. Increased risk of cerebral venous sinus thrombosis with third-generation oral contraceptives. Lancet 1998;351:1404.
41. Martinelli I, Taioli E, Palli D, Mannucci PM. Risk of cerebral vein thrombosis and oral contraceptives. Lancet 1998;352:326.
42. Oral contraceptives and liver cancer: results of the Multicentre International Liver Tumor Study (MILTS). Contraception 1997;56:275-84.
43. Heinemann LA, Weimann A, Gerken G, Thiel C, Schlaud M, DoMinh T. Modern oral contraceptive use and benign liver tumors: the German Benign Liver Tumor Case-Control Study. Eur J Contracept Reprod Health Care 1998;3:194-200.
44. Lewis MA, Spitzer WO, Heinemann LA, MacRae KD, Bruppacher R, Thorogood M. Third generation oral contraceptives and risk of myocardial infarction: an international case-control study. BMJ 1996;312:88-90.
45. Cosmi B, Legnani C, Bernardi F, Coccheri S, Palareti G. Role of family history in identifying women with thrombophilia and higher risk of venous thromboembolism during oral contraception. Arch Intern Med 2003;163:1105-9.
46. Chang CL, Donaghy M, Poulter N. Migraine and stroke in young women: case-control study: the World Health Organisation Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception. BMJ 1999;318:13-8.
47. Tzourio C, Kittner SJ, Bousser MG, Alperovitch A. Migraine and stroke in young women. Cephalalgia 2000;20:190-9.
48. Tzourio C, Tehindrazanarivelo A, Iglesias S, et al. Case-control study of migraine and risk of ischaemic stroke in young women. BMJ 1995;310:830-3.
49. Collaborative Group on Hormonal Factors in Breast Cancer. 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. Lancet 1996;347:1713-27.
50. Marchbanks PA, McDonald JA, Wilson HG, et al. Oral contraceptives and the risk of breast cancer. N Engl J Med 2002;346:2025-32.
51. Grabrick DM, Hartmann LC, Cerhan JR, et al. Risk of breast cancer with oral contraceptive use in women with a family history of breast cancer. JAMA 2000;284:1791-8.
52. Heimdal K, Skovlund E, Moller P. Oral contraceptives and risk of familial breast cancer. Cancer Detect Prev 2002;26:23-7.
53. Ursin G, Henderson BE, Haile RW, et al. Does oral contraceptive use increase the risk of breast cancer in women with BRCA1/BRCA2 mutations more than in other women? Cancer Res 1997;57:3678-81.
54. Narod SA, Dube MP, Klijn J, et al. Oral contraceptives and the risk of breast cancer in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 2002;94:1773-9.
55. Ngelangel C, Munoz N, Bosch FX, et al. Causes of cervical cancer in the Philippines: a case-control study. J Natl Cancer Inst 1998;90:43-9.
56. Delgado-Rodriguez M, Sillero-Arenas M, Martin-Moreno JM, Galvez-Vargas R. Oral contraceptives and cancer of the cervix uteri: a meta-analysis. Acta Obstet Gynecol Scand 1992;71:368-76.
57. Moreno V, Bosch FX, Munoz N, et al. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study. Lancet 2002;359:1085-92.
58. Thomas DB, Ray RM, Koetsawang A, et al. Human papillomaviruses and cervical cancer in Bangkok. I. Risk factors for invasive cervical carcinomas with human papillomavirus types 16 and 18 DNA. Am J Epidemiol 2001;153:723-31.
59. Fernandez E, La Vecchia C, Franceschi S, et al. Oral contraceptive use and risk of colorectal cancer. Epidemiology 1998;9:295-300.
60. Chiaffarino F, Parazzini F, La Vecchia C, Marsico S, Surace M, Ricci E. Use of oral contraceptives and uterine fibroids: results from a case-control study. Br J Obstet Gynaecol 1999;106:857-60.
61. Samadi AR, Lee NC, Flanders WD, Boring JR III, Parris EB. Risk factors for self reported uterine fibroids: a case-control study. Am J Public Health 1996;86:858-62.
62. Thorneycroft IH. Cycle control with oral contraceptives: a review of the literature. Am J Obstet Gynecol 1999;180:280-7.
63. ACOG Committee on Practice Bulletins-Gynecology. The use of hormonal contraception in women with coexisting medical conditions: number 18, July 2000. Int J Gynaecol Obstet 2001;75:93-106.
64. Improving access to quality care in family planning: medical eligibility criteria for contraceptive use. 2nd ed. Geneva: World Health Organization, 2000:1-11.