Combined estrogen-progestin oral contraceptives: Patient selection, counseling, and use

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INTRODUCTION

Combined estrogen-progestin oral contraceptives (COCs), also known as birth control pills, provide reliable contraception as well as several noncontraceptive benefits. COCs contain an estrogen component and one of a dozen different progestins (table 1). Low-dose COCs (formulations containing <50 mcg ethinyl estradiol) are a safe and reliable contraceptive option for the vast majority of women [1,2]. For healthy, nonsmoking women, COCs may be continued until the age of menopause.

This topic will review the general principles of the use of COCs, including pharmacology, mechanisms of action, indications, contraindications, efficacy, and the different preparations that are available. Side effects and risks that may be associated with COCs, other forms of estrogen-progestin contraception, progestin-only oral contraceptives, and the selection of contraception in general are discussed separately.

- (See "Combined estrogen-progestin contraception: Side effects and health concerns".)
- (See "Contraception: Transdermal contraceptive patches".)
- (See "Contraception: Hormonal contraceptive vaginal rings".)
- (See "Contraception: Progestin-only pills (POPs)".)
- (See "Contraception: Counseling and selection".)

In this topic, when discussing study results, we will use the terms "women" or "patients" as they are used in the studies presented. We encourage the reader to consider the specific counseling and treatment needs of transgender and gender diverse individuals.

OUR APPROACH TO COC SELECTION

All COCs are effective and have similar advantages and disadvantages. Factors to take into consideration when selecting a COC include a patient's past experience with COCs, patient preferences, clinical characteristics, insurance coverage, relative safety considerations (side effects and relative risks may vary based on estrogen dose and progestin type and dose), and cost. Shared decision making that takes into account patient preferences will improve adherence to any contraceptive method [3]. Therefore, if a patient requests a particular pill, it is reasonable to prescribe it. Otherwise, we consider the following factors:

- **Generic versus brand name –** In the United States, we prefer generic COCs due to affordability. Brand name COCs are more expensive out-of-pocket and have higher co-pays for women with health insurance coverage.

- **Monophasic versus multiphasic –** We prefer monophasic COCs as the initial prescription due to ease of use and consistent hormone dose, which improves adherence, a key component in COC effectiveness. Multiphasic COCs require more careful adherence to a specific sequential order in which to take the pills each cycle. Furthermore, multiphasic pills cannot be transitioned to continuous or extended-cycle use the way that monophasic pills can if the patient desires, although supporting data are limited [4]. There are also concerns that the changing hormone levels in multiphasic COCs could exacerbate mood symptoms in susceptible women (eg, those with premenstrual syndrome or premenstrual dysphoric disorder). (See "Treatment of premenstrual syndrome and premenstrual dysphoric disorder", section on 'Combined estrogen-progestin contraception'.)

- **Cyclic versus extended-cycle versus continuous use –** Patients should be queried regarding achieving the frequency of withdrawal bleeding they desire. Some may prefer monthly withdrawal bleeding, while others may opt for every three months (84/7 formulations) or prefer no withdrawal bleeds (365 day formulations).

- **Ethinyl estradiol dose –** Women should be prescribed a COC with 35 mcg of ethinyl estradiol or less. The data regarding safety of 20 mcg versus 25, 30, or 35 mcg ethinyl estradiol COCs suggest less risk with 20 mcg formulas but are not strong enough to endorse higher safety with 20 mcg pills [5-8]. Nevertheless, it makes sense to start with a 20 mcg dose, and that can then be increased if unscheduled bleeding is a problem [9]. COCs containing 50 mcg of ethinyl estradiol should generally not be used for

contraception but are available for the acute treatment of uterine bleeding. (See "Managing an episode of acute uterine bleeding".)

- **Progestin type** – Given that all COCs are antiandrogenic when the combined effects of both estrogen and progestin are considered, we do not preferentially prescribe based on particular progestin when considering hyperandrogenic symptoms. Part of the reason for this choice is that the data surrounding venous thromboembolism risk and progestin type are conflicting [10]. There may be a slightly increased risk with newer progestins (gestodene, desogestrel, and drospirenone) compared with levonorgestrel; however, the absolute risk is extremely low for all COCs. Hence, the evidence is not compelling enough to change prescribing patterns [7,11]. This issue is reviewed in more detail separately. (See "Combined estrogen-progestin contraception: Side effects and health concerns", section on 'Cardiovascular effects'.)

- **21/7 versus 24/4** – We prefer 24/4 to 21/7 formulations if feasible due to emerging evidence about increased efficacy associated with efforts to lower the estrogen content (especially for obese women) and decreased hormone withdrawal side effects during the hormone-free interval [12].

MECHANISMS OF ACTION

The main contraceptive efficacy of COCs is suppression of ovulation by inhibition of gonadotropin-releasing hormone (GnRH) from the hypothalamus, as well as inhibition of both luteinizing hormone (LH) and follicle-stimulating hormone (FSH), and disruption of the mid-cycle LH surge. These effects are mediated by both the progestin and estrogen component of the COC working synergistically, but it is estrogen's ability to suppress FSH and thus prevent folliculogenesis that is likely the most important mechanism (table 2). The additional estrogen exposure in pills with a shorter pill-free interval, pills with an additional 10 mcg ethinyl estradiol in the placebo week, or continuous-use pills results in a more complete suppression of FSH and less folliculogenesis. However, a substantial number of women can still develop follicles while taking a low-dose COC [13,14]. Additionally, the estrogen component stabilizes sufficient endometrium production to maintain a regular withdrawal bleeding pattern (cycle control).

Additional progestin-related mechanisms that contribute to the contraceptive effect include:

- Effects on the endometrium, rendering it less suitable for implantation. Long-term cyclic or daily progestin exposure leads to endometrial decidualization and eventual atrophy.

- Thickening of cervical mucus, which becomes less permeable to penetration by sperm.

- Impairment of normal tubal motility and peristalsis.

The effects of progestins are discussed in detail separately. (See "Contraception: Progestin-only pills (POPs)", section on 'Mechanism and duration of action'.)

CANDIDATES

Eligibility — Information to help guide a patient through the contraceptive options and method selection is presented separately. (See "Contraception: Counseling and selection".)

We and other experts use both the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) comprehensive tables of medical conditions and personal characteristics that may affect contraceptive choice [15,16]. While these advisory documents are generally similar, clinicians should select whichever best fit their population. Summary tables can be found through the CDC's Summary Chart of US Medical Eligibility Criteria and the WHO Medical Eligibility Criteria for Contraceptive Use 2015. COCs can be given from menarche until menopause in otherwise eligible women [15].

Unacceptable risk — Based upon the CDC's Summary Chart of US Medical Eligibility Criteria and the WHO Medical Eligibility Criteria for Contraceptive Use 2015 Category 4 rating, some common medical conditions that represent an "unacceptable health risk" for COC initiation include [15,16]:

- Age ≥35 years and smoking ≥15 cigarettes per day
- Multiple risk factors for arterial cardiovascular disease (such as older age, smoking, diabetes, and hypertension)
- Hypertension (systolic ≥160 mmHg or diastolic ≥100 mmHg)
- Venous thromboembolism (VTE; unless on anticoagulation) (see "Contraception: Counseling for women with inherited thrombophilias", section on 'Personal history of venous thrombosis')
- Known ischemic heart disease
- History of stroke
- Complicated valvular heart disease (pulmonary hypertension, risk for atrial fibrillation, history of subacute bacterial endocarditis)
- Current breast cancer
- Severe (decompensated) cirrhosis

- Hepatocellular adenoma or malignant hepatoma
- Migraine with aura
- Diabetes mellitus of >20 years duration or with nephropathy, retinopathy, or neuropathy

The risk of VTE in individuals with known thrombogenic variants is elevated at baseline, a risk that is further increased with COC use. In general, estrogen-containing contraceptives should be avoided for these people. However, COCs may be used in carefully counseled patients, especially those with only mild thrombophilias (eg, heterozygous factor V Leiden or prothrombin variant) and no personal or family history of VTE, with a strong medical rationale for COC use. (See "Contraception: Counseling for women with inherited thrombophilias", section on 'No personal or family history of VTE, but positive testing for inherited thrombophilia'.)

The risks associated with COCs, particularly for the cardiovascular system, are presented in detail elsewhere. (See "Combined estrogen-progestin contraception: Side effects and health concerns".)

Risks outweigh benefits — Based upon the CDC's Summary Chart of US Medical Eligibility Criteria and the WHO Medical Eligibility Criteria for Contraceptive Use 2015 Category 3 rating, there are also medical conditions for which the "theoretical or proven health risks usually outweigh the advantages" of using the method [15,16]. Nevertheless, the method still may be used if nothing else is available or acceptable to the patient and they have been counseled about the potential risks. Follow-up may be needed to ensure that continued use is safe.

Some of these conditions include [15-17]:

- Age ≥35 years and smoking <15 cigarettes per day
- Hypertension (systolic 140 to 159 mmHg or diastolic 90 to 99 mmHg)
- Hypertension adequately controlled on medications (See "Contraception: Hormonal contraception and blood pressure".)
- Past breast cancer and no evidence of current disease for five years
- Current gallbladder disease
- Malabsorptive bariatric surgery (see "Contraception: Counseling for females with obesity", section on 'Contraception pre- and post-bariatric surgery')
- Superficial venous thrombosis (acute or history)

- Inflammatory bowel disease with risk factors for VTE (active or extensive disease, surgery, immobilization, corticosteroid use, vitamin deficiencies, or fluid depletion)

The risks and side effects of COCs are discussed in detail separately. (See "Combined estrogen-progestin contraception: Side effects and health concerns".)

COUNSELING POINTS

In addition to the discussions below for COCs, summaries of efficacy, advantages, and disadvantages of all contraceptive options can be found at The Contraceptive Choice Project, Planned Parenthood, and BedSider.org.

Efficacy — When taken properly, COCs are a highly effective form of contraception (figure 1). Although the perfect-use failure rate is 0.3 percent, the typical-use failure rate approximates 7 percent (ethinyl estradiol formulas), due primarily to missed pills, drug-drug interactions, or failure to resume therapy after the pill-free interval (table 3) [18]. COCs are available in many formulations (table 1). There is no evidence that generic COCs are less effective than brand name COCs or that different COCs have different perfect-use failure rates, although few comparative studies have been performed [19-21]. The author typically prescribes generic formulations as they are lower cost. Other drug factors that impact efficacy include:

- **Estrogen dose –** Efficacy appears to be similar across a wide range of estrogen doses, which likely reflects the multiple effects of exogenous estrogen and the impact of the progestin component. (See 'Mechanisms of action' above.)

  In a meta-analysis of 13 trials, contraceptive efficacy appeared to be similar with COCs containing 20 mcg ethinyl estradiol when compared with pills with >20 mcg of ethinyl estradiol [5]. An even lower dose estrogen preparation, containing only 10 mcg of ethinyl estradiol, is also available, which may have similar contraceptive efficacy but definitive conclusions are limited because of the high discontinuation rates reported in the studies [22]. However, the incidence of unscheduled bleeding may differ according to estrogen dose, as discussed below.

- **Estrogen type –** The typical-use failure rate for COCs containing ethinyl estradiol approximates 7 percent (table 3) [18]. Studies suggest that COCs containing estradiol valerate (with dienogest) and estetrol (with drospirenone) are also highly effective [23-26]. One COC type is not clearly superior as long-term typical-use data are limited for estradiol valerate- and estetrol-containing formulations.

  For example, in a secondary analysis of pooled data from two multicenter trials evaluating estetrol with drospirenone, the unintended pregnancy rate was 0.09 percent

per cycle (which equates to 1.2 percent for 13 cycles, 31 on-treatment pregnancies in 26,455 at-risk cycles) for the entire group, ages 16 to 50 years [24].

- **Progestin type –** Efficacy appears to be similar across the multiple synthetic progestins used in COCs (table 2), although comparative trial data are limited [5,27-31].

- **Duration of hormone-free interval** – Since the original oral contraceptive was first introduced in 1960, most birth control pill formulations have had 21 days of hormonally active pills followed by seven days of placebo pills (known as 21/7 regimens). Alternate formulations that either reduce the pill-free interval or introduce low doses of estrogen during the traditional placebo week (known as 24/4 regimens) have been created with the goal of reducing the duration of hormone-free time and resultant side effects (eg, withdrawal bleeding, menstrual migraines) [12,32]. With the shorter hormone-free interval of four days compared with seven days, ovarian follicular activity is better suppressed [33-35]. This enhanced follicular suppression has the potential to lead to increased efficacy, as reported in one study [36].

- **Impact of obesity –** While oral contraceptives are generally effective are preventing pregnancy in patients with obesity, they may be less forgiving of imperfect use. (See "Contraception: Counseling for females with obesity", section on 'Efficacy'.)

Advantages — In addition to high contraceptive efficacy, COCs have many advantages including rapid reversibility, regulation of menstrual bleeding, decreased menstrual blood loss, and dysmenorrhea, as well as population-level reductions in the risk of ovarian and endometrial cancers. Due to these effects and the ability of COCs to suppress ovulation, they have a number of noncontraceptive uses and benefits (table 4).

Noncontraceptive uses — COCs are also used widely to treat a variety of gynecologic disorders including:

- **Menstrual cycle disorders –** COCs are often used in women with menstrual cycle disorders, such as oligomenorrhea due to polycystic ovary syndrome, abnormal uterine bleeding (eg, midcycle spotting or heavy menstrual bleeding), menstrual migraines, and premenstrual syndrome or premenstrual dysphoric disorder (although COCs are not considered first-line therapy for this).

  - (See "Treatment of polycystic ovary syndrome in adults", section on 'Menstrual dysfunction'.)

  - (See "Abnormal uterine bleeding in nonpregnant reproductive-age patients: Management", section on 'Estrogen-progestin contraceptives'.)

  - (See "Hormonal contraception for menstrual suppression".)

- (See "Estrogen-associated migraine headache, including menstrual migraine", section on 'Can estrogen-containing contraceptives reduce migraine headache frequency?'.)
- (See "Treatment of premenstrual syndrome and premenstrual dysphoric disorder".)
- (See "Uterine fibroids (leiomyomas): Treatment overview", section on 'Medical therapy'.)

- **Pelvic pain disorders** – Women with pelvic pain (eg, endometriosis-related or chronic pelvic pain) or dysmenorrhea often benefit from the hormonal and endometrial suppression associated with COC use to reduce their symptoms. Continuous or extended-cycle COCs are often more effective in this population compared with cyclic use.
  - (See "Endometriosis: Treatment of pelvic pain", section on 'Estrogen-progestin contraceptives'.)
  - (See "Chronic pelvic pain in adult females: Treatment", section on 'Specific role of empiric hormonal therapy'.)
  - (See "Dysmenorrhea in adult females: Treatment", section on 'Hormonal contraception'.)
- **Ovarian cysts** – COCs are often prescribed to women with a history of painful ovarian cysts to suppress ovulation and subsequent formation of new cysts. COCs do not appear to aid regression of existing functional ovarian cysts [37,38].
- **Hyperandrogenism** – COCs can reduce the dermatologic manifestations of hyperandrogenism, such as acne and hirsutism, which are particularly common in women with polycystic ovary syndrome or nonclassic congenital adrenal hyperplasia due to 21-hydroxylase deficiency. The relevant mechanisms of action for this population include:
  - Inhibition of gonadotropin secretion and thereby a decrease in ovarian androgen secretion.
  - An increase in serum sex hormone-binding globulin concentrations, which results in increased binding of androgens and a decrease in serum-free androgen concentrations.
  - Inhibition of adrenal androgen secretion [39]; the mechanism of the last effect is not well understood.

These issues are presented in greater detail in separate reviews:

- (See "Management of hirsutism in premenopausal women", section on 'Combined estrogen-progestin oral contraceptives'.)
- (See "Treatment of polycystic ovary syndrome in adults".)
- (See "Diagnosis and treatment of nonclassic (late-onset) congenital adrenal hyperplasia due to 21-hydroxylase deficiency", section on 'Women'.)

- **Other disorders** – COCs can also be used as hormone replacement in women with primary hypogonadism or premature ovarian insufficiency. (See "Pathogenesis and causes of spontaneous primary ovarian insufficiency (premature ovarian failure)" and "Management of primary ovarian insufficiency (premature ovarian failure)".)

- **Cancer risk reduction** – Women at increased risk of endometrial and ovarian cancer can benefit from COC use to reduce their cancer risk as well as to provide a highly effective contraceptive [40]. There is a similar reduction in risk for women with *BRCA1* or *BRCA2* ovarian cancers [41]. Although a history of COC use has been associated with reduced risk of colorectal cancer in some studies, the body of evidence conflicts, and it is not known if prophylactic use of COCs reduces colorectal cancer risk.

  - (See "Endometrial carcinoma: Epidemiology, risk factors, and prevention", section on 'Use of hormonal contraception'.)
  - (See "Cancer risks and management of BRCA1/2 carriers without cancer", section on 'Oral contraceptives'.)

- **Bone health** – Perimenopausal women who use COCs have improved bone density compared with nonusers [42]. COCs are also useful for the treatment of hot flashes and abnormal uterine bleeding in this population [43].

  - (See "Clinical manifestations and diagnosis of menopause", section on 'Long-term consequences of estrogen deficiency'.)
  - (See "Treatment of menopausal symptoms with hormone therapy", section on 'Use of oral contraceptives during the menopausal transition'.)

Risks and side effects — The risks and side effects of COCs are influenced by the type and dose of estrogen and the progestin. These issues are reviewed in detail separately. (See "Combined estrogen-progestin contraception: Side effects and health concerns".)

Briefly, common issues that we discuss with patients initiating or using COCs include:

- **Frequent patient concerns** – We review that patients may experience breast tenderness, nausea, and bloating when starting a COC. These symptoms typically resolve quickly. Other concerns can include unscheduled bleeding, which typically resolves within three months, and the possible impact of COCs on mood and sexual function. There is no evidence that COCs cause weight gain. (See "Combined estrogen-progestin contraception: Side effects and health concerns", section on 'Common side effects'.)

- **Venous thromboembolism (VTE)** – COC use has been associated with an increased risk of VTE. The risk of VTE varies with estrogen dose and patient factors such as age, obesity, and smoking status. While the relative risk is increased, the absolute increase in risk is still low for most women and does not outweigh the numerous benefits of this contraceptive method, particularly when compared with the VTE risk during pregnancy and the postpartum period [44]. (See "Combined estrogen-progestin contraception: Side effects and health concerns", section on 'Cardiovascular effects'.)

- **Cardiovascular risk** – COC use has been associated with increased risks of hypertension, myocardial infarction, and stroke in certain populations. However, the absolute risk of myocardial infarction and stroke attributable to COCs is low in women of reproductive age [10]. COCs can rarely cause a mild elevation in blood pressure in the range of 3 to 5 mmHg, which is unlikely to be clinically significant in healthy women. (See "Combined estrogen-progestin contraception: Side effects and health concerns", section on 'Cardiovascular effects'.)

- **Cancer risk** – COC use does **not** appear to increase the overall risk of cancer [40]. The impact of COC use on breast cancer risk is a subject of active debate as the data conflict. At least one study has reported a differing risk of breast cancer with COC use based on hormone receptor subtype. Women who have taken COCs also appear to have a slightly increased risk for developing cervical cancer [45]. By contrast, COC use is associated with reduced risk of developing ovarian and endometrial cancers. These issues are presented in detail separately. (See "Combined estrogen-progestin contraception: Side effects and health concerns", section on 'Effects on cancer development'.)

Impact on STI acquisition — The impact of sexually transmitted infection (STI) acquisition in women using COCs appears to vary by type of infection. Two systematic reviews reported that COC use positively correlates with chlamydia infections but not with gonorrhea, herpes simplex virus-2, trichomoniasis, syphilis, and human papillomavirus [46,47]. While COCs may be associated with increased rates of chlamydia, the rates of pelvic inflammatory disease (PID) do not appear to be increased [48].

One study reported similarly increased rates of bacterial vaginosis, trichomoniasis, and *Candida* vaginitis among women initiating either COCs or a levonorgestrel intrauterine device, which makes sexual exposure the likely risk factor for these infections and not the type of contraceptive method [49]. Other studies have reported reduced rates of bacterial vaginosis in women using COCs [50,51]. Data generally do not support any influence of COC use on acquisition of HIV [52-55]. There are no restrictions on COC use among women with STIs, PID, or HIV [15,56].

We discuss STI risk with all women presenting for contraceptive counseling. Women at risk for acquiring an STI are advised to use condoms (male or female) in addition to their contraceptive method. (See "Internal (formerly female) condoms", section on 'Sexually transmitted infections' and "External (formerly male) condoms", section on 'Protection from STIs'.)

HORMONE COMPONENTS

Estrogen — The discovery in 1938 that the addition of a 17-alpha-ethinyl group to estradiol resulted in both an orally active estrogen compound and a dramatic increase in estrogenic potency was a major advance in steroid biochemistry. This compound, known as mestranol, was the estrogen used in the first COCs. Mestranol is metabolized to ethinyl estradiol in its first pass through the liver.

- **Estrogens used in COCs –** Most, but not all, COCs contain ethinyl estradiol as the estrogen component (table 1).
  - **Ethinyl estradiol** – Ethinyl estradiol, the mostly commonly used estrogen in combined oral contraceptive pills, is a potent synthetic estrogen (like most analogs of naturally occurring hormone) with similar but not identical metabolic effects to estradiol regardless of the route of administration because of its long half-life and slow metabolism [57]. By contrast, some newer COC combinations utilize natural estradiol rather than ethinyl estradiol.
  - **Other estrogens –** COCs containing estradiol valerate with the progestin dienogest, 17-beta estradiol with nomegestrol acetate, and estetrol with drospirenone have been released (table 1) [23-26,58]. Two milligrams of estradiol valerate is approximately equivalent to 10 mcg of ethinyl estradiol [59]. These estrogens appear to have less effect on hemostasis, fibrinolysis markers, lipids, and adrenal steroids compared with ethinyl estradiol [25,60]. Whether the estradiol valerate, 17-beta estradiol, or estetrol COCs will be safer than those formulated with ethinyl estradiol with respect to thromboembolism risk is unknown [7,61]. Additional

information on COCs containing other estrogens is available in the estradiol-dienogest and estetrol-drospirenone drug information monographs.

- **Estrogen doses –** While early COC preparations contained up to 150 mcg of mestranol, available COCs contain, on average, 20 to 35 mcg of ethinyl estradiol. A few 50 mcg dose pills are still manufactured, and there is a 10 mcg pill available as well (table 1) [1]. While universal consensus on the dose categories is lacking, we think of COCs based on the amount of ethinyl estradiol, or its equivalent, as below:

  - **High dose –** In general, high-dose COCs contain ≥50 mcg ethinyl estradiol or its equivalent. Initial COCs contained 150 mcg of mestranol or ethinyl estradiol. However, common side effects such as nausea and vomiting, as well as high risk of venous thromboembolism, subsequently led to their discontinuation [62]. The next formulations contained 100 and then 50 mcg of ethinyl estradiol, which improved tolerability, but side effects and risks remained significant. In general, formulations with 50 mcg ethinyl estradiol pills are utilized for the acute treatment of abnormal uterine bleeding. (See "Abnormal uterine bleeding in nonpregnant reproductive-age patients: Management".)

  - **Low dose –** Contemporary low-dose COCs contain 20 to 35 mcg of ethinyl estradiol. COCs with 20 to 25 mcg ethinyl estradiol were introduced as options for individuals who did not tolerate the 30 or 35 mcg products, as well as for business-related reasons such as patent expiration and competition for market advantage. Compared with 30 to 35 mcg ethinyl estradiol COCs, COCs containing 20 mcg are more likely to result in bleeding disturbances, including amenorrhea and irregular, frequent bleeding, or spotting [5]. However, many of the clinical trials comparing different doses of estrogen used COCs that also contained different types of progestins. As a result, it is unclear whether the higher frequency of bleeding was due to the lower estrogen dose or to different progestin types.

  - **Ultra-low dose –** COCs with less than 20 mcg ethinyl estradiol are available in multiphasic combination COC products (table 1). While dose reductions from 150 mcg ethinyl estradiol to 30 to 35 mcg resulted in a markedly improved safety profile for COCs, it is unknown if subsequent dose reductions to 20 or 10 mcg will further decrease adverse events [5,6]. For comparison, the contraceptive vaginal rings release 13 to 15 mcg ethinyl estradiol per day. (See "Contraception: Hormonal contraceptive vaginal rings".)

- **Increased risk of thromboembolism –** In general, the increased risk of venous thromboembolism is related to estrogen's stimulation of liver proteins involved in the clotting system. The progestin component may modulate this effect significantly, and more antiandrogenic progestins are thought to allow a fuller expression of the

estrogen component [10]. Due to this feature, concerns have been raised about possible increased risk of deep venous thrombosis with the third-generation progestins (gestodene and desogestrel, but **not** norgestimate) and antiandrogenic progestins (drospirenone and cyproterone acetate) when compared with COCs containing levonorgestrel (table 1) [6,44]. This issue is reviewed separately. (See "Combined estrogen-progestin contraception: Side effects and health concerns", section on 'Cardiovascular effects' and 'Progestin' below.)

- **Impact on other hormones** – The estrogen component of COC pills, like any estrogen taken orally, raises the serum concentrations of thyroxine-binding globulin (TBG), cortisol-binding globulin (CBG), and sex hormone-binding globulin (SHBG). As a result, the serum concentrations of total thyroxine (T4), triiodothyronine (T3), cortisol, estradiol, and testosterone increase, but the serum concentrations of free T4, T3, cortisol, estradiol, and testosterone do not change. This effect of oral estrogen administration needs to be considered when evaluating tests of thyroid, adrenal, and gonadal function in women taking any estrogen orally.

Progestin

- **Progestins** – The designation of first-, second-, third-, and fourth-generation progestin refers to when the group of progestins was introduced into the market, not on structural and physiologic differences (table 5). In general, third- and fourth-generation progestins are less androgenic and have fewer side effects than earlier generation progestins. Modifications to levonorgestrel created the third-generation progestins desogestrel, gestodene, and norgestimate [63,64]. However, some of these later generation progestins (gestodene and desogestrel, but not norgestimate) have also been associated with a slightly greater risk of venous thromboembolism [6,64]. (See "Combined estrogen-progestin contraception: Side effects and health concerns", section on 'Venous thromboembolism'.)

  Progestins can also be divided based upon their structural derivation into estranes and gonanes (derived from testosterone) and pregnanes (derived from progesterone) (table 2). The majority of progestins used in COCs are derived from testosterone and are, therefore, in the estrane and gonane classes. Individual progestins vary in their progestin potency, androgenicity, and side effects. (table 6). Norethindrone and norethindrone acetate are in the class of progestins referred to as the estranes (table 2). Ethynodiol diacetate, another progestin in this category, has more estrogenic activity than other progestins in this class. A second class of progestins known as gonanes (or 13-ethylgonanes) are also derived from testosterone and include norgestrel and levonorgestrel.

- **Antiandrogenic progestins –** Sometimes referred to as fourth-generation progestins, newer preparations have been developed that have some antiandrogenic activity (table 6). These include a compound derived from drospirenone (a spironolactone analog), dienogest, and cyproterone acetate, which is available worldwide but not in the United States (table 2) [63,64].

  Drospirenone is structurally related to spironolactone; it has progestogenic, antiandrogenic, and anti-mineralocorticoid activity [65]. Monophasic COCs containing either 20 or 30 mcg of ethinyl estradiol with 3 mg of drospirenone are available [66]. Drospirenone appears to be a very weak antiandrogen; the 3 mg dose is estimated to be equivalent to only 25 mg of spironolactone. The 20 mcg preparation has a four-day pill-free interval, as opposed to the standard seven-day interval, and it is approved for the treatment of premenstrual dysphoric disorder (but not for premenstrual syndrome [eg, women with milder symptoms]) [67,68]. Although drospirenone is technically an antiandrogen, drospirenone-containing COCs have no advantage over other COCs for treating hirsutism or acne [69].

  (See "Treatment of premenstrual syndrome and premenstrual dysphoric disorder", section on 'Combined estrogen-progestin contraception'.)

  (See "Management of hirsutism in premenopausal women", section on 'Choice of pill'.)

  Although drospirenone has potential potassium-sparing effects (due to its anti-mineralocorticoid activity), healthy women taking COCs containing drospirenone are no more likely to develop hyperkalemia than women taking other COC preparations [70-72]. Package labeling recommends potassium monitoring in the first month for women who take additional medications that predispose to hyperkalemia (eg, spironolactone, nonsteroidal anti-inflammatory drugs [NSAIDs], angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, potassium-sparing diuretics, and aldosterone antagonists) [73]. However, in one study, short-term coadministration of an ethinyl estradiol-drospirenone COC with indomethacin was associated with the same mean serum potassium and same low rate of serum potassium values above 5 mEq/L as indomethacin alone [71]. In clinical practice, we do not check potassium levels on women taking NSAIDs with drospirenone-containing COCs. However, we would consider potassium monitoring for the rare patient taking a drospirenone-containing COC along with the anti-hypertensives and diuretics listed above. Package labeling also advises against prescribing drospirenone to women with renal disease or adrenal insufficiency [74].

Androgenicity — Whether the differing androgenic activity of the available progestins in COCs has any meaningful clinical effects has been a matter of debate (table 6). Any effect of the progestin will depend on the type, dose, potency, and estrogen/progestin balance in

the COC formulation [75,76]. Estrogen is known to decrease low-density lipoprotein (LDL) and increase high-density lipoprotein (HDL), triglycerides, cholesterol, and SHBG. A progestin, depending on its level of androgenicity, may be neutral or may partially reverse some of these effects when the two hormones are taken together. The overall effect of all COCs, however, is antiandrogenic, regardless of the type of progestin used. There is no evidence that a certain type of progestin in a COC formulation is any more effective in treating hyperandrogenic symptoms, such as acne or hirsutism, for example, than another type [69,77,78], nor are any changes in lipid profiles typically clinically meaningful for the average woman [79].

DOSING REGIMENS

Mono- or multiphasic — COCs are available as mono- or multiphasic formulations (table 1). Monophasic pills contain the same dose of estrogen and progestin in each of the 21 to 24 hormonally active pills.

Multiphasic pills vary the dose of either or both hormones during the active pill phase. Multiphasic COCs were introduced as a strategy to reduce hormone dose and, thus, hormone-related side effects and unscheduled bleeding, as well as for business-related reasons such as patent expiration and competition for market advantage. However, there are no data that these preparations have any important clinical advantages; the contraceptive efficacy appears to be similar across all COC types. Biphasic formulations may be associated with more unscheduled bleeding compared with triphasic pills and therefore are not used [27,29,31].

Cyclic use — Cyclic pill packs typically provide hormone pills for 21 days of a 28-day cycle (monophasic, biphasic, or triphasic dosing regimens), followed by 7 days of placebo pills that result in a withdrawal bleed (also known as a 21/7 regimen). The original intent of the regimen was to provide a monthly bleed that patients would interpret as menstruation. This was required at the time for pill acceptance and to reassure the woman that she was not pregnant [12]. Today, with the lower doses of hormones used in COCs, it is recognized that seven days off hormones is not necessary. An alternative is the 24/4 regimen which provides four days of placebo or low-dose estrogen pills. The shorter the pill-free window, the less likely it is that folliculogenesis will occur [33-35,80]. With a standard seven-day pill-free interval, follicles may develop and secrete enough estradiol to "repair" or stimulate proliferation of the thin endometrium that is a normal consequence of the progestin in the pill [35]. With a four-day pill-free interval, on the other hand, endometrial atrophy may become more likely (which can result in more unscheduled bleeding in early cycles). Then again, the four-day hormone-free interval may be associated with increased efficacy [36]. Furthermore, shortening the hormone-free interval may reduce symptoms associated with

hormone withdrawal (eg, mood symptoms, headache, pelvic pain) [12]. (See "Hormonal contraception for menstrual suppression".)

Continuous or extended use — Continuous or extended-cycle COC regimens allow the user to choose if and when she will have withdrawal bleeding. Today, we know that menstrual suppression is safe, and the withdrawal bleed provided by the hormone-free interval is not medically necessary.

- **Continuous –** With continuous regimens, the patient takes a combined estrogen-progestin pill every day for a year.
- **Extended –** Extended-cycle preparations are similar to continuous regimens, except that seven-day intervals of placebo or low-dose estrogen administration are inserted approximately every three months (84/7 regimen). These formulations are packaged so that the three-month supply is dispensed at one time in a convenient package. Sunday start is advised for new users of extended regimens.

Contraceptive efficacy, safety, and patient satisfaction are similar for cyclic, extended, and continuous regimens, while menses-related symptoms are typically reduced with combinations that reduce the frequency of withdrawal bleeding [9]. However, women using extended or continuous COCs may have more unpredictable bleeding or spotting events, which is due to the development of a thin, atrophic endometrium with continuous progestin exposure. Unscheduled bleeding is a common problem with continuous regimens in early cycles (the first three to six months) [81,82], but the frequency decreases over time and becomes similar to that for cyclic regimens [9,83,84]. Unscheduled bleeding is not a sign of decreased contraceptive efficacy, nor is it associated with an increased risk of endometrial hyperplasia [85]. Women should be counseled about potential changes in bleeding patterns prior to initiating these regimens. If the patient desires treatment for persistent unscheduled bleeding with continuous or extended-cycle COC regimens, they can opt to discontinue use for three to four consecutive days (except during the first 21 days of using the method) to give themselves a hormone-free interval [86,87]. This will ideally allow for a coordinated withdrawal bleed and reduce further unscheduled bleeding.

The reduction or elimination of withdrawal bleeding has been found helpful for the following:

- **Endometriosis –** The strategy with this approach is to induce decidualization and subsequent atrophy of endometrial tissue. This regimen may be as effective as a gonadotropin-releasing hormone agonist for pain control. (See "Endometriosis: Treatment of pelvic pain" and "Hormonal contraception for menstrual suppression".)
- **Premenstrual dysphoric disorder (PMDD) –** To reduce symptoms of PMDD by avoiding hormonal fluctuations. (See "Treatment of premenstrual syndrome and

premenstrual dysphoric disorder", section on 'Combined estrogen-progestin contraception'.)

- **Hyperandrogenism –** (See 'Noncontraceptive uses' above.)
- **Lifestyle needs –** For lifestyle reasons, many women without any underlying disease or disorder prefer to take the pill continuously to minimize the frequency of menses or avoid having their period during a specific event, such as a sports competition or vacation.
- **Management of menopausal symptoms in perimenopausal women –** Hot flashes recur if COCs are given in a cyclic regimen but will remain suppressed with a continuous regimen. (See "Treatment of menopausal symptoms with hormone therapy", section on 'Use of oral contraceptives during the menopausal transition'.)
- **Dysmenorrhea –** (See "Dysmenorrhea in adult females: Treatment".)

ADMINISTRATION AND USE

COCs are available over the counter in the majority of countries worldwide but by prescription only in 30 percent of countries, including the United States [88].

Screening requirements — Hormonal contraception can be safely provided after a medical history and blood pressure measurement; a pelvic examination is not required [87]. Important factors to screen for in the patient's medical history include concurrent medications, smoking, hypertension, diabetes, venous and arterial thromboembolism, migraine with aura, breast cancer, and postpartum status. While known thrombogenic mutations are a contraindication to COCs, it is not recommended that testing be performed in the general population prior to initiating COCs [17,87,89]. Although breast examinations, Pap smears, and screening for sexually transmitted diseases are important, most groups, including the Centers for Disease Control and Prevention, the World Health Organization, and the Royal College of Obstetricians and Gynaecologists, agree that these procedures are not necessary before a first prescription for COCs [11,15,16]. Documentation of body mass index (BMI) prior to starting COCs is suggested because obese women are at greater risk for venous thromboembolism (VTE) with COC use and weight changes can be monitored. (See "Combined estrogen-progestin contraception: Side effects and health concerns", section on 'Cardiovascular effects' and "Combined estrogen-progestin contraception: Side effects and health concerns", section on 'Weight gain'.)

The 2016 United States Selected Practice Recommendations for Contraceptive Use provide an overview of factors to consider when initiating contraception in healthy women, such as how to help a woman initiate use of a contraceptive method, which examinations

and tests are needed before initiating use, what regular follow-up is needed, and how to address problems that often arise during use (table 7) [87].

Initiation — COCs can be started any time during the cycle (algorithm 1) as long as pregnancy is reasonably excluded (table 8) [87]. There are several options for starting the pill.

- We use the **quick start** method in which the woman begins taking COCs on the day that she is given the prescription [90,91]. This approach is evidence-based.
- An alternative is the **Sunday start** approach where the woman starts the pill on the first Sunday after her period begins. The patient should be informed that a Sunday start avoids withdrawal bleeding on a weekend, and she can decide if that is a priority. Sunday start is advised for patients taking extended-cycle regimens. (See 'Continuous or extended use' above.)
- **Back-up contraception –** If the patient will start taking the pill >5 days after the onset of menses, then back-up (ie, nonhormonal) contraception is advised.
  - **Duration –** Most patients are advised to use an additional, nonhormonal, contraceptive for the first seven days of the cycle [87]. Patients taking dienogest-containing pills are advised to use back-up contraception for a total of nine days [92]. Examples of nonhormonal contraception include condoms and pericoital methods.
    - (See "Internal (formerly female) condoms".)
    - (See "External (formerly male) condoms".)
    - (See "Pericoital (on demand) contraception: Diaphragm, cervical cap, spermicides, and sponge".)
  - **Rationale –** Back-up contraception is advised because follicular development and breakthrough ovulation are more common in patients who delay starting the pill after menses when compared with patients who start on day 1 of menses [93]. If the patient is concerned about the possibility of pregnancy, she should be instructed to check a pregnancy test at home or in the office two weeks after initiating COCs. Patients can be reassured that any exposure to COCs will not adversely affect an early pregnancy or cause congenital anomalies.

COCs can also be started in the following settings:

- **First day of menses** (known as the **first day start**) **–** The advantage of this approach is that it provides the maximum contraceptive effect in the first cycle, and backup

contraception for the first seven days of use is not needed as it is with the first two options.

- **Pregnancy loss or abortion –** COCs can also be started within the first seven days following first- or second-trimester spontaneous or induced abortion. Backup contraception is needed for seven days unless COCs are started immediately after the abortion [87]. (See "Contraception: Postabortion".)

- **Postpartum –** Postpartum women should not use combined hormonal contraceptives for at least the first 21 days after delivery because of the increased risk for VTE during this time period [15,94]. Breastfeeding women should avoid combined hormonal contraceptives until 30 days postpartum due to theoretical effects on lactation. Postpartum women with other risk factors for VTE (eg, age 35 years or more, previous VTE, thrombophilia, immobility, transfusion at delivery, peripartum cardiomyopathy, BMI 30 kg/m^2, postpartum hemorrhage, postcesarean delivery, preeclampsia, or smoking) generally should not use combined hormonal contraceptives until six weeks after delivery whether breastfeeding or not. This topic is reviewed in detail elsewhere. (See "Contraception: Postpartum counseling and methods", section on 'Counseling regarding venous thromboembolism risk and hormonal contraception in the postpartum period'.)

COCs are prescribed as a monthly or an extended-cycle regimen, and a one-year supply is provided [87]. Providing a one-year prescription or, even better, a supply for a full year of pills has been shown to improve access to and continuation rates of the pill as well as anticipated cost savings [95,96].

Follow-up — Contraceptive follow-up can be addressed during routine periodic examinations scheduled for other health maintenance issues [87]. A specific follow-up examination just to address contraception is not needed for most women; potential exceptions include adolescents or women with multiple medical issues. Women should be encouraged to return if they have any concerns about their method or want to discontinue or switch methods.

Missed pills — Missed pills (particularly if the seven-day hormone-free interval is extended on either end) are a common cause of contraceptive failure. Our approach outlined here is similar to that suggested by the 2016 United States Selected Practice Recommendations for Contraceptive Use [87].

- **Missing a single pill** – If a single pill is missed anywhere in the packet, women should be instructed to take the missed pill as soon as it is noticed and then continue taking one pill each day as prescribed [87]. Depending on when she remembers her missed

pill, she may end up taking two pills on the same day. No additional contraception is required because one missed pill does not reverse ovarian suppression [11].

- **Missing two or more pills**
  - The remaining pills should be taken at the usual time, **and** backup contraception, such as male or female condoms, is generally needed if two or more consecutive hormonal pills are missed [11,87]. The risk of ovulation is thought to be increased following two or more missed pills, particularly in the first week of pill taking after the hormone-free interval, based on studies reporting less ovarian activity with continuous pill regimens compared with regimens that include a hormone-free interval [84,97-99].
  - If two or more pills are missed in the **first week** of the cycle and unprotected intercourse occurs during this week, use of emergency contraception (with the exception of ulipristal acetate) could decrease the risk of pregnancy. Use of progestin-containing contraceptives at the same time as ulipristal acetate could lower the efficacy. (See "Emergency contraception".)
  - If pills were missed in the **last** week of hormone pills (week 3, days 15 to 21 of a 28-day pack), the patient should finish that last week of hormone pills (week 3), then skip week 4 (placebo pills), and immediately move on to a new pill pack the next day. If she is unable to start a new pack, backup contraception should be used until hormonal pills from a new pack are taken for seven consecutive days.
- **Extra pills –** If the patient takes two pills in one day by mistake, she should resume her normal schedule of taking one pill daily the next day; she should not skip a day. She will complete the pill pack one day early.

Return of menses after stopping — For many women, menses returns within 30 days after stopping the pill. Almost all women should experience return of menses and fertility by 90 days after cessation of COCs. This is true for standard 28-day regimens, as well as the extended and continuous regimens (figure 2). Therefore, women who do not menstruate three months after stopping the pill should undergo the same evaluation for amenorrhea as any woman with amenorrhea. (See "Combined estrogen-progestin contraception: Side effects and health concerns", section on 'Return of fertility'.)

Duration of use — Hormonal contraception can be continued until the age of menopause (average age 50 to 51 years) in healthy, nonsmoking, normal-weight women [15,43,87]. There is no need for periodic pill-free intervals. Women can use COCs for years and stop only for pregnancy and/or menopause.

Fertility in perimenopause — While the risk of pregnancy declines during perimenopause, ovulatory cycles are still present in about 23 percent of cycles within one year of the final menstrual period [100]. The median age at which women lose their natural fertility is 41 years but can range up to 51 years [101].

Age-based cessation of contraceptives — Major medical organizations recommend that females at risk for pregnancy continue to use contraception until menopause or up to age 50 to 55 years [87,102]. The rationales for age-based management is that menopause is a retrospective diagnosis (after the cessation of menses for 12 months) and hormonal contraceptives will mask menstrual change. While the average age of menopause is 52 years in the United States, it can vary from ages 40 to 60 years [102,103].

The decision to stop using contraception as women approach their older reproductive years should consider their age, frequency of sexual intercourse, and male partner fertility, as well as the risks of carrying a pregnancy given their age and any other medical problems the patient may have. Single measurements of follicle-stimulating hormone (FSH) and estradiol levels in the perimenopausal period can be unreliable indicators of menopause given the dramatic hormonal fluctuations during this time. Furthermore, for individuals taking combined oral contraceptives, amenorrhea and laboratory measurements will not be a reliable indicator of menopause. (See "Clinical manifestations and diagnosis of menopause", section on 'Women taking oral contraceptives'.)

DRUG INTERACTIONS

The metabolism of COCs is accelerated by any drug that increases liver microsomal enzyme activity such as phenobarbital, phenytoin, griseofulvin, and rifampin. As a result, the contraceptive efficacy of a COC is likely to be decreased in women taking these drugs [15,104-107].

- **Antiseizure medications** – We take the same approach as the Centers for Disease Control and Prevention and suggest that women taking antiseizure medications including phenytoin, carbamazepine, barbiturates, primidone, topiramate, felbamate, or oxcarbazepine should generally not use COCs because the antiseizure medication may reduce the efficacy of the hormonal contraceptive [15]. However, COCs are reasonable if the patient understands the risks and cannot use other methods. When a COC is chosen, a formulation containing a minimum of 30 mcg of ethinyl estradiol should be used, and consideration should be given to using progestins with a longer half-life (drospirenone, desogestrel, levonorgestrel) and a continuous regimen or a preparation with a four-day hormone-free interval. (See "Overview of the management of epilepsy in adults", section on 'Contraception'.)

Antiseizure medications that do not appear to reduce contraceptive efficacy include gabapentin, levetiracetam, valproate, zonisamide, and tiagabine [15]. By contrast, COCs increase lamotrigine clearance, resulting in a decrease in plasma lamotrigine concentrations by 45 to 60 percent [108,109]. This interaction raises concerns about adequate seizure control if a COC and lamotrigine are used in combination, and the lamotrigine dose may need to be adjusted [108,110,111]. To avoid fluctuating levels of lamotrigine, we recommend using continuous dosing of the COC rather than cyclic. (See "Overview of the management of epilepsy in adults", section on 'Contraception'.)

- **Antibiotics –** Rifampin is the only antibiotic proven to decrease serum ethinyl estradiol and progestin levels in women taking COCs [106]; similar to liver enzyme-inducing antiseizure medications, other methods of contraception are recommended [15].

  For women taking antibiotics other than rifampin with COCs, backup contraception is not required. In spite of anecdotal reports of COC failure, other antibiotics have **not** been proven to affect the pharmacokinetics of ethinyl estradiol [111]. While a database review reported a sevenfold increased rate of unintended pregnancy for patients taking non-enzyme-inducing antibiotics compared with control medications, this study was based on self-report and therefore subject to recall bias [112].

- **Antifungals –** Griseofulvin, an antifungal agent, has been associated with contraceptive failure in several case reports [105]. However, data are limited, and the World Health Organization concludes that hormonal contraception is reasonable for women on griseofulvin [16].

- **Antiretrovirals –** Drug interactions between COCs and many of the drugs used to treat HIV infection are discussed elsewhere. (See "HIV and women", section on 'Choice of contraception'.)

- **St. John's wort –** Limited evidence suggests that St. John's wort coadministration with COCs may increase the risk of ovulation and unscheduled bleeding [113]. The mechanism is thought to be via induction of cytochrome P450, which could increase COC metabolism and theoretically reduce therapeutic efficacy. The effect would depend on the dose of St. John's wort, which varies across products.

SPECIAL POPULATIONS

Adolescents — COCs may be challenging for adolescents to use successfully due to the daily adherence required and the need to refill a prescription each month. They will benefit from support surrounding COC adherence. (See "Contraception: Issues specific to adolescents".)

Obesity — Obese women who are not perimenopausal can use COCs, as the benefits are generally believed to outweigh the risks [15,17]. COCs should be used with caution in obese perimenopausal women, as the risk of venous thromboembolism increases with both age and body mass index; risk appears to be twice as high as for nonobese women. Although there have been concerns that being overweight or obese may decrease the efficacy of COCs, evidence suggests that COC efficacy is similar for normal-weight and overweight/obese women [114]. Practically, adherence to COCs likely plays a larger role in COC failure than the contribution of obesity. (See "Contraception: Counseling for females with obesity", section on 'Risk of thromboembolism' and "Contraception: Counseling for females with obesity", section on 'Oral contraceptives'.)

Postpartum and/or lactating — We, and other experts, following the World Health Organization and the American College of Obstetricians and Gynecologists recommendations for nonhormonal and hormonal contraception in postpartum women, including those who are lactating [16,17]. COCs should not be used in the early postpartum weeks because of the high risk of thromboembolism [15,16]. This topic is reviewed in detail elsewhere. (See "Contraception: Postpartum counseling and methods", section on 'Short-acting hormonal contraception'.)

Perimenopause — COCs containing 20 mcg of ethinyl estradiol are often used for nonsmoking perimenopausal women who desire contraception but who also have irregular or heavy menses and/or hormonally related symptoms that impair quality of life [43]. These preparations provide more than enough estrogen to relieve vasomotor flushes (which often begin during the perimenopausal transition). One problem that perimenopausal women often experience when taking COCs is recurrence of hot flashes and premenstrual mood disturbances during the seven-day pill-free interval. Some preparations contain 10 mcg of ethinyl estradiol on five of the seven "placebo" days, which may be helpful in relieving these symptoms. Continuous administration of the pill is another way to avoid the recurrence of hot flashes. COCs containing only 10 mcg of ethinyl estradiol are now also available and can be a good option for this population (table 4). Because age is an independent risk factor for cardiovascular disease and thromboembolism, perimenopausal women with other medical conditions such as obesity, diabetes, and hypertension should avoid estrogen-containing contraception [17]. (See 'Dosing regimens' above and "Treatment of menopausal symptoms with hormone therapy", section on 'Use of oral contraceptives during the menopausal transition'.)

- (See "Combined estrogen-progestin contraception: Side effects and health concerns", section on 'Cardiovascular effects'.)
- (See "Overview of the causes of venous thrombosis", section on 'Obesity'.)
- (See "Overview of the causes of venous thrombosis", section on 'Age'.)

RESOURCES FOR PATIENTS AND CLINICIANS

- bedsider.org – A free website developed by the National Campaign to Prevent Teen and Unplanned Pregnancy, a private nonprofit group
- CHOICE Project – A free website sponsored by the Washington University School of Medicine in St. Louis that provides resources on contraceptive options and training resources for clinicians
- Center for Young Women's Health – A free website run by Boston Children's Hospital that addresses reproductive health needs of teens and young adults
- Beyond the Pill – A free website run by the University of California San Francisco
- SexandU.ca – An educational site run by the Society of Obstetricians and Gynaecologists of Canada that includes descriptions of various methods and a tool to help with selection of birth control
- Planned Parenthood – A nonprofit organization dedicated to reproductive health, with resources for patients and clinicians
- ACOG Contraceptive FAQs – American College of Obstetricians and Gynecologists (ACOG) addresses frequently asked questions (FAQs) about contraception
- ACOG LARC Program – ACOG Long-Acting Reversible Contraception (LARC) Program
- United States Medical Eligibility Criteria for Contraceptive Use
- United States Selected Practice Recommendations for Contraceptive Use
- UK Medical Eligibility Criteria for Contraceptive Use
- World Health Organization (WHO) Medical Eligibility Criteria for Contraceptive Use

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

- **Our approach** – In general, we prefer generic, monophasic, low dose (≤35 mcg of ethinyl estradiol), and 24/4 cycle pills. Pills containing 50 mcg of estrogen should not be used for contraception. (See 'Our approach to COC selection' above.)
  - **Monophasic versus other regimens** – Monophasic pills contain the same dose of estrogen and progestin in each of the hormonally active pills. Biphasic or triphasic pills have varying doses of hormones across the cycle (usually the progestin). There are no proven advantages to the multiphasic regimens (ie, less unscheduled bleeding or efficacy). (See 'Dosing regimens' above.)
  - **Hormone types and dose** – Most COCs on average contain 20 to 35 mcg of ethinyl estradiol. Newer formulations include estradiol valerate, estetrol, and 17-beta estradiol (table 1). Most available progestins have varying degrees of progestogenic and androgenic activity (table 2 and table 6). However, when combined with estrogen, the overall effect of COCs is antiandrogenic. (See 'Hormone components' above.)
- **Mechanism of action and efficacy** – While combined estrogen-progestin oral contraceptives (COCs) have several mechanisms of contraceptive action, the most important is inhibition of folliculogenesis and the midcycle luteinizing hormone surge so that ovulation does not occur. (See 'Mechanisms of action' above.)

When taken properly, COCs are a highly effective form of contraception with a typical-use failure rate of approximately 7 percent for products containing ethinyl estradiol (figure 1 and table 1). Unintended pregnancies commonly result from missed pills or failure to resume therapy after the seven-day pill-free interval. (See 'Efficacy' above.)

- **Starting combined oral contraceptives**
  - **Initial evaluation** – Hormonal contraception can be safely provided after a medical history and blood pressure measurement; a pelvic examination is not required. Additional testing is not warranted in medically uncomplicated individuals. (See 'Initiation' above.)
  - **Assess medical comorbidities** – Both the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) provide comprehensive tables of medical conditions and personal characteristics that may affect contraceptive choice. (See 'Candidates' above.)
    - WHO Medical Eligibility Criteria for Contraceptive Use 2015
    - CDC's Summary Chart of US Medical Eligibility Criteria
  - **When to start** – COCs can be started at any time during the cycle. The preferred approach is the quick start method in which the individual begins taking COCs on the day that the prescription is given (once pregnancy has been reasonably excluded) regardless of menstrual cycle timing (algorithm 1). Backup contraception is used for an additional seven days (table 7). (See 'Administration and use' above.)
- **Missed pills** – We suggest that backup contraception be used for seven days after two missed pills, regardless of pill dose (**Grade 2C**). (See 'Missed pills' above.)
- **Drugs that impact COC metabolism** – The metabolism of COCs is accelerated by any drug that increases liver microsomal enzyme activity, such as many of the antiseizure medications, including phenytoin and phenobarbital. The metabolism of COCs is **not** affected by antibiotics, with the exception of rifampin. (See 'Drug interactions' above.)
- **Continuous or extended-use contraceptives** – Contraceptive efficacy, safety, and patient satisfaction are similar for cyclic, extended, and continuous regimens. Menses-related symptoms are typically reduced with combinations that reduce the frequency of withdrawal bleeding. However, individuals using extended or continuous COCs may have more unpredictable bleeding or spotting events in the first three to six months of use compared with cyclic use; this unscheduled bleeding will decrease over time. (See 'Continuous or extended use' 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.*

Graphic 69223 Version 52.0

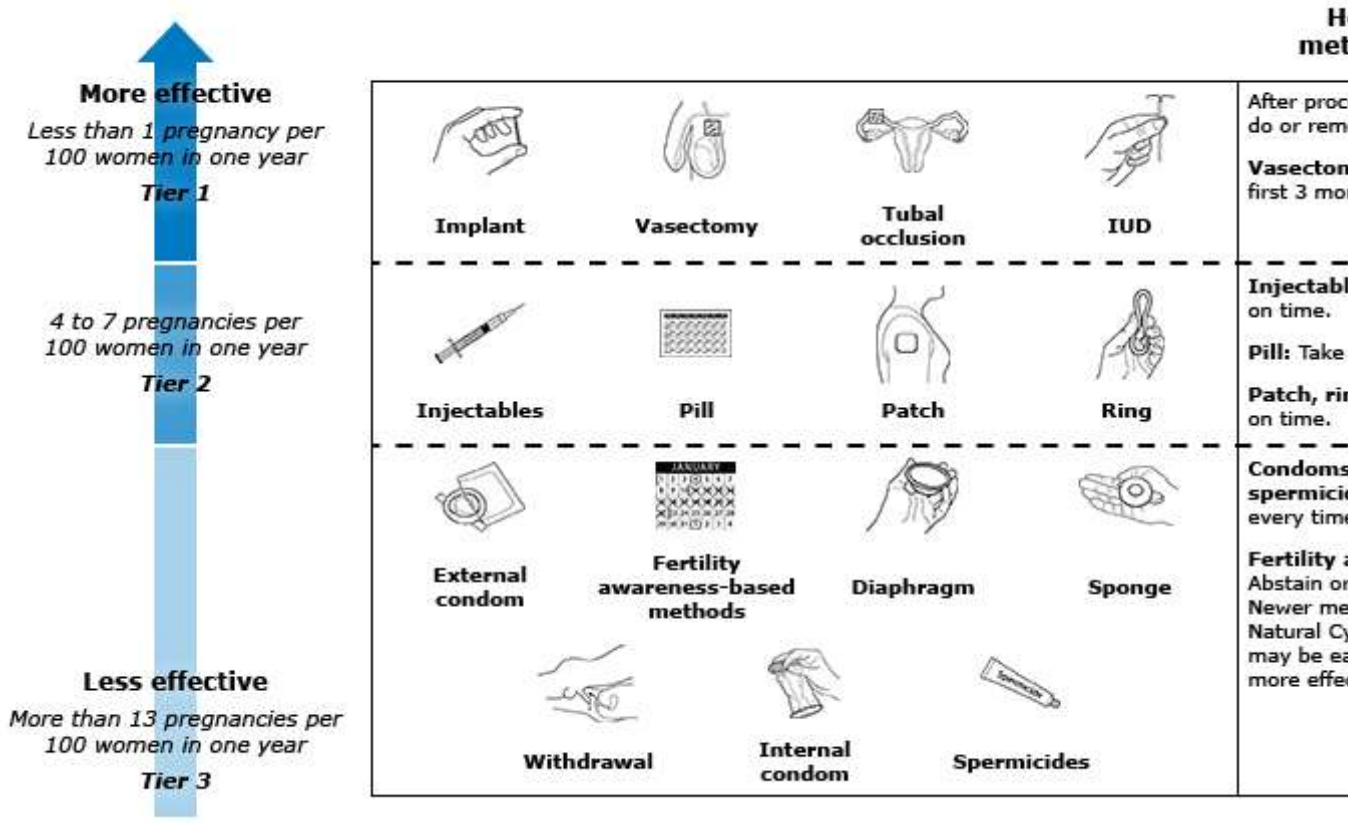
Classification of progestins used in combined oral contraceptive pills

Structurally related to testosterone	
Ethinylated	
▪ Estranes	Norethindrone, norethindrone acetate, ethynodiol diacetate, norethynodrel
▪ 13-Ethylgonanes	Levonorgestrel, desogestrel, norgestimate, gestodene
Non-ethinylated	Dienogest, drospirenone
Structurally related to progesterone	
Pregnane-derivative	Cyproterone acetate
19-norpregnane derivative	Nomegestrol acetate

Courtesy of Rebecca Allen, MD.

Graphic 120135 Version 1.0

Contraceptive methods and comparison of typical effectiveness



IUD: intrauterine device.

Graphic 119765 Version 5.0

Percentage of women experiencing unintended pregnancy during the first year of contraceptive use (typical and perfect use) and the percentage continuing use at the end of the first year: United States

Method	Percent of women experiencing an unintended pregnancy within the first year of use (%)		Percent of women continuing use at one year (%)[Δ]
	Typical use*	Perfect use[¶]	
No method[◇]	85	85	
Spermicides[§]	21	16	42
Internal condom[¥]	21	5	41
Withdrawal	20	4	46

Diaphragm[‡]	17	16	57
Sponge	17	12	36
Parous women	27	20	
Nulliparous women	14	9	
Fertility awareness-based methods[†]	15		47
Ovulation method[†]	23	3	
TwoDay method[†]	14	4	
Standard Days method[†]	12	5	
Natural Cycles[†]	8	1	
Symptothermal method[†]	2	0.4	
External condom[¥]	13	2	43
Combined and progestin-only pills	7	0.3	67
Evra patch	7	0.3	67
NuvaRing	7	0.3	67
Depo-Provera	4	0.2	56
Intrauterine contraceptives**			
ParaGard (copper T)	0.8	0.6	78
Mirena (52 mg LNG)	0.7	0.5	80
Skyla (13.5 mg LNG)	0.4	0.3	
Kyleena (19.5 mg LNG)	0.2	0.2	
Liletta (52 mg LNG)	0.1	0.1	
Nexplanon	0.1	0.1	89
Tubal occlusion	0.5	0.5	100
Vasectomy	0.15	0.1	100
Emergency contraceptives: Use of emergency contraceptive pills or placement of a copper intrauterine contraceptive after unprotected intercourse substantially reduces the risk of pregnancy.			
Lactational amenorrhea method: LAM is a highly effective, **temporary** method of contraception.[¶¶]			

Estimates of the probability of pregnancy during the first year of typical use for fertility awareness-based methods, withdrawal, the external condom, the pill, and Depo-Provera are taken from the 2006 to 2010 National Survey of Family Growth (NSFG) corrected for under-reporting of abortion.

LNG: levonorgestrel; LAM: lactational amenorrhea method; FABM: fertility awareness-based methods; NSFG: National Survey of Family Growth; LH: luteinizing hormone.

* Among typical couples who initiate use of a method (not necessarily for the first time), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any reason other than pregnancy. Data from United States populations.

¶ Among couples who initiate use of a method (not necessarily for the first time) and who use it perfectly (both consistently and correctly), the percentage who experience an accidental pregnancy during the first year if they do not stop use for any other reason.

Δ Among couples attempting to avoid pregnancy, the percentage who continue to use a method for 1 year.

◇ This estimate represents the percentage who would become pregnant within 1 year among women now relying on reversible methods of contraception if they abandoned contraception altogether.

§ 150 mg gel, 100 mg gel, 100 mg suppository, 100 mg film.

¥ Without spermicides.

‡ With spermicidal cream or jelly.

† Approximately 80% of segments of FABM use in the 2006 to 2010 NSFG were reported as calendar rhythm. Specific FABM methods are too uncommonly used in the United States to permit calculation of typical use failure rates for each using NSFG data; rates provided for individual methods are derived from clinical studies. The Ovulation and TwoDay methods are based on evaluation of cervical mucus. The Standard Days method avoids intercourse on cycle days 8 through 19. Natural Cycles is a fertility app that requires user input of basal body temperature (BBT) recordings and dates of menstruation and optional LH urinary test results. The Symptothermal method is a double-check method based on evaluation of cervical mucus to determine the first fertile day and evaluation of cervical mucus and temperature to determine the last fertile day.

** All of these estimates are low, below 1%, and we caution readers not to put any emphasis on the differences among these very small probabilities.

¶¶ However, to maintain effective protection against pregnancy, another method of contraception must be used as soon as menstruation resumes, the frequency or duration of breastfeeds is reduced, bottle feeds are introduced, or the baby reaches 6 months of age.

Graphic 120134 Version 6.0

Potential noncontraceptive benefits of cyclic estrogen-progestin contraceptives

• Reduction in dysmenorrhea
• Reduction in pelvic pain related to endometriosis
• Reduction of menorrhagia, with improvement in iron deficiency anemia related to blood loss
• Reduction in risk of ectopic pregnancy
• Reduction in symptoms associated with premenstrual syndrome and premenstrual dysphoric disorder
• Reduction in risk of benign breast disease
• Reduction in development of new ovarian cysts (true for higher dose estrogen pills only, which suppress ovulation), but no effect on existing ovarian cysts
• Reduction in ovarian cancer, including some hereditary forms, such as those associated with mutations in the *BRCA1* or *BRCA2* gene, presumably due to inhibition of ovarian stimulation
• Reduction in endometrial cancer, due to the progestin effect
• Reduction in colorectal cancer in current users
• Reduction in moderate acne
• Reduction in hirsutism
• More regular menstrual cycles

In addition, there may be a reduction in postmenopausal hip fracture risk for women who use estrogen-containing contraceptives in their 40s. Also, extended cycle or continuous estrogen-progestin contraception can reduce symptoms of menstrual migraine.

Graphic 82147 Version 3.0

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

Graphic 87416 Version 1.0

Level of androgenic activity of progestins in contraceptive pills

Level of activity	Generic name(s)
High	Norgestrel
	Levonorgestrel
Middle	Norethindrone
	Norethindrone acetate
Low	Ethynodiol
	Norgestimate
	Desogestrel
	Drospirenone
	Dienogest

Graphic 78782 Version 8.0

How to start contraception

Contraceptive method	When to start (if the provider is reasonably certain that the woman is not pregnant)	Additional contraception (ie, back-up) needed	Examinations or tests needed before initiation*
Copper 380 mm^2 IUD	Anytime	Not needed[¶]	Bimanual examination and cervical inspection[Δ]
Levonorgestrel 52 mg, 19.5 mg, and 13.5 mg IUDs	Anytime	▪ 52 mg IUD: Not needed[¶] ▪ 19.5 mg or 13.5 mg IUD: If inserted >7 days after menses started, use back-up method or abstain for 7 days	Bimanual examination and cervical inspection[Δ]
Etonogestrel implant	Anytime	If >5 days after menses started, use back-up method or abstain for 7 days	None
Injectable	Anytime	If >7 days after menses started, use back-up method or abstain for 7 days	None
Combined hormonal contraceptive	Anytime	If >5 days after menses started, use back-up method or abstain for 7 days	Blood pressure measurement
Progestin-only pill	Anytime	If >5 days after menses started, use back-up method or abstain for 2 days	None

IUD: intrauterine device; BMI: body mass index; STD: sexually transmitted disease; CDC: Centers for Disease Control and Prevention.

* Weight (BMI) measurement is not needed to determine medical eligibility for any methods of contraception, because all methods can be used (United States Medical Eligibility Criteria for Contraceptive Use 2010, US MEC 1) or generally can be used (US MEC 2) among obese women. However, measuring weight and calculating BMI (weight [kg]/height [m^2]) at baseline might be helpful for monitoring any changes and counseling women who might be concerned about weight change perceived to be associated with their contraceptive method.

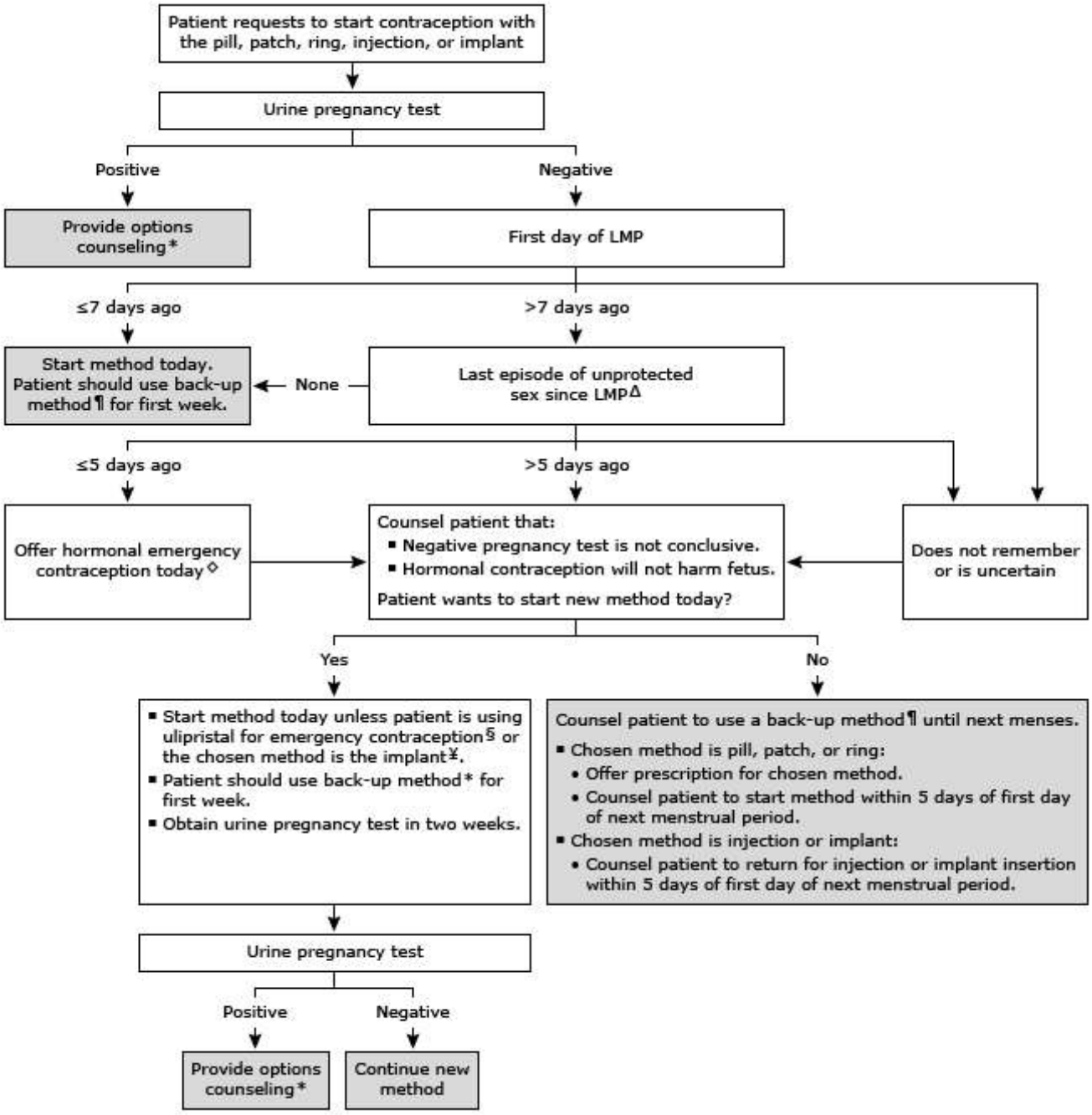
¶ The copper 380 mm^2 and levonorgestrel 52 mg IUDs both act as emergency contraception and therefore do not require additional contraception.

Δ Most women do not require additional STD screening at the time of IUD insertion if they have already been screened according to CDC's STD Treatment Guidelines (available at http://www.cdc.gov/std/treatment). If a woman has not been screened according to guidelines, screening can be performed at the time of IUD insertion, and insertion should not be delayed. Women with purulent cervicitis or current chlamydial infection or gonorrhea should not undergo IUD insertion (US MEC 4). Women who have a very high individual likelihood of STD exposure (eg, those with a currently infected partner) generally should not undergo IUD insertion (US MEC 3). For these women, IUD insertion should be delayed until appropriate testing and treatment occurs.

Reproduced from: US Selected Practice Recommendations for Contraceptive Use, 2013: Adapted from the World Health Organization Selected Practice Recommendations for Contraceptive Use, 2nd ed. MMWR Morb Mortal Wkly Rep 2013; 62:1.

Graphic 89825 Version 8.0

Quick-start (same-day start) approach to initiation of new birth control method: Pill, patch, ring, DMPA injection, implant



DMPA: depot medroxyprogesterone acetate; LMP: last menstrual period.

* Refer to UpToDate content on early pregnancy and pregnancy termination.

¶ Patient should use a barrier back-up method such as condoms for the first week after starting a new method.

Δ Unprotected sex includes episodes of sex in which a method of contraception was used but may not have been effective (eg, breakage of condom, multiple skipped pills).

◇ Refer to UpToDate content on emergency contraception.

§ For women using ulipristal for emergency contraception, progestin-containing contraception (ie, the pill, patch, ring, injection, and implant) should not be used for 5 days following ulipristal. For

women taking levonorgestrel or combined estrogen-progestin emergency contraception, the new contraceptive method can be started after the emergency contraception. ◇

¥ If the patient would like the contraceptive implant, some providers prefer to offer a single injection of DMPA today and ask the patient to return for the implant within 5 days of the first day of her next menstrual period (to avoid the need for implant removal if the repeat urine pregnancy test is positive).

Adapted from: Quick Start Algorithm for Hormonal Contraception. RHEDI/The Center for Reproductive Health Education In Family Medicine, Montefiore Medical Center (Accessed on July 7, 2016).

Graphic 56863 Version 11.0

Checklist used to assess the possibility of pregnancy

The provider can be reasonably certain that the patient is not pregnant if the patient has no symptoms or signs of pregnancy and meets ANY of the following criteria:
☐ The patient has not had intercourse since last normal menses.
☐ The patient has been correctly and consistently using a reliable method of contraception.
☐ The patient is within 7 days from the first day of menstrual bleeding.
☐ The patient is within 4 weeks postpartum (for nonlactating patients).
☐ The patient is within the first 7 days postabortion or miscarriage.
☐ The patient is fully or nearly fully breastfeeding, amenorrheic, and less than 6 months postpartum.

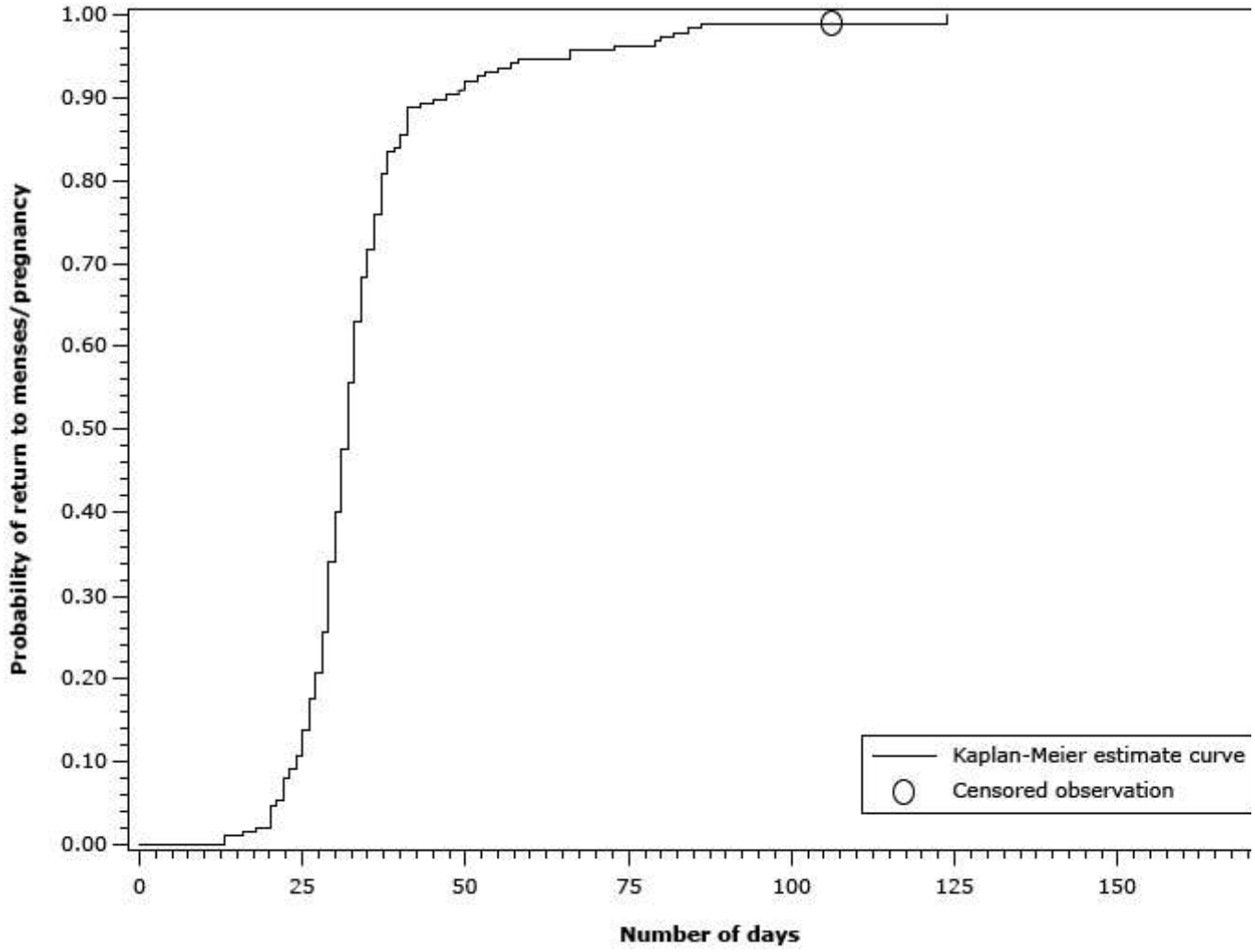
A systematic review of studies evaluating the performance of a pregnancy checklist compared with urine pregnancy test to rule out pregnancy concluded the negative predictive value of a checklist similar to the one above was 99 to 100%.

Data from:

1. *Tepper NK, Marchbanks PA, Curtis KM. Use of a checklist to rule out pregnancy: A systematic review. Contraception 2013; 87:661.*
2. *Curtis KM, Tepper NK, Jatlaoui TC, et al. United States Medical Eligibility Criteria for Contraceptive Use, 2016. MMWR Recomm Rep 2016; 65:1.*

Graphic 67567 Version 19.0

Time to return to spontaneous menses or pregnancy: Kaplan-Meier survival function estimates in the completer population



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Contributor Disclosures

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