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Wolters Kluwer

Combined estrogen-progestin contraception: Side effects and health concerns

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INTRODUCTION

Since the development and approval of the first combined oral contraceptive (COC) pill, combined estrogen-progestin hormonal contraception (CHC) has evolved from high-dose estrogen formulations (150 mcg) to very low doses (10 and 20 mcg). Simultaneously, dosing mechanisms have expanded to include vaginal rings and the transdermal patch. While most women are candidates for CHC use and do well on them, the safety and side effect profiles must be considered as women balance their long-term need for birth control with the management and treatment of any concurrent medical conditions.

This topic will discuss CHC side effects, common health concerns, and use in women with medical conditions. Where possible, we report research findings by CHC type, though we frequently make recommendations for the CHC patch and ring that are an extrapolation of the oral contraceptive pill data. Detailed information on contraceptive selection and CHC types are presented separately.

- (See ["Contraception: Counseling and selection"](#).)
- (See ["Combined estrogen-progestin oral contraceptives: Patient selection, counseling, and use"](#).)

- (See "[Contraception: Transdermal contraceptive patches](#)".)
 - (See "[Contraception: Hormonal contraceptive vaginal rings](#)".)
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COMMON PATIENT QUESTIONS

Weight gain — Use of CHCs does not appear to result in significant weight change, either gain or loss. In a meta-analysis of 49 trials that included 85 weight change comparisons for 52 unique contraceptive pairs (contraceptive compared with placebo or a different contraceptive), most comparisons reported no substantial differences in weight [1]. For the four trials that compared a contraceptive with placebo or no contraceptive, COC or contraceptive patch use did not lead to weight gain.

Mood changes — The use of CHCs appears to be safe for women with mood disorders, and we do not restrict their use in women with depression. For any woman initiating CHC use who reports negative mood symptoms, we advise evaluation for clinical depression and consideration of alternative contraceptive methods on an individual basis. Our approach is consistent with both the World Health Organization and the US Centers for Disease Control and Prevention [2-4].

COCs with 35 mcg or less of ethinyl estradiol appear to have minimal effects on mood symptoms, unlike older, higher estrogen formulations (50 mcg or greater), although all formulations have not been evaluated [5,6]. Potential confounding variables that impact studies of CHC on mood include retrospective data, observational design, presence of underlying mood disorders, phase of treatment cycle, presence of other socioeconomic factors associated with mood disorders, and absence of patient counseling [7-11]. While the available prospective data are conflicting, most studies suggest that CHC use does not negatively impact mood for most women.

- In a prospective study of over 1700 young women who initiated COC use, most women reported no change in mood symptoms after initiating a COC, but small numbers experienced an increase or a decrease in moodiness [12]. Of the 60 percent of women who discontinued the COC by six months, only 34 percent did so because of side effects, including mood. This discontinuation rate is similar to that reported by others [13].

- In a prospective study of over 6600 sexually active women who were part of the United States National Longitudinal Study of Adolescent Health, users of hormonal contraception were less likely to report a suicide attempt in the last year compared with women using nonhormonal or no contraception [14]. Of note, women with a history of depression are less likely to choose hormonal contraception options but more likely to discontinue them when compared with women without a history of depression [15].
- By contrast, a Danish registry study of over one million women reported that users of hormonal contraception were more likely than nonusers to subsequently start an antidepressant (rate ratio 1.23, 95% CI 1.22-1.25) [16]. However, the overall risk was low; the crude incidence rates of first antidepressant use was 2.2 per 100 woman-years in hormonal contraceptive users compared with 1.7 per 100 woman-years in nonusers.

Libido — The ovarian androgen suppression seen with CHC administration has raised concerns of a negative impact on libido. However, for most women, CHC use does not appear to significantly impact sexual function; mixed results have been reported [17-19]. As examples:

- A systematic review on the subject found that the majority of women experienced no change in sexual desire after initiating COCs, while a minority of users reported increased (22 percent) or decreased (15 percent) desire [20].
- In a cross-sectional analysis of nearly 2000 women surveyed six months after starting a new contraceptive, 24 percent of women reported lacking interest in sex across all contraceptive types [21]. Compared with control women using a [copper intrauterine device](#), women using COCs or the contraceptive patch reported similar levels of lack of desire while the women using the contraceptive vaginal ring more commonly reported lack of interest [21].

At least one study reported that presence of a partner was equally important to the reduction in libido noted by users of hormonal contraception [19].

Return of fertility — COC use may slightly delay time to conception; however, this effect is limited to the first several months after COC discontinuation [22]. Among 187 women who were observed after discontinuation of COCs after approximately one year of

continuous use, 97 percent had spontaneous menses within 90 days [23]. Median time to return to menses was 32 days. Secondary analysis of the European Active Surveillance Study on Oral Contraceptives, a large prospective cohort study of COC users, showed that the pregnancy rate after discontinuation resembled that of the general population: 79.4 percent within one year of stopping COCs [24].

CHC use in women who are postpartum, lactating, or postabortion is presented separately.

- (See "[Postpartum contraception: Counseling and methods](#)".)
- (See "[Contraception: Postabortion](#)".)

Noncontraceptive benefits — CHCs offer many desirable side effects that often outweigh the less frequent risks [25]. By inhibiting ovulation, CHCs eliminate the risk of developing functional cysts, which can cause pain and may result in ovarian torsion [26]. Endometrial atrophy also reduces menstrual flow and cramping, and CHCs can therefore be used to treat heavy menstrual bleeding, abnormal uterine bleeding (due to anovulation or fibroids), and dysmenorrhea (either primary or due to endometriosis) [27-29]. Cyclic CHC use increases menstrual regularity while continuous CHC use results in menstrual suppression. By increasing production of sex hormone binding globulin, CHCs reduce free androgen concentrations and improve acne and hirsutism [30,31]. Although headache and mood problems are sometimes cited as negative effects of CHC use, CHCs, particularly when dosed continuously, can also serve as treatment for these problems. Furthermore, CHCs protect against certain types of cancer. COCs do not increase overall risk of cancer. (See '[Effects on cancer development](#)' below.)

These and other benefits are summarized separately. (See "[Combined estrogen-progestin oral contraceptives: Patient selection, counseling, and use](#)", section on '[Noncontraceptive uses](#)'.)

COMMON SIDE EFFECTS

Early side effects — Nausea, breast tenderness, and headaches are usually minor and infrequent complaints (<10 percent of women) after CHC initiation and are less common with current formulations [32]. Usually, these symptoms resolve within the first months of

use; however, they can sometimes be bothersome enough to cause discontinuation shortly after CHC initiation [12,32].

Unscheduled bleeding — Also known as breakthrough bleeding, unscheduled bleeding is the most common early side effect after CHC initiation, affecting one-half of women during the first cycle of use and quickly improving over subsequent months [33,34]. If patients are adherent, they can be reassured that unscheduled bleeding does not signify decreased contraceptive efficacy [35]. Unscheduled bleeding does not vary with timing of initiation; therefore, waiting until menses to start CHC use confers no advantage to a woman's bleeding pattern [36]. Formulations with 20 mcg ethinyl estradiol or 24/4 dosing (ie, 24 days of hormone pills with 4 days of placebo) are associated with higher rates of unscheduled bleeding than formulations with ≥ 30 mcg ethinyl estradiol and 21/7 day COC regimens, respectively [37-41]. The various dose and scheduling options for oral contraceptive pills are presented elsewhere. (See "[Combined estrogen-progestin oral contraceptives: Patient selection, counseling, and use](#)", section on 'Dosing regimens'.)

We counsel patients that unscheduled bleeding can also occur as a consequence of prolonged or pronounced endometrial atrophy or of medication nonadherence; the effect primarily depends on the ratio of ethinyl estradiol to progestin dosing, with higher doses of progestins being primarily responsible for bleeding from an atrophic endometrium on COCs. (See "[Evaluation and management of unscheduled bleeding in women using contraception](#)", section on 'Estrogen-progestin contraceptives'.)

Amenorrhea — Amenorrhea occurs intentionally with continuous and extended CHC regimens. However, amenorrhea may also occur unintentionally with 21/7 or 24/4 cyclic dosing schedules. Particularly with the lowest dose COC formulations, the low ethinyl estradiol level (relative to the much larger progestin doses) is inadequate to stimulate endometrial growth, which results in a lack of withdrawal bleeding ([table 1](#)) [35]. Women who are concerned about pregnancy can be reassured that amenorrhea does not signify decreased contraceptive effectiveness as long as they have taken the medication correctly and consistently. For women who want the reassurance of a monthly withdrawal bleed, one option is to increase the estrogen dose of the COC, although this has not been studied.

Amenorrhea may also occur after discontinuation of CHCs but is not a consequence of CHC use itself and does not indicate that a patient is not ovulatory or that the patient

cannot get pregnant [17,42]. In order to rule out an underlying abnormality, we evaluate women who do not menstruate after 90 days from discontinuing CHCs. (See "[Evaluation and management of secondary amenorrhea](#)".)

EFFECT ON ALL-CAUSE MORTALITY

CHC use does not appear to impact overall mortality based on large, longitudinal studies of women using COCs. However, older age (over 35 years) and tobacco use do increase mortality risk in CHC users [43,44].

- In the Oxford-Family Planning Association study that followed over 17,000 women for up to 32 years, the adjusted rate ratio for all-cause mortality was 0.89 (95% CI 0.77-1.02) among women who had ever used COCs [43].
 - In the Nurses' Health Study that prospectively followed nearly 122,000 women for up to 36 years, there was no association between history of COC use and all-cause mortality [45].
 - The Royal College of General Practitioners' Oral Contraception Study, which followed over 46,000 women for up to 39 years, reported a mortality benefit for COC users (adjusted relative risk 0.88, 95% CI 0.82-0.93) [46].
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CARDIOVASCULAR EFFECTS

Hypertension — COCs may cause a mild elevation in blood pressure within the normal range; however, overt hypertension is unusual with current COC formulations [47,48]. Before initiating a COC in a patient, high blood pressure should be excluded using proper measurement technique [49].

- (See "[Contraception: Hormonal contraception and blood pressure](#)".)
- (See "[Blood pressure measurement in the diagnosis and management of hypertension in adults](#)".)

Venous thromboembolism — A three- to fivefold increased relative risk of venous thromboembolism (VTE) has been reported in COC users (all types) [50]. Data on the

relative and absolute risks of VTE in pregnancy and with various COC formulations are presented in the table ([table 2](#)).

- **Absolute versus relative risk** – Since the rate of VTE in young women is low, the absolute risk of VTE in COC users is approximately 0.06 per 100 pill-years [\[51,52\]](#). This risk is greatest in the first few months of use and is considerably lower than that seen in pregnancy and the early postpartum period (0.2 per 100 years) [\[52-55\]](#). The absolute risk is higher among women with associated conditions such as thrombophilia [\[50\]](#). Other contributors are those predisposing to thromboembolism including smoking, obesity, polycystic ovary syndrome, older age, and immobilization [\[56\]](#).
- **Impact of progestin on VTE risk** – Some evidence suggests that the progestin component ([table 3](#)) may affect the thrombosis risk along with estrogen, although the data are not uniformly consistent [\[57-61\]](#). For example, thrombosis risk appears to be lower with second-generation oral contraceptives (norgestrel or [levonorgestrel](#)) than third-generation compounds (desogestrel, gestodene) ([table 2](#)) [\[62\]](#). Risk may be higher still with unclassified oral contraceptives containing a mineralocorticoid-derived progestational component such as [drospirenone](#) [\[63,64\]](#).

Myocardial infarction and stroke — The reduction in estrogen content since initial CHC introduction has increased safety substantially, and arterial thrombotic events (myocardial infarction and stroke) are now rare among users of available forms of COCs. The absolute risk of stroke in a young woman is low, at 5 to 10 per 100,000 woman-years, and doubles in women using CHCs [\[65,66\]](#). For United States women aged 18 to 44 years, the baseline prevalence of stroke ranged from 0.6 to 0.7 percent between 2006 and 2010 [\[67\]](#). The risk of stroke in women using CHCs rises with increasing age from 3.4 per 100,000 woman-years in adolescents to 64.4 events per 100,000 woman-years among women 45 to 49 years old [\[68\]](#). However, as with VTE events, the absolute risks of arterial thrombotic events are lower with use of CHCs than during either pregnancy or the postpartum period [\[53,69-73\]](#).

A 2015 meta-analysis of the risk of myocardial infarction and stroke associated with COCs reported a 1.6 times higher overall risk of arterial thrombosis among COC users compared with nonusers [\[74\]](#). This quite substantial risk appeared to increase with higher estrogen doses and did not vary by progestogen type. Compounds containing [levonorgestrel](#) and

30 mcg of estrogen appeared to be safest.

Lipid changes and metabolic effects — COCs can negatively impact lipid and carbohydrate metabolism but usually not in a clinically meaningful manner. However, for subgroups of women, such as those with polycystic ovarian syndrome, these changes can be significant. (See "[Clinical manifestations of polycystic ovary syndrome in adults](#)", [section on 'Dyslipidemia'](#).)

COCs raise serum triglycerides, with an estimated change of 25 mg/dL after six months of use, but this difference is typically not clinically significant in otherwise healthy women [75,76]. Limited data regarding the transdermal patch and monthly vaginal ring have shown that they have comparable or even milder effects on triglyceride concentrations and insulin sensitivity compared with COCs [77,78]. In contrast with older formulations of COCs [79], modern formulations of pills are not thought to appreciably impact low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels [76,80,81]. COC preparations with less androgenic progestins, such as desogestrel, confer a small and likely clinically insignificant improvement in lipid profiles (for example, 10 to 12 percent increase in HDL cholesterol with [norethindrone](#) and desogestrel compared with 5 percent decrease with [levonorgestrel](#)) [76,82]. Women with preexisting dyslipidemia who initiate CHCs may experience an increased risk of cardiovascular events and VTE, but the evidence for this is poor, and the effect is likely minimal [83].

COCs have been shown to increase plasma insulin and glucose levels and reduce insulin sensitivity; however, these effects are negligible for current formulations and among women of normal weight without polycystic ovary syndrome [84-86]. Carbohydrate metabolism does not differ noticeably among different modern contraceptive formulations [87]. Further, there is no evidence that COC use influences the risk of developing diabetes or affects glycemic control [88].

USE IN PATIENTS WITH MEDICAL DISORDERS

Eligibility criteria (WHO and CDC) — While data are numerous regarding the safety of CHCs in healthy women, the smaller literature regarding CHC use in women with underlying medical conditions has been reviewed and summarized by the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC). Information is provided as documents discussing medical eligibility criteria (MEC; [WHO](#)

[MEC 5th Edition](#) and [US MEC 2016](#)), a summary table ([US MEC table](#)), and as applications for handheld devices [[2,4,89,90](#)]. These documents classify contraceptive method use into four categories of risk that consider the contraceptive method and underlying medical conditions of the patient ([table 4](#)).

For most sexually active women of reproductive age, lack of contraception will eventually lead to pregnancy. Therefore, any negative side effects, health concerns, or health risks attributable to the CHC must be weighed against the risk of pregnancy for the individual woman. Decisions regarding contraception in women with chronic medical conditions are particularly crucial, as unintended pregnancy may pose substantial risk to both the woman and fetus. We, and other experts, rely on the MEC documents above, and we have incorporated the US MEC categories for use of CHC in the setting of medical conditions below. One limitation is that much of the research, and therefore the medical guidance, is based on studies of estrogen-progestin oral contraceptive pills; there is far less research on the CHC transdermal patch and the ring. Pharmacokinetics and use of the contraceptive vaginal ring and transdermal patch are presented in detail elsewhere.

- (See "[Contraception: Hormonal contraceptive vaginal rings](#)".)
- (See "[Contraception: Transdermal contraceptive patches](#)".)

Contraindications — Based upon the WHO and CDC tables above, some of the medical conditions that represent an unacceptable health risk (contraindications) for CHC use include [[2,4](#)]:

- Age ≥ 35 years and smoking ≥ 15 cigarettes per day
- Two or more risk factors for arterial cardiovascular disease (such as older age, smoking, diabetes, and hypertension)
- Hypertension (systolic ≥ 140 mmHg or diastolic ≥ 90 mmHg for the CDC and systolic ≥ 160 mmHg or diastolic ≥ 100 mmHg for the WHO)
- Venous thromboembolism – Women with a history of thromboembolism not receiving anticoagulation or women with an acute embolic event
- Known thrombogenic mutations
- Known ischemic heart disease

- History of stroke
- Complicated valvular heart disease (pulmonary hypertension, risk for atrial fibrillation, history of subacute bacterial endocarditis)
- Breast cancer
- Cirrhosis
- Migraine with aura
- Hepatocellular adenoma or malignant hepatoma

Common medical issues

Thrombophilia and thrombosis — Use of CHCs in women with inherited thrombophilia or prior thrombotic event requires comparison of individual thrombosis risk ([table 5](#)) with the risks of pregnancy and the postpartum period for these women. Risk of venous embolism, options for contraception (including CHCs), and the role of screening are reviewed in separate discussions.

- (See ["Contraception: Counseling for women with inherited thrombophilias"](#).)
- (See ["Contraception: Counseling for women with inherited thrombophilias", section on 'Estrogen-progestin methods'](#).)
- (See ["Screening for inherited thrombophilia in asymptomatic adults", section on 'Oral contraceptives'](#).)

As there are no known interactions between COCs and [warfarin](#) anticoagulation, there are no contraindications to COC use in women with indications for oral anticoagulation. There are few data regarding risk of non-vitamin K antagonist oral anticoagulation agents. However, it is generally recommended that women with acute deep vein thrombosis requiring anticoagulation use progestogen-only or other contraceptive methods [\[91\]](#). (See ["Contraception: Counseling for women with inherited thrombophilias"](#).)

Neurologic disease — Common neurologic disorders that impact contraceptive selection include headache and seizure disorders.

Headache and migraine — At the time of CHC counseling, the diagnosis of tension,

cluster, and migraine headache both with and without aura should be carefully considered. Accurate diagnosis of migraines and associated aura is essential for contraceptive counseling, as both migraines and exogenous estrogen use independently increase the risk of stroke and compound that risk when they occur together [65,92-95]. For headache classification, we use the International Classification of Headache Disorders, 3rd edition, the official criteria of the International Headache Society (IHS) [96]. The evaluation of headache and related topics are presented in detail separately.

- (See "[Evaluation of headache in adults](#)".)
- (See "[Tension-type headache in adults: Pathophysiology, clinical features, and diagnosis](#)".)
- (See "[Pathophysiology, clinical manifestations, and diagnosis of migraine in adults](#)".)

Women with tension and cluster headaches can safely be started on CHCs with appropriate follow-up to assess for any worsening headache symptoms [2]. If new headache symptoms are consistent with migraines, the patient should consider discontinuing CHC use, especially if the patient develops an aura or a second risk factor for stroke (eg, reaches age 35, develops hypertension). A systematic review of seven available case-control studies demonstrated a two to four times increased risk of stroke associated with modern CHC doses in the setting of migraine disease [65]. Only one study examined this risk by migraine subtype and reported an elevated risk of stroke among women with migraine with aura compared with women with no migraine (odds ratio 1.5, 95% CI 1.1-2.0) [97]. The interaction of hormones and migraine headache is presented separately. (See "[Estrogen-associated migraine, including menstrual migraine](#)", section on '[Does estrogen use increase stroke risk in patients with migraine?](#)'.)

Seizure disorders — Women with seizure disorders require effective contraception as part of their care plan because pregnancy may worsen seizure activity and negatively affect maternal and fetal outcomes [98,99]. Furthermore, fetal exposure to certain antiepileptic medications can increase risk of fetal malformations by two- to threefold [100]. Seizure disorders are not a contraindication to CHC use [2]. However, some antiseizure medications induce hepatic enzymes that increase the metabolism of CHC steroids [101,102], which then increases the risk of breakthrough ovulation [101,103], vaginal bleeding [101,103-105], and contraceptive failure [84]. (See "[Management of epilepsy during preconception, pregnancy, and the postpartum period](#)", section on '[Birth](#)

[control'](#) and ["Combined estrogen-progestin oral contraceptives: Patient selection, counseling, and use", section on 'Drug interactions'.](#))

Other neurologic disorders — The association of pseudotumor cerebri with prothrombotic abnormalities (antithrombin III deficiency and antiphospholipid antibodies) and an increased risk of cerebral vein thrombosis is also thought to represent an unacceptable risk for COC use [22,65,106]. However, data on this issue are very limited. (See ["Idiopathic intracranial hypertension \(pseudotumor cerebri\): Clinical features and diagnosis"](#).)

Gastrointestinal disorders — Use of COCs is associated with a small increased incidence of inflammatory bowel diseases (IBD), ulcerative colitis, and Crohn disease, perhaps through thrombotic effects on the microvasculature, with relative risks of 1.3 to 1.7 [107]. There are no absolute contraindications to COC use in women with an IBD diagnosis; lower or no estrogen-containing compounds are preferred, and those with known thrombotic tendencies may benefit from alternative methods of contraception. (See ["Definitions, epidemiology, and risk factors for inflammatory bowel disease in adults"](#).)

A variety of liver diseases has been variably associated with oral contraceptive use, including focal nodular hyperplasia, hepatic adenomas, and hepatocellular carcinoma. Of these, the strongest relationship is with hepatic adenomas and use of progestogen-only compounds [108]. COCs are contraindicated in such patients [2,109]. COC use does not appear to be associated with the development of hepatocellular carcinoma [110,111].

Use of COCs is acceptable in women with diabetes unless there is evidence of microvascular disease (including nephropathy, retinopathy, and/or neuropathy) or established atherosclerosis/vascular disease [2,109]. However, use of lower dose estrogen or progestin-only compounds has been recommended because of the multiple predisposing factors toward thromboembolism often found in diabetics [88]. (See ["Pregestational \(preexisting\) diabetes: Preconception counseling, evaluation, and management", section on 'Contraception and timing of pregnancy'](#).)

The year following bariatric surgery represents a time of substantial change in gastrointestinal function, nutrient absorption, and drug metabolism. Because of the risk for malabsorption, COCs and progestogen-only pills should be used cautiously, if at all, with a preference for nonoral hormonal contraception or nonhormonal methods [106].

(See ["Fertility and pregnancy after bariatric surgery", section on 'Contraception'.](#))

Obesity — Women with obesity can be offered all contraceptive options, including combined estrogen-progestin contraceptives [2,4,112]. Use and potential concerns regarding efficacy and adverse events in women with obesity are presented separately. (See ["Contraception: Counseling for females with obesity".](#))

EFFECTS ON CANCER DEVELOPMENT

Overall cancer risk — COCs do not increase overall risk of cancer. Long-term cancer risks and benefits were evaluated in two different observational studies (the Royal College of General Practitioners' Oral Contraception Study [n = 46,000 women] and UK Biobank Study [n = 256,661 women]) that followed participants for up to 80 years [110,113]. Among these individuals, use of COCs was associated with protection against ovarian, endometrial, and colorectal cancers. Breast and cervical cancer risk temporarily increased with current or recent use of COCs, but this association disappeared within two to five years of discontinuation and, therefore, was outweighed by the above oncoprotective effects, which persisted for over 30 years in both studies.

Breast cancer — COCs are associated with little to no increased risk of breast cancer. Any effect appears to be temporary and limited to current or recent COC use.

Many epidemiologic studies demonstrate no association [114-120].

- In three large prospective cohort studies, including the Nurses' Health Study, the RCGP study, and the Oxford-Family Planning Association contraceptive study, neither long-term past COC use nor current use was associated with an increased risk of breast cancer [116,119,120].
- In a population-based, case-control study of 4574 women with breast cancer and 4682 controls, breast cancer risk did not differ significantly among current (relative risk [RR] 1.0, 95% CI 0.8-1.3) or past COC users (RR 0.9, 95% CI 0.8-1.0) [117].

By contrast, some studies have reported an association between COC use and breast cancer [110,113,121-123], although the absolute risk was low in each study. It is unknown whether this association is a biologic effect or a result of increased diagnosis, or whether varying COC formulations might have different effects.

- In a 1996 meta-analysis of over 53,000 women from 54 studies in 25 countries, COC use was associated with increased risk of breast cancer (RR 1.24, 95% CI 1.15-1.33), which waned during the years after discontinuation (RR 1.16 after one to four years, RR 1.07 after five to nine years) and disappeared after 10 or more years [122]. Duration of COC use and formulation of COCs had no effect on breast cancer risk after adjusting for recency of use.
- In a 2017 prospective cohort study of 1.8 million women from a Danish registry who were followed for an average of 11 years, current or recent COC users exhibited a greater risk of breast cancer compared with women who had never used COCs (RR 1.19, 95% CI 1.13-1.26) [121]. This risk was comparable to the RR of breast cancer among users of any hormonal contraception compared with nonusers (RR 1.20, 95% CI 1.14-1.26) and increased with longer duration of use. The absolute increase in diagnosed breast cancer cases among COC users was small: 13 per 100,000 person-years (approximately one additional case per 7690 women per year). For women under age 35 years (the age group most likely to use COCs), the absolute increased risk was 2 per 100,000 person-years (one additional case per 50,000 women per year).
- A 2020 observational study of over 256,000 women reported an excess risk of breast cancer among COC users compared with nonusers, limited to the first two years after pill discontinuation (hazard ratio 1.55, 95% CI 1.06-2.28) [113]. No excess breast cancer risk was seen with increasing duration of COC use (analyzed from <2 to >35 years of use).

For women with a personal history of breast cancer, COCs are not recommended (United States Medical Eligibility Criteria category 4 [unacceptable risk] for current breast cancer, category 3 [risks outweigh the benefits] for past and no evidence of disease for five years) [2]. However, women with breast cancer susceptibility genes (such as *BRCA*) or a family history of breast cancer may safely use COCs.

- A systematic review of 10 individual studies and the meta-analysis described above showed that COC use did not significantly affect risk of breast cancer among women with a family history of breast cancer [124].
- In a meta-analysis investigating COC use among *BRCA1* and *BRCA2* mutation carriers, COC use had an increased but nonstatistically significant association with breast cancer (odds ratio [OR] 1.21, 95% CI 0.93-1.58) [125].

Cervical cancer — Long-term cervical cancer risk does not appear to increase among COC users compared with nonusers (incidence rate ratio 1.31, 99% CI 0.84-2.04) [110]. However, stratification by time since COC use reveals that current or recent use (<5 years) is associated with increased risk of cervical cancer (incidence rate ratio 2.32, 99% CI 1.24-4.34) [110]. A meta-analysis of 24 studies including nearly 17,000 women with cervical cancer and nearly 36,000 controls confirms this effect, with the increased RR of cervical cancer declining with time from cessation and risk returning to that of never-users by 10 years [126]. In this study, risk of cervical cancer was also associated with duration of COC use.

Women with human papillomavirus who use COCs may be at particular risk for cervical cancer [127]. However, screening for cervical cancer should not be a prerequisite for the provision of contraception [128]. (See "[Virology of human papillomavirus infections and the link to cancer](#)", section on 'Cervical cancer'.)

Ovarian cancer — Ever-use of COCs is associated with a decreased risk of ovarian cancer compared with never-use (incidence rate ratio 0.67, 99% CI 0.50-0.89; OR 0.72, 95% CI 0.65-0.81), and this protection appears to last over 30 years [110,113]. Modern COC formulations with lower doses of estradiol and new progestin types are as effective as older COCs at preventing ovarian cancer [129]. This is reviewed in detail separately. (See "[Epithelial carcinoma of the ovary, fallopian tube, and peritoneum: Incidence and risk factors](#)", section on 'Oral contraceptives'.)

COCs may be used as chemoprevention among *BRCA1* and *BRCA2* mutation carriers. This is reviewed in detail separately. (See "[Risk-reducing salpingo-oophorectomy in patients at high risk of epithelial ovarian and fallopian tube cancer](#)", section on 'Chemoprevention'.)

Endometrial cancer — COC ever-use is associated with a decreased risk of endometrial cancer (incidence rate ratio 0.66, 99% CI 0.48-0.89), compared with never-use, and this protection may last for over 30 years [110,113]. This is reviewed in detail separately. (See "[Endometrial carcinoma: Epidemiology, risk factors, and prevention](#)", section on 'Use of hormonal contraception'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and

regions around the world are provided separately. (See ["Society guideline links: Contraception"](#).)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see ["Patient education: Hormonal birth control \(The Basics\)"](#) and ["Patient education: Choosing birth control \(The Basics\)"](#))
- Beyond the Basics topics (see ["Patient education: Long-acting methods of birth control \(Beyond the Basics\)"](#) and ["Patient education: Hormonal methods of birth control \(Beyond the Basics\)"](#) and ["Patient education: Birth control; which method is right for me? \(Beyond the Basics\)"](#))

SUMMARY AND RECOMMENDATIONS

- Common patient concerns include the impact of combined estrogen-progestin hormonal contraceptives (CHCs) on weight, mood, libido, future fertility, and noncontraceptive effects. In general, CHC use does not negatively impact these variables. (See ["Common patient questions"](#) above.)
- Common early side effects of CHC use include nausea, breast tenderness, headaches, and unscheduled bleeding. These symptoms are typically mild and resolve within a few cycles. Unscheduled bleeding can also occur outside of CHC initiation, and

amenorrhea can develop as well. (See ['Common side effects'](#) above.)

- CHC use does not appear to impact overall mortality. (See ['Effect on all-cause mortality'](#) above.)
- Based mainly on data from combined estrogen-progestin oral contraceptive (COC) pills, CHCs are associated with increased relative risk of venous and arterial thrombotic events. However, the absolute risk remains low in most healthy, nonsmoking women. (See ['Cardiovascular effects'](#) above.)
- For most sexually active women of reproductive age, lack of contraception will eventually lead to pregnancy. Therefore, any negative side effects, health concerns, or health risks attributable to the CHC must be weighed against the risk of pregnancy for the individual woman. (See ['Use in patients with medical disorders'](#) above.)
- CHC use in women with underlying medical conditions has been reviewed and summarized by the World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC). Information is provided as documents discussing medical eligibility criteria (MEC; [WHO MEC 5th Edition](#) and [US MEC 2016](#)), a summary table ([US MEC table](#)), and as applications for handheld devices. These documents classify contraceptive method use into four categories of risk that consider contraceptive method and underlying medical conditions of the patient ([table 4](#)). (See ['Eligibility criteria \(WHO and CDC\)'](#) above.)
- Contraindications to CHC use include factors or illnesses that increase the risk of cardiovascular disease or thromboembolic risk. (See ['Contraindications'](#) above.)
- COCs do not increase overall risk of cancer, including breast cancer. Any increase in breast cancer appears to be temporary and limited to current or recent COC use. CHC ever-use decreases the risks of ovarian and endometrial cancers. (See ['Effects on cancer development'](#) above.)

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GRAPHICS

Selected hormonal contraceptives: Oral contraceptives (birth control pills) and other delivery methods

United States brand name	Progestin (mg)*	Estrogen (micrograms)	Notes
Monophasic combinations			
Beyaz 28 [¶]	Drospirenone (3)	Ethinyl estradiol (20)	Also approved for acne and premenstrual dysphoric disorder. In patients with conditions requiring chronic therapy with medications that may increase potassium, monitor serum potassium during the first treatment cycle and periodically thereafter if patient begins medication or develops a condition that increases risk for hyperkalemia.
Gianvi 28 ^Δ			
Loryna 28 ^Δ			
Nikki 28 ^Δ			
Yaz ^Δ			
Amethyst 28	Levonorgestrel (0.09)	Ethinyl estradiol (20)	
Aviane 28	Levonorgestrel (0.1)	Ethinyl estradiol (20)	Packaged as active tablets for 21 days and placebo for 7 days.
Balcoltra 28			
Falmina 28			
Larissia 28			
Lessina 28			
Lutera 28			
Orsythia 28			
Sronyx 28			
Blisovi Fe 1/20 [◇]	Norethindrone acetate (1)	Ethinyl estradiol (20)	Available in a 28-day regimen with active pills for 24 days and ferrous fumarate for 4 days.
Gemmily			
Junel Fe 1/20 28 ^{◇§}			
Larin Fe 1/20 ^{◇§}			
Loestrin Fe 1/20 28 [◇]			
Melodetta 24 Fe chewable [§]			
Microgestin Fe 1/20 28 [◇]			
Minastrin Fe 1/20 chewable			
Taytulla capsules			
Apri 28	Desogestrel (0.15)	Ethinyl estradiol (30)	Packaged as active tablets for 21 days and placebo for 7 days.
Cyred Eq 28			
Emoquette 28			

Enskyce 28			
Juleber 28			
Reclipsen 28			
Ocella 28 [¥]	Drospirenone (3)	Ethinyl estradiol (30)	In patients with conditions requiring chronic therapy with medications that may increase potassium, monitor serum potassium during the first treatment cycle and periodically thereafter if patient begins medication or develops a condition that increases risk for hyperkalemia.
Safyral 28 [¶]			
Tydemy 28 [¶]			
Yasmin 28 [¥]			
Zarah 28 [¥]			
Chateal 28	Levonorgestrel (0.15)	Ethinyl estradiol (30)	Packaged as active tablets for 21 days and placebo for 7 days.
Kurvelo 28			
Levora 0.15/30			
Marlissa 28			
Portia 28			
Blisovi Fe 1.5/30	Norethindrone acetate (1.5)	Ethinyl estradiol (30)	Packaged as active tablets for 21 days and ferrous fumarate tablets for 7 days.
Larin FE 1.5/30 [‡]			
Loestrin Fe 1.5/30 28 [‡]			
Microgestin Fe 1.5/30 28			
Junel Fe 1.5/30 28			
Cryselle 28	Norgestrel (0.3) [†]	Ethinyl estradiol (30)	Packaged as active tablets for 21 days and placebo for 7 days.
Elinest 28			
Low-Ogestrel 28			
Kelnor 28	Ethinodiol diacetate (1)	Ethinyl estradiol (35)	Packaged as active tablets for 21 days and placebo for 7 days.
Pirmella 1/35			
Zovia 1/35E 28			
Balziva 28	Norethindrone (0.4)	Ethinyl estradiol (35)	Packaged as active tablets for 21 days and placebo for 7 days.
Briellyn 28			
Philith 28			
Vyfemla			
Brevicon 28	Norethindrone (0.5)	Ethinyl estradiol (35)	Packaged as active tablets for 21 days and placebo for 7 days.
Necon 0.5/35 28			
Nortrel 0.5/35 28			
Wera			
Alyacen 1/35 28	Norethindrone (1)	Ethinyl estradiol (35)	Packaged as active tablets for 21 days and placebo for 7 days.
Cyclafem 1/35			
Dasetta 1/35 28			
Nortrel 1/35 28 [‡]			

Ortho-Novum 1/35 28			
Femynor	Norgestimate (0.25)	Ethinyl estradiol (35)	Packaged as active tablets for 21 days and placebo for 7 days.
Mili			
MonoNessa 28			
Ortho-Cyclen 28			
Previfem 28			
Sprintec 28			
VyLibra			
Cleo-35, Cyestra-35, Diane 35 Not available in the United States; Canadian product shown	Cyproterone (2)	Ethinyl estradiol (35)	Labeled approval in Canada is for treatment of acne.
Kelnor 1/50 28	Ethinodiol diacetate (1)	Ethinyl estradiol (50)	Packaged as active tablets for 21 days and placebo for 7 days. NOTE: Pills containing 50 mcg of ethinyl estradiol are not indicated for routine contraceptive use because of increased risk of cardiovascular events compared with lower-dose oral contraceptive pills.
Ogestrel 0.5/50 28	Norgestrel (0.5) [†]	Ethinyl estradiol (50)	Packaged as active tablets for 21 days and placebo for 7 days. NOTE: Pills containing 50 mcg of ethinyl estradiol are not indicated for routine contraceptive use because of increased risk of cardiovascular events compared with lower-dose oral contraceptive pills.
Zoely ^Δ	Nomegestrol acetate (2.5)	Estradiol (as hemihydrate) (1.5 milligrams)	Not available in the United States; United Kingdom and European Union product shown.
Multiphasic combinations			
Natazia 28	Dienogest (0,2,3,0)	Estradiol valerate (3,2,2,1) NOTE: Estradiol strength listed in milligrams (mg)	Packaged as active tablets for 26 days and placebo for 2 days.
Lo Loestrin Fe	Norethindrone acetate (1,0)	Ethinyl estradiol (10,10)	Packaged as active tablets for 26 days and ferrous fumarate for 2 days.
Azurette 28	Desogestrel (0.15,0,0)	Ethinyl estradiol (20,0,10)	Packaged as active tablets

Bekyree 28			for 26 days and placebo for 2 days or ferrous fumarate for Lo Loestrin Fe.
Kariva 28			
Mircette 28			
Pimtree 28			
Viorele 28			
Volnea 28			
Estrostep Fe 28	Norethindrone acetate (1,1,1)	Ethinyl estradiol (20,30,35)	Also approved for acne.
Tilia Fe 28			Packaged as active tablets for 21 days and ferrous fumarate tablets for 7 days.
Tri-Legest Fe 28 [§]			
Ortho Tri-Cyclen Lo 28	Norgestimate (0.18,0.215,0.25)	Ethinyl estradiol (25,25,25)	Packaged as active tablets for 21 days and placebo for 7 days.
Tri-Lo-Marzia			
Tri-Lo-Sprintec			
TriNessa Lo			
Caziant 28	Desogestrel (0.1,0.125,0.15)	Ethinyl estradiol (25,25,25)	Packaged as active tablets for 21 days and placebo for 7 days.
Cyclessa 28			
Velivet			
Enpresse 28	Levonorgestrel (0.05,0.075,0.125)	Ethinyl estradiol (30,40,30)	
Levonest 28 [¥]			
Myzilra 28 [¥]			
Trivora 28 [¥]			
Ortho Tri-Cyclen 28	Norgestimate (0.18,0.215,0.25)	Ethinyl estradiol (35,35,35)	Also approved for acne. Packaged as active tablets for 21 days and placebo for 7 days.
Tri-Femynor 28			
Tri-Linyah 28			
Tri-Previfem 28			
Tri-Sprintec 28			
TriNessa 28			
Alyacen 7/7/7 28	Norethindrone (0.5,0.75,1)	Ethinyl estradiol (35,35,35)	Packaged as active tablets for 21 days and placebo for 7 days.
Cyclafem 7/7/7 28			
Dasetta 7/7/7 28			
Nortrel 7/7/7 28			
Ortho-Novum 7/7/7 28			
Pirmella 7/7/7			
Aranelle 7/9/5 28	Norethindrone (0.5,1,0.5)	Ethinyl estradiol (35,35,35)	Packaged as active tablets for 21 days and placebo for 7 days.
Leena 7/9/5 28			
Extended combinations			
Amethia Lo 91	Levonorgestrel (0.1)	Ethinyl estradiol (20,10)	Packaged as a 91-day regimen: 84 days of the combination and 7 days of ethinyl estradiol only.
Camrese Lo 91			
LoJaimiess 91			

LoSeasonique 91			
Fayosim 91	Levonorgestrel (0.15)	Ethinyl estradiol (20,25,30,10)	Packaged as a 91-day regimen: 84 days of the combination and 7 days of ethinyl estradiol only.
Rivelsa 91			
QuarteSe 91			
Amethia 91	Levonorgestrel (0.15)	Ethinyl estradiol (30,10)	Packaged as a 91-day regimen: 84 days of the combination and 7 days of ethinyl estradiol only.
Ashlyna			
Camrese 91			
Jaimiess 91			
Seasonique 91			
Introvale 91	Levonorgestrel (0.15)	Ethinyl estradiol (30)	Packaged as a 91-day regimen: active tablets for 84 days and placebo for 7 days.
Jolessa 91			
Quasense 91			
Continuous combinations			
May use any monophasic 21/7 combination by taking active hormone pills for 28 or more days continuously. Refer to example (Amethyst) at right; any progestin may be used, and higher doses of ethinyl estradiol may be used in some women. Refer to the topic in UpToDate.	Levonorgestrel (0.09)	Ethinyl estradiol (20)	
Progestin-only			
Camila 28	Norethindrone (0.35)	None	Packaged as active tablets for 28 days.
Deblitane			
Errin 28			
Heather			
Incassia			
Jencycla			
Jolivette 28			
Lyleq			
Nora-BE 28			
Norlyda			
Ortho Micronor			
Sharobel			
Slynd	Drospirenone (4)	None	Packaged as active tablets for 24 days and placebo for 4 days. In patients with conditions requiring chronic therapy with

			medications that may increase potassium, monitor serum potassium during the first treatment cycle and periodically thereafter if patient begins medication or develops a condition that increases risk for hyperkalemia.
Transdermal patch, weekly			
Xulane Zafemy	Norelgestromin (releases 0.15 mg/day)	Ethinyl estradiol (releases 35 mcg/day)	May have diminished efficacy in women ≥ 90 kg. A new patch is applied every 7 days for 3 weeks followed by a patch-free week. This is therapeutically equivalent to Ortho Evra, which is no longer available in the United States.
Twirla	Levonorgestrel (releases 0.12 mg/day)	Ethinyl estradiol (releases 30 mcg/day)	Contraindicated in women with BMI ≥ 30 kg/m ² due to decreased efficacy and increased risk of VTE. Diminished efficacy was observed in women with BMI ≥ 25 kg/m ² . A new patch is applied every 7 days for 3 weeks followed by a patch-free week.
Vaginal ring, monthly			
NuvaRing EluRyng	Etonogestrel (releases 0.12 mg/day)	Ethinyl estradiol (releases 15 mcg/day)	Ring is inserted for 3 weeks followed by 1 week without ring in place. A new ring is inserted 7 days after the last was removed.
Annovera	Segesterone (releases 0.15 mg/day)	Ethinyl estradiol (releases 13 mcg/day)	Ring is inserted for 3 weeks followed by 1 week without ring in place. The ring is then reinserted for the first 21 days of subsequent 28-day cycles. One system provides contraception for 13 28-day cycles (1 year). Not yet adequately evaluated in women with BMI >29 kg/m ² .

- Oral and IUD emergency contraceptive options are listed in a table that is available separately in UpToDate.
- Generic (non-branded) products are also available for most combination oral contraceptives in the United States.
- Descriptions are for US-available products unless noted otherwise. Consult local product information before use.

Fe: contains iron; BMI: body mass index; VTE: venous thromboembolism; IUD: intrauterine device.

* Different progestins are not equivalent on a milligram basis. Refer to the UpToDate overview of combined hormonal contraceptives for guidance on selection.

¶ Also contains 451 mcg of levomefolate calcium per tablet. Beyaz is taken for 24 days followed by 4 days of levomefolate calcium alone. Safyral and Tydemy are taken for 21 days followed by 7 days of levomefolate calcium alone.

Δ Taken as active pills for 24 days and placebo for 4 days.

◇ Packaged as active tablets for 21 days and ferrous fumarate tablets for 7 days.

§ Also available as a 21-day regimen that does not contain iron.

¥ Packaged as active tablets for 21 days and placebo for 7 days.

‡ Also available in a 21-day regimen.

† The progestin norgestrel contains two isomers; only levonorgestrel is bioactive. The amount of norgestrel in each tablet is twice the amount of levonorgestrel.

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Additional data from:

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Graphic 69223 Version 42.0

Relative risk compared with absolute risk for venous thromboembolism by characteristic

Variable	Relative risk compared with nonpregnant women without the risk factor	Absolute risk
Nonpregnant, not taking hormones	1.0	VTE: 1 to 5/10,000 woman-years ^[1]
Pregnancy	4.29 (95% CI 3.49-5.22; $p < 0.001$) compared with nonpregnant women ^[4]	VTE: 5 to 20/10,000 woman-years ^[1] PE: 1/10,000 woman-years
Postpartum	4.29 (95% CI 3.49-5.22; $p < 0.001$) compared with nonpregnant women ^[4]	VTE: 40 to 65/10,000 woman-years ^[1] PE: 16 per 10,000 woman-years
Progestin type	RR of VTE: ^[2,3]	
	Non-use versus first-generation (norethindrone COC) users: 3.2 (95% CI 2.0-5.1)	
	Non-use versus second-generation (levonorgestrel COC) users: 2.8 (95% CI 2.0-4.1)	
	Non-use versus third-generation (desogestrel COC) users: 3.8 (95% CI 2.7-5.4)	
	Second versus first generation: 0.9 (95% CI 0.6-1.4)	
	Third versus first generation: 1.2 (95% CI 0.8-1.9)	
	Third versus second generation: 1.3 (95% CI 1.0-1.8)	
Estrogen dose	20 mcg ethinyl estradiol with levonorgestrel versus non-use: 2.2 (95% CI 1.3-3.6)	
	30 mcg ethinyl estradiol with levonorgestrel versus 20 mcg ethinyl estradiol with levonorgestrel: 1.1 (95% CI 0.7-1.7)	
	50 mcg ethinyl estradiol with levonorgestrel versus 20 mcg ethinyl estradiol with levonorgestrel: 2.3 (95% CI 1.3-4.2) ^[2,3]	
Thrombophilias	Factor V Leiden: 2.6 no OC, 64.7 first/second generation, 29.6 third generation	
	Other heritable thrombophilia: 2.6 no OC, 63.3 first/second generation; 52.5 third generation ^[4]	

Although drospirenone is not listed, limited data suggest combined oral contraceptive pills containing drospirenone may be associated with a higher relative risk of VTE compared with second-generation (rate ratio 1.65, 95% CI 1.02-2.65) and third-generation (rate ratio 1.43, 95% CI 1.15-1.78) combined oral contraceptive pills.^[6]

VTE: venous thromboembolism; CI: confidence interval; PE: pulmonary embolism; RR: relative risk; COC: combined oral contraceptives; OC: oral contraceptives.

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Graphic 121107 Version 1.0

Classification of progestins used in combined oral contraceptive pills

First generation
<ul style="list-style-type: none"> ▪ Norethindrone acetate ▪ Ethynodiol diacetate ▪ Lynestrenol ▪ Norethynodrel
Second generation
<ul style="list-style-type: none"> ▪ dl-Norgestrel ▪ Levonorgestrel
Third generation
<ul style="list-style-type: none"> ▪ Desogestrel ▪ Gestodene ▪ Norgestimate
Unclassified
<ul style="list-style-type: none"> ▪ Drospirenone ▪ Cyproterone acetate

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Graphic 87416 Version 1.0

Categories of medical eligibility criteria for contraceptive use

Category	Description
1	A condition for which there is no restriction for the use of the contraceptive method.
2	A condition for which the advantages of using the method generally outweigh the theoretical or proven risks.
3	A condition for which the theoretical or proven risks usually outweigh the advantages of using the method.
4	A condition that represents an unacceptable health risk if the contraceptive method is used.

Reprinted from: *Medical eligibility criteria for contraceptive use: A WHO family planning cornerstone, 5th ed, Geneva 2015, Copyright © 2015. Available at: https://www.who.int/reproductivehealth/publications/family_planning/MEC-5/en/ (accessed on April 29, 2019).*

Graphic 121115 Version 1.0

Prevalence of inherited thrombophilia and associated VTE risk

Thrombophilia	Prevalence (%)		Relative risk of a first episode of VTE compared with controls
	General population	Individuals with VTE	
AT deficiency	0.02 to 0.2%	1 to 7%	16-fold increased
Protein C deficiency	0.2 to 0.5%	2 to 5%	7-fold increased
Protein S deficiency	Unknown	1%	5-fold increased
Factor V Leiden*	2 to 5%	12 to 18%	4- to 5-fold increased
Prothrombin G20210A*	2%	5 to 8%	3- to 4-fold increased

These prevalences and risk estimates were aggregated from multiple studies. Refer to UpToDate content on specific inherited thrombophilias for further information on risk factors, indications for testing, and management. For FVL and prothrombin G20210A, values refer to heterozygotes. If the individual is homozygous for the defect, the risk of VTE is expected to be considerably higher. VTE risk also depends on other factors such as age and comorbidities.

VTE: venous thromboembolism; AT: antithrombin; FVL: factor V Leiden.

* Applies to White populations; prevalence is much lower in other groups.

Graphic 108016 Version 8.0

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