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. Of note, while there are emerging data on molecular markers for efficacy and side effects and on differences in the impact of race and ethnicity on use of CHCs, the evidence does not yet support inclusion of specific recommendations for clinical care in these areas.

- (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".)

In this topic, when discussing study results, we will use the terms "woman/en" or "patient(s)" as they are used in the studies presented. However, we encourage the reader to consider the specific counseling and treatment needs of transmasculine and gender-expansive individuals.

COMMON PATIENT QUESTIONS

Patients initiating CHCs often have questions about potential side effects, such as weight gain, mood changes, libido, and return of fertility. Although individual experiences may vary, these are generally uncommon side effects of CHCs, and we review the evidence for this below. Future studies, including large population and complex genetics studies, may help predict response to CHCs to some extent. We will wait for further development of the literature and clinician experience with these genetic studies to help guide recommendations for the incorporation of these genetic studies into clinical practice.

In addition to reviewing potential side effects, we discuss common noncontraceptive benefits that patients may be interested in learning to provide a balanced presentation of the methods.

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 — While the available prospective data are conflicting, most studies suggest that CHC use does not negatively impact mood for most women.

- **Patients with mood disorders –** 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].
- **COC impact on mood –** 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 [7-13].

- 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 [14]. 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 [15].

- 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 [16]. 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 [17].

- 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) [18]. 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.

- **Impact of placebo pills (hormonal withdrawal)** – Mood changes experienced by pill users during hormone-free intervals appear to be similar to those experienced by patients with natural cycles during the menstrual phase [13].

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 [19-21]. 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 [22].

- 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 [23]. 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 [23].

At least one study reported that presence of a partner was equally important to the reduction in libido noted by users of hormonal contraception [21].

Return of fertility — COC use may slightly delay time to conception; however, this effect is limited to the first several months after COC discontinuation [24]. 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 [25]. 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 [26].

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

- (See "Contraception: Postpartum counseling and methods".)
- (See "Contraception: Postabortion".)

Noncontraceptive benefits — CHCs offer many desirable side effects that often outweigh the less frequent risks [27]. In particular, CHCs reduce the risk of:

- **Ovarian cysts** – By inhibiting ovulation, CHCs eliminate the risk of developing functional cysts, which can cause pain and may result in ovarian torsion [28]. (See "Adnexal mass: Differential diagnosis", section on 'Ovulatory'.)
- **Menstrual bleeding and cramping** – Endometrial atrophy also reduces menstrual flow and cramping (ie, dysmenorrhea), 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) [29-31]. Cyclic CHC use increases menstrual regularity while continuous CHC use results in menstrual suppression.
  - (See "Dysmenorrhea in adult females: Clinical features and diagnosis".)
  - (See "Abnormal uterine bleeding in nonpregnant reproductive-age patients: Terminology, evaluation, and approach to diagnosis".)
  - (See "Hormonal contraception for menstrual suppression".)

- **Acne and hirsutism –** By increasing production of sex hormone binding globulin, CHCs reduce free androgen concentrations and improve acne and hirsutism [32,33].
  - (See "Acne vulgaris: Overview of management".)
  - (See "Management of hirsutism in premenopausal women", section on 'Combined estrogen-progestin oral contraceptives'.)
- **Other symptoms –** 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.
- **Cancer –** COCs do not increase overall risk of cancer. In fact, CHCs protect against certain types 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 [34]. Usually, these symptoms resolve within the first months of use; however, they can sometimes be bothersome enough to cause discontinuation shortly after CHC initiation [14,34].

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 [35,36]. If patients are adherent, they can be reassured that unscheduled bleeding does not signify decreased contraceptive efficacy [37]. 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 [38]. 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 [39-43]. 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 individuals using hormonal 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) [37]. 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 [19,44]. 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".)

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 [2,4,45,46]. These documents classify contraceptive method use into four categories of risk that consider the contraceptive method and underlying medical conditions of the patient (table 2).

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 3) 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".)

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 [47]. (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 [48-52]. For headache classification, we use the International Classification of Headache Disorders, 3rd edition, the official criteria of the International Headache Society (IHS) [53]. The evaluation of headache and related topics are presented in detail separately.

- (See "Evaluation of headache in adults".)
- (See "Pathophysiology, clinical manifestations, and diagnosis of migraine in adults".)
- (See "Migraine-associated stroke: risk factors, diagnosis, and prevention".)

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 [51]. 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) [54].

The interaction of hormones and migraine headache is presented separately.

- (See "Estrogen-associated migraine headache, including menstrual migraine".)
- (See "Migraine-associated stroke: risk factors, diagnosis, and prevention".)

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 [55,56]. Furthermore, fetal exposure to certain antiepileptic medications can increase risk of fetal malformations by two- to threefold [57]. Seizure disorders are not a contraindication to CHC use [2]. However, some antiseizure medications induce the hepatic cytochrome P450 system, which increases the metabolism of CHC steroids [58,59], which then increases the risk of breakthrough ovulation [58,60], vaginal bleeding [58,60-62], and contraceptive failure [63]. (See "Management of epilepsy during preconception, pregnancy, and the postpartum period", section on 'Contraception' 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 [24,51,64]. 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 [65]. 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".)

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 [66]. COCs are contraindicated in such patients [2,67]. COC use does not appear to be associated with the development of hepatocellular carcinoma [68,69].

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 [2,67]. 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 [70]. (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 [64]. (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 [2,4,71]. Use and potential concerns regarding efficacy and adverse events in women with obesity are presented separately. (See "Contraception: Counseling for females with obesity".)

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 [72,73]. Before initiating a COC in a patient, high blood pressure should be excluded using proper measurement technique [74].

- (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) [75]. Data on the relative and absolute risks of VTE in pregnancy and with various COC formulations are presented in the table (table 4). (See "Contraception: Counseling for women with inherited thrombophilias", section on 'Estrogen-progestin methods'.)

- **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 [76,77]. 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) [77-80]. The absolute risk is higher among women with associated conditions such as thrombophilia [75]. Other contributors are those predisposing to thromboembolism including smoking, obesity, polycystic ovary syndrome, older age, and immobilization [81].

- **Genetic VTE risk factors –** COC use further increases the risk of VTE in patients with genetic thrombophilias. The magnitude of increased risk varies by thrombophilia type (ie, heterozygosity, homozygosity, polygenic risk score). The complex interaction of inherited thrombophilia and hormonal contraception is presented in detail in related content. (See "Contraception: Counseling for women with inherited thrombophilias".)

- **Impact of progestin on VTE risk –** Some evidence suggests that the progestin component (table 5) may affect the thrombosis risk along with estrogen, although the data are not uniformly consistent [82-86]. For example, thrombosis risk appears to be lower with norgestrel- or levonorgestrel-containing oral contraceptives compared with those containing desogestrel or gestodene (table 4) [87,88]. Risk may be higher still with oral contraceptives containing a mineralocorticoid-derived progestational component such as drospirenone [89,90]. The approach to progestin contraceptive use for individuals with known thrombophilias is presented separately. (See "Contraception: Counseling for women with inherited thrombophilias", section on 'Progestin-only methods'.)

- **Impact of NSAID use –** Some [91,92], but not all [93] observational studies suggest an association between nonsteroidal anti-inflammatory drugs (NSAIDs) use and risk of VTE. Concern has also been raised that there may be an additive VTE risk in patients who use both COCs and NSAIDs, however, the observed absolute excess risks are very low [94]. A Danish national cohort study reported that for 2 million women followed for 21 million person-years, NSAID use increased VTE incidence compared with non-use, and VTE risk was further magnified in patients taking both NSAIDs and hormonal contraceptives [94]. The number of VTE events per 100,000 women was four (range 3 to 5) in those using only NSAIDs; 11 (range 7 to 15) in those using NSAIDs and combined oral contraceptive pills with <50 mcg ethinyl estradiol or medroxyprogesterone injection; and 23 (range 19 to 27) for those using NSAIDs and estrogen-progestin patches or vaginal rings, oral pills containing ≥50 mcg of ethinyl estradiol, or oral pills containing the progestins desogestrel, gestodene, drospirenone, or the anti-androgen cyproterone. Potential limitations include the study's definitions of contraceptive risk, reliance on prescription data, possible exclusion of over-the-counter NSAID use, patient selection bias for the hormonal contraceptives, and possibility of residual or unmeasured confounding, including limited data on smoking and obesity. However, the inclusion of a relatively healthy population adds weight to this finding. Patients who require NSAID treatment may benefit from avoiding high-risk contraceptives, particularly if they have other VTE risk factors.

  NSAIDs appear to interfere with cyclooxygenase (COX)-2 derived prostaglandins and promote platelet aggregation. Detailed discussions of NSAIDs and their adverse effects are presented separately.

- (See "NSAIDs: Adverse cardiovascular effects", section on 'Pathophysiology'.)
- (See "Nonselective NSAIDs: Overview of adverse effects".)
- (See "NSAIDs: Adverse cardiovascular effects".)

- **Risk of recurrent VTE –** Predicting the risk of VTE recurrence for individuals who experience COC-related VTE has been complicated by conflicting data [83,95-97]. In an attempt to resolve the debate, a cohort study recorded VTE events for 322 women over a mean of 5.7 years to predict recurrent VTE risk in individuals with a first COC-related VTE event compared with those with first VTE that was unprovoked (nonusers) [98]. All participants had completed five to seven months of anticoagulation and were no longer anticoagulated. While the trends were toward reduced recurrence risk for those whose first VTE occurred with COC use, the findings were not statistically significant.

  Results included:

  - **Recurrence risk per patient-year –** Former COC users: 1.1 percent (95% CI 0.3-2.9) per patient-year, compared with nonusers: 3.2 percent (95% CI 2.4-4.3) per patient-year, hazard ratio 0.37, CI 0.1-1.0
  - **Recurrence risk with low-risk HERDOO2 score –** Former COC users: 0.4 (0.0-2.1) versus, for nonusers, 1.4 (95% CI 0.7-2.5) patient-years, hazard ratio 0.3, 95% CI 0.0-2.0
  - **VTE risk for users and nonusers below age 50 –** Former COC users: 1.2, 95% CI 0.3-3.0 versus, for nonusers, 2.7 (95% CI 1.6-4.3), hazard ratio 0.5, 95% CI 0.2-1.4

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 current users of available forms of COCs. A history of COC use does not appear to increase risk long-term risk of myocardial infarction or cardiovascular events [99].

- **Myocardial infarction –** 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 [100]. 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.
- **Stroke –** The absolute risk of stroke in a young female is low, at 5 to 10 per 100,000 woman-years, and doubles in people using CHCs [51,101,102]. For women in the United States aged 18 to 44 years, the baseline prevalence of stroke ranged from 0.6 to 0.7 percent between 2006 and 2010 [103]. 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 [104]. 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 [78,105-109].

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 [110,111]. 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 [112,113]. In contrast with older formulations of COCs [114], modern formulations of pills are not thought to appreciably impact low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels [111,115,116]. 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) [111,117]. 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 [118].

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 [63,119,120]. Carbohydrate metabolism does not differ noticeably among different modern contraceptive formulations [121]. Further, there is no evidence that COC use influences the risk of developing diabetes or affects glycemic control [70].

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 [68,122]. 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 appear to be associated with little to no increased risk of breast cancer based on observational data. Any effect appears to be temporary and limited to current or recent (within five to seven years) COC use [123,124].

- **Data supporting no association –** Many epidemiologic studies demonstrate no association [125-131].
  - 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 [127,130,131].
  - 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) [128].
- **Studies raising concern for increased risk –** By contrast, some studies have reported an association between COC use and breast cancer [68,122,124,132-134], 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 [133]. 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) [132]. 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) [122]. No excess breast cancer risk was seen with increasing duration of COC use (analyzed from <2 to >35 years of use).

- **Patients with personal history of breast cancer** – For patients 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 [135].

  - 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) [136].

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) [68]. 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) [68]. 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 [137]. 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 [138]. However, screening for cervical cancer should not be a prerequisite for the provision of contraception [139]. (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 0.65-081), and this protection appears to last over 30 years [68,122]. Modern COC formulations with lower doses of estradiol and new progestin types are as effective as older COCs at preventing ovarian cancer [140]. 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 [68,122]. This is reviewed in detail separately. (See "Endometrial carcinoma: Epidemiology, risk factors, and prevention", section on 'Use of hormonal contraception'.)

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 [141,142].

- 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 [141].
- 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 [143].
- 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) [144].

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 concerns –** 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 based on data from population-based studies. While there are emerging data on molecular markers for efficacy and side effects and on differences in the impact of race and ethnicity on use of CHCs, the evidence does not yet support inclusion of specific recommendations for clinical care in these areas. (See 'Common patient questions' above.)
- **Possible early side effects –** 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.)
- **Comparison of pregnancy-related risks with risks from CHC use –** For most heterosexually active females 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. (See 'Use in patients with medical disorders' above.)
    - **Contraindications to CHC use –** Contraindications to CHC use include factors or illnesses that increase the risk of cardiovascular disease or thromboembolic risk. (See 'Contraindications' above.)

- **CHC use in those with medical comorbidities** – CHC use in people 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 2). (See 'Eligibility criteria (WHO and CDC)' above.)

- **Risk of thrombotic events** – 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.)

- **Impact on cancer risk** – 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.)

- **Impact on mortality** – CHC use does not appear to impact overall mortality. (See 'Effect on all-cause mortality' above.)

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GRAPHICS

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

Progestin (mg)*	Estrogen (micrograms)	United States brand name	Notes
Monophasic combinations			
Drospirenone (3)	Ethinyl estradiol (20)	▪ Beyaz ▪ Jasmiel ▪ Lo-Zumandimine ▪ Loryna ▪ Nikki ▪ Vestura ▪ Yaz	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. Packaged as active tablets for 24 days and placebo for 4 days; except Beyaz, which contains 451 mcg of levomefolate per tablet (24 active tablets and 4 levomefolate tablets).
Levonorgestrel (0.09)	Ethinyl estradiol (20)	▪ Amethyst ▪ Dolishale	
Levonorgestrel (0.1)	Ethinyl estradiol (20)	▪ Afirmelle ▪ Aubra EQ ▪ Aviane ▪ Balcoltra ▪ Delyla ▪ Falmina ▪ Joyeaux ▪ Lessina ▪ Lutera ▪ Sronyx ▪ Tyblume ▪ Vienva	Packaged as active tablets for 21 days and placebo for 7 days.
Norethindrone acetate (1)	Ethinyl estradiol (20)	▪ Aurovela 24 FE	Packaged as active pills for 24 days and ferrous fumarate for 4 days.

		▪ Blisovi 24 Fe ▪ Charlotte 24 Fe chewable tablets ▪ Finzala chewable tablets ▪ Gemmily capsules ▪ Hailey 24 Fe ▪ Junel Fe 24 ▪ Larin 24 Fe ▪ Merzee capsules ▪ Mibelas 24 Fe chewable tablets ▪ Microgestin 24 Fe ▪ Minastrin 24 Fe chewable tablets ▪ Tarina 24 Fe ▪ Taysofy capsules ▪ Taytulla capsules	
		▪ Aurovela FE 1/20 ▪ Blisovi FE 1/20 ▪ Hailey FE 1/20 ▪ Junel FE 1/20 ▪ Larin Fe 1/20 ▪ Loestrin Fe 1/20 ▪ Microgestin FE 1/20 ▪ Tarina FE 1/20 EQ	Packaged as active tablets for 21 days and ferrous fumarate for 7 days.
		▪ Aurovela 1/20 ▪ Junel 1/20 ▪ Larin 1/20 ▪ Loestrin 1/20	Packaged as active tablets for 21 days (does not contain iron).

		▪ Microgestin 1/20	
Norethindrone (0.8)	Ethinyl estradiol (25)	▪ Generess FE chewable tablets ▪ Kaitlib Fe chewable tablets ▪ Layolis FE chewable tablets	Packaged as active tablets for 24 days and ferrous fumarate for 4 days.
Desogestrel (0.15)	Ethinyl estradiol (30)	▪ Apri ▪ Cyred ▪ Cyred EQ ▪ Enskyce ▪ Isibloom ▪ Juleber ▪ Kalliga ▪ Reclipsen	Packaged as active tablets for 21 days and placebo for 7 days.
Drospirenone (3)	Ethinyl estradiol (30)	▪ Ocella ▪ Safyral ▪ Syeda ▪ Tydemy ▪ Yasmin ▪ Zumandimine	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. Packaged as active tablets for 21 days and placebo for 7 days; except Safyral and Tydemy, which contain 451 mcg of levomefolate per tablet (21 active tablets and 7 levomefolate tablets).
Levonorgestrel (0.15)	Ethinyl estradiol (30)	▪ Altavera ▪ Ayuna ▪ Chateal EQ ▪ Kurvelo ▪ Levora 0.15/30 ▪ Marlissa ▪ Portia-28	Packaged as active tablets for 21 days and placebo for 7 days.

Norethindrone acetate (1.5)	Ethinyl estradiol (30)	▪ Aurovela Fe 1.5/30 ▪ Blisovi Fe 1.5/30 ▪ Junel FE 1.5/30 ▪ Hailey FE 1.5/30 ▪ Larin Fe 1.5/30 ▪ Loestrin Fe 1.5/30 ▪ Microgestin FE 1.5/30	Packaged as active tablets for 21 days and ferrous fumarate for 7 days.
		▪ Aurovela 1.5/30 ▪ Junel 1.5/30 ▪ Hailey 1.5/30 ▪ Larin 1.5/30 ▪ Loestrin 1.5/30 ▪ Microgestin 1.5/30	Packaged as active tablets for 21 days (does not contain iron).
Norgestrel (0.3)¶	Ethinyl estradiol (30)	▪ Cryselle-28 ▪ Elinest ▪ Low-Ogestrel	Packaged as active tablets for 21 days and placebo for 7 days.
Ethynodiol diacetate (1)	Ethinyl estradiol (35)	▪ Kelnor 1/35 ▪ Zovia 1/35	Packaged as active tablets for 21 days and placebo for 7 days.
Norethindrone (0.4)	Ethinyl estradiol (35)	▪ Balziva ▪ Briellyn ▪ Philith ▪ Vyfemla	Packaged as active tablets for 21 days and placebo for 7 days.
		▪ Wymzya Fe chewable tablets	Packaged as active tablets for 21 days and ferrous fumarate for 7 days.
Norethindrone (0.5)	Ethinyl estradiol (35)	▪ Necon 0.5/35 (28) ▪ Nortrel 0.5/35 (28) ▪ Wera	Packaged as active tablets for 21 days and placebo for 7 days.

Norethindrone (1)	Ethinyl estradiol (35)	▪ Alyacen 1/35 ▪ Dasetta 1/35 ▪ Nortrel 1/35 (28) ▪ Nylia 1/35 ▪ Pirmella 1/35	Packaged as active tablets for 21 days and placebo for 7 days. Nortrel 1/35 is also available as a 21-day regimen (packaged without placebo).
Norgestimate (0.25)	Ethinyl estradiol (35)	▪ Estarylla ▪ Femynor ▪ Mili ▪ Mono-Linyah ▪ Nymyo ▪ Sprintec 28 ▪ VyLibra	Packaged as active tablets for 21 days and placebo for 7 days.
Cyproterone (2)	Ethinyl estradiol (35)	▪ Cleo-35 ▪ Cyestra-35 ▪ Diane-35	Labeled approval in Canada is for treatment of acne; provides reliable contraception if taken as recommended for treatment of acne. Packaged as active tablets for 21 days. Not available in the United States; Canadian product shown.
Ethynodiol diacetate (1)	Ethinyl estradiol (50)	▪ Kelnor 1/50	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.**
Drospirenone (3)	Estetrol (14.2) NOTE: Estetrol strength listed in **milligrams (mg)**	▪ Nextstellis	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.

Nomegestrol acetate (2.5)	Estradiol (as hemihydrate) (1.5) NOTE: Estradiol strength listed in **milligrams (mg)**	▪ Zoely	Packaged as active tablets for 24 days and placebo for 4 days. Not available in the United States; United Kingdom and European Union product shown.
Multiphasic combinations			
Dienogest (0,2,3,0)	Estradiol valerate (3,2,2,1) NOTE: Estradiol strength listed in **milligrams (mg)**	▪ Natazia	Packaged as active tablets for 26 days and placebo for 2 days.
Norethindrone acetate (1,0)	Ethinyl estradiol (10,10)	▪ Lo Loestrin Fe	Packaged as active tablets for 26 days and ferrous fumarate for 2 days.
Desogestrel (0.15,0,0)	Ethinyl estradiol (20,0,10)	▪ Azurette ▪ Kariva ▪ Mircette ▪ Pimtrea ▪ Simliya ▪ Viorele ▪ Volnea	Packaged as active tablets for 26 days and placebo for 2 days.
Norethindrone acetate (1,1,1)	Ethinyl estradiol (20,30,35)	▪ Tilia Fe ▪ Tri-Legest Fe	Also approved for acne. Packaged as active tablets for 21 days and ferrous fumarate for 7 days.
Norgestimate (0.18,0.215,0.25)	Ethinyl estradiol (25,25,25)	▪ Tri-Lo-Estarylla ▪ Tri-Lo-Marzia ▪ Tri-Lo-Mili ▪ Tri-Lo-Sprintec ▪ Tri-Vylibra Lo	Packaged as active tablets for 21 days and placebo for 7 days.
Desogestrel (0.1,0.125,0.15)	Ethinyl estradiol (25,25,25)	▪ Velivet	Packaged as active tablets for 21 days and placebo for 7 days.
Levonorgestrel (0.05,0.075,0.125)	Ethinyl estradiol (30,40,30)	▪ Enpresse-28 ▪ Levonest ▪ Trivora (28)	Packaged as active tablets for 21 days and placebo for 7 days.
Norgestimate (0.18,0.215,0.25)	Ethinyl estradiol (35,35,35)	▪ Tri-Estarylla ▪ Tri-Linyah	Also approved for acne.

		▪ Tri-Mili ▪ Tri-Nymyo ▪ Tri-Sprintec ▪ Tri-VyLibra	Packaged as active tablets for 21 days and placebo for 7 days.
Norethindrone (0.5,0.75,1)	Ethinyl estradiol (35,35,35)	▪ Alyacen 7/7/7 ▪ Dasetta 7/7/7 ▪ Nortrel 7/7/7 ▪ Nylia 7/7/7 ▪ Pirmella 7/7/7	Packaged as active tablets for 21 days and placebo for 7 days.
Norethindrone (0.5,1,0.5)	Ethinyl estradiol (35,35,35)	▪ Aranelle ▪ Leena	Packaged as active tablets for 21 days and placebo for 7 days.
Extended combinations (91-day regimens)			
Levonorgestrel (0.1,0)	Ethinyl estradiol (20,10)	▪ Camrese Lo ▪ LoJaimiess ▪ LoSeasonique	Packaged as a 91-day regimen: 84 days of the combination and 7 days of 10 mcg ethinyl estradiol only.
Levonorgestrel (0.15,0.15,0.15,0)	Ethinyl estradiol (20,25,30,10)	▪ Fayosim ▪ Quartette ▪ Rivelsa	Packaged as a 91-day regimen: 84 days of the combination and 7 days of 10 mcg ethinyl estradiol only.
Levonorgestrel (0.15,0)	Ethinyl estradiol (30,10)	▪ Amethia ▪ Ashlyna ▪ Camrese ▪ Daysee ▪ Jaimiess ▪ Seasonique ▪ Simpesse	Packaged as a 91-day regimen: 84 days of the combination and 7 days of 10 mcg ethinyl estradiol only.
Levonorgestrel (0.15)	Ethinyl estradiol (30)	▪ Introvale ▪ Iclevia ▪ Jolessa ▪ Setlakin	Packaged as a 91-day regimen: active tablets for 84 days and placebo for 7 days.
Continuous combinations			
May use any monophasic 21/7 combination (eg, Amethyst [levonorgestrel 0.09 mcg-ethinyl estradiol 20 mcg]) by taking active hormone pills for 28 or more days continuously. Any progestin may be used, and higher doses of ethinyl estradiol may be used in some women. Refer to UpToDate topic.			
Progestin-only			
Norethindrone (0.35)	None	▪ Camila ▪ Deblitane ▪ Errin	Packaged as active tablets for 28 days.

		▪ Heather ▪ Incassia ▪ Jencycla ▪ Lyleq ▪ Lyza ▪ Nora-BE ▪ Norlyroc ▪ Sharobel	
Drospirenone (4)	None	▪ Slynd	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.
Norgestrel (0.075)	None	▪ Opill	Packaged as active tablets for 28 days. Approved for over-the-counter use in the United States.
Desogestrel (0.075)	None	▪ Cerazette ▪ Cerelle ▪ Hana ▪ Lovima ▪ Zelleta	Packaged as active tablets for 28 days. Not available in the United States or Canada; United Kingdom product shown.
Transdermal patch, weekly			
Norelgestromin (releases 0.15 mg/day)	Ethinyl estradiol (releases 35 mcg/day)	▪ Xulane ▪ Zafemy	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. These products are therapeutically equivalent to Ortho Evra patch, which is no longer available in the United States.
Levonorgestrel (releases 0.12 mg/day)	Ethinyl estradiol (releases 30 mcg/day)	▪ Twirla	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			
Etonogestrel (releases 0.12 mg/day)	Ethinyl estradiol (releases 15 mcg/day)	▪ NuvaRing ▪ EluRyng ▪ EnilloRing ▪ Haloette	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.
Segesterone (releases 0.15 mg/day)	Ethinyl estradiol (releases 13 mcg/day)	▪ Annovera	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.

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

Adapted from:

1. The Medical Letter on Drugs and Therapeutics, October 8, 2018; Vol. 60 (1557): 161-168.

2. The Medical Letter on Drugs and Therapeutics, May 15, 2023; Vol. 65 (1676): 73-82.

3. Lexicomp online. Copyright © 1978-2023 by Lexicomp, Inc. All rights reserved.

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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.

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

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 2.0

Classification of progestins used in combined oral contraceptive pills

First generation
▪ Norethindrone acetate ▪ Ethynodiol diacetate ▪ Lynestrenol ▪ Norethynodrel
Second generation
▪ dl-Norgestrel ▪ Levonorgestrel
Third generation
▪ Desogestrel ▪ Gestodene ▪ Norgestimate
Unclassified
▪ Drospirenone ▪ Cyproterone acetate

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Graphic 87416 Version 1.0

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