CONTRACEPTION

The most common goal of contraception is the prevention of pregnancy. However, some patients use contraceptive methods for other benefits. Contraceptives are usually classifies as *hormonal* and *nonhormonal* contraceptives. Others classified them as *oral* and *nonoral* contraceptives.

❖ HORMONAL CONTRACEPTION PHARMACOLOGY

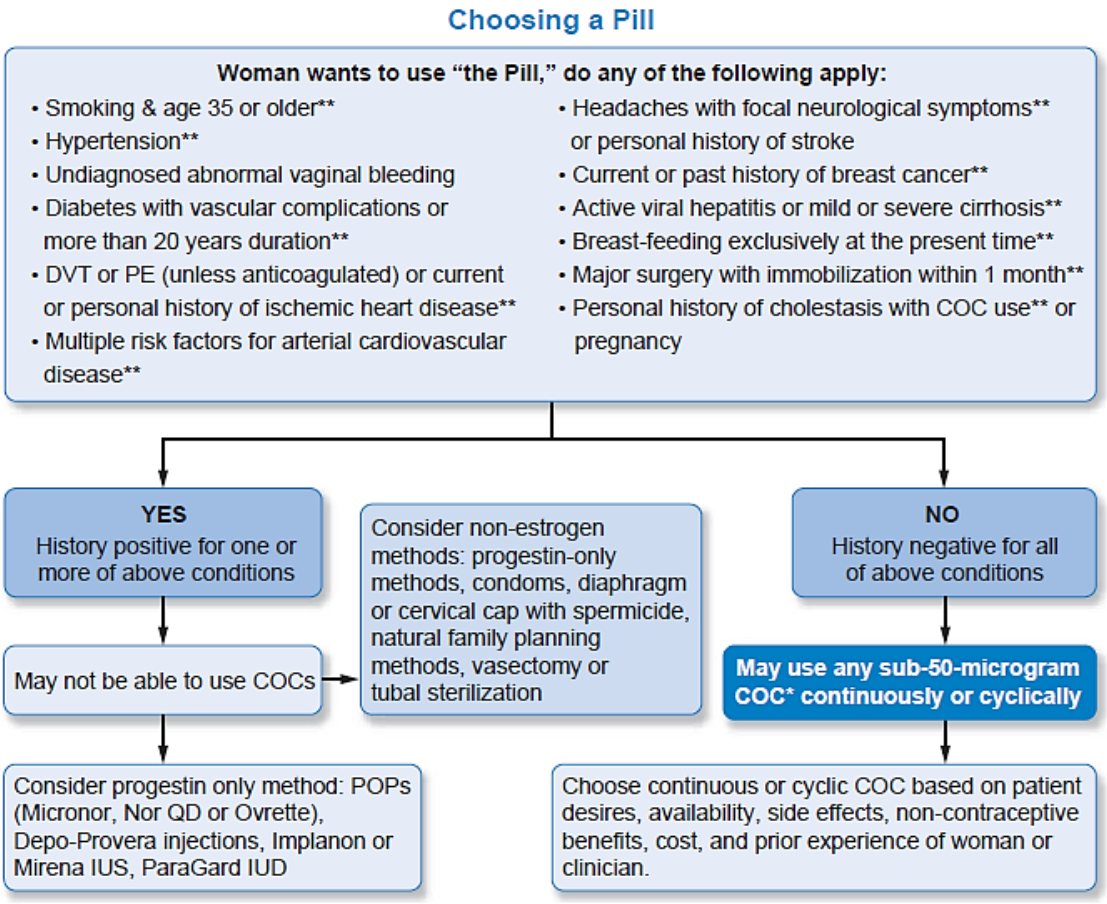
Hormonal contraceptives include combinations of estrogens and progestins known as *combination hormonal contraceptives* (CHCs) or *progestin-only contraceptives*. The primary mechanism by which CHCs prevent pregnancy is through inhibition of ovulation. Estrogens prevent the development of the dominant follicle by suppressing follicle stimulating hormone (FSH) secretion and stabilize the endometrial lining to minimize breakthrough bleeding. Progestins prevent ovulation by suppressing luteinizing hormone (LH) secretion. Ovulation is prevented by this suppression of the midcycle surge of both FSH and LH and mimics the physiologic changes that occur during pregnancy.

Progestin-only contraceptives hamper the transport of sperm through the cervical canal by thickening cervical mucus and causing alterations in the endometrial lining (so that it is not favorable for implantation) and in the fallopian tubes (affecting ovum transport).

A. HORMONAL ORAL CONTRACEPTIVES

1. Oral Contraceptives (Combination)

Combined oral contraceptives (COCs) contain a synthetic estrogen and one of several steroids with progestational activity. Most oral contraceptives contain one of three types of estrogen: *ethinyl estradiol (EE)*, which is pharmacologically active; *mestranol*, which is converted by the liver to EE; or *estradiol valerate*, which is metabolized to estradiol and valeric acid. Many different progestins are found in the various oral contraceptives. These include *norethindrone, norethindrone acetate, ethynodiol diacetate, norgestrel, levonorgestrel, desogestrel, norgestimate, drospirenone, and dienogest*. Doses of EE generally range from 10 to 50 mcg with 10- to 25-mcg formulations considered very low dose, 30- to 35-mcg formulations, low dose, and 50-mcg formulations, high dose.



❖ Length of Active Hormone: 21-, 24-, Or 28 Day

The COCs are available in a variety of cycle lengths. The most common is the 28-day pack that contains 21 days of active pills (pills that contain estrogen and progestin) followed by 7 days of placebo pills. Some newer products contain 24 days of active pills followed by 4 days of placebo as they may shorten menses and minimize the hormonal withdrawal side effects (e.g., headaches, mood changes) that some women experience during the placebo week. The 21-day pill packs contain only the active pills. Most patients are instructed to take one pill daily for 21 days and then take nothing for 1 week. Many clinicians prefer the use of 28-day pill packs to minimize confusion. After taking the last pill of a 28-day pack, the patient should begin a new pack the next day.

❖ Multiphasic Oral Contraceptives

COCs are available in monophasic, biphasic, triphasic, and quadriphasic preparations. Monophasic preparations contain fixed doses of estrogen and progestin in each active pill. Although all four preparations contain both estrogens and progestins, biphasic, triphasic, and quadriphasic preparations contain varying proportions of one or both hormones during the pill cycle. These preparations were introduced to reduce a patient's cumulative exposure to progestins, as well as to mimic more closely the hormonal changes of the menstrual cycle.

❖ When to Start Oral Contraceptives

Female should start the first cycle of COCs according to the manufacturer's package instructions or according to one of the following recommendations:

Quick start: Take the first COC tablet as soon as possible regardless of cycle day.

Day 1 start: Take the first tablet in the COC pack on the first day of menses.

Sunday start: Take the first tablet in the COC pack on the first Sunday after the beginning of menstruation. If menses begins on Sunday, start that day.

❖ COC Administration and Missed Dose Instructions

Female should take her COC at the same time each day. For the majority of COCs, most manufacturers recommend that if she forgets to take one pill, she should take two pills on the day she remembers (e.g., if she forgets her pill on Monday, she should take two pills on Tuesday). Then she should take the remaining pills as usual. A backup method of contraception is not necessary.

If she misses two pills in a row in week 1 or 2 of her pack, she must take two pills on the day she remembers and two pills the next day. She should use an alternative method of contraception for 7 days after missing the pills and may consider emergency contraception.

If a woman misses two pills in a row during the third week (for day 1 starters), she must discard the rest of the pack, start a new pack on that same day, and use an alternative contraceptive method for 7 days. For Sunday starters, she should keep taking one pill every day until Sunday, then start a new pack on Sunday. She must use an alternative method of contraception for 7 days after missing the pills and may consider emergency contraception. She may miss her menstrual period this month.

If a woman misses three or more pills in a row during the first 3 weeks (for day 1 starters), she must discard the rest of her pack, start a new pack that same day, and use an alternative method of contraception for 7 days; Sunday starters should keep taking one pill every day until Sunday, start a new pack on Sunday, and use an alternative method of contraception for 7 days after missing the pills, and they may consider emergency contraception. Women may not have a menstrual period this month.

❖ Noncontraceptive Benefits of Combination Oral Contraceptives

In addition to preventing pregnancy, there are several noncontraceptive benefits associated with the use of COCs.

- *Reduction in the risk of endometrial cancer*
- *Reduction in the risk of ovarian cancer*
- *Improved regulation of menstruation and reduction in the risk of anemia***:** Women who take oral contraceptives typically experience more regular menstrual cycles with less cramping and dysmenorrhea, have a smaller volume of menstruum and

experience fewer days of menstruation each month and consequently experience less blood loss with each menstrual period. In addition, some COC formulations contain iron, which may also minimize the risk for anemia.

- *Reduction in the risk of fetal neural tube defects*: COC formulations that contain a source of folate in every pill are also available.
- *Relief from symptoms associated with premenstrual dysphoric disorder (PMDD)*: These agents are most effective at targeting the physical symptoms associated with the disorder and less effective in treating mood-related symptoms.
- *Relief of benign breast disease*: Women who use oral contraceptives are less likely to develop benign breast cysts or fibroadenomas and are less likely to experience progression of such conditions.
- *Prevention of ovarian cysts*: Because oral contraceptives suppress ovarian stimulation, women who take them are less likely to develop ovarian cysts.
- *Decrease in symptoms related to endometriosis*: COC use has been linked to a decreased incidence of symptomatic endometriosis.
- *Improvement in acne control*: All COCs can improve acne by increasing the quantity of sex hormone–binding globulin and thereby decreasing free testosterone concentrations.

❖ **Potential Risks of Combination Oral Contraceptives**

Although there are many noncontraceptive benefits associated with the use of COCs, their use is not without risk or potential for adverse effects.

- *Cardiovascular events and hypertension:* Hypertension secondary to oral contraceptive use is thought to occur in up to 3% of women and is believed to be attributed to the effect that estrogens and progestins can have on aldosterone activity. Given this and the risk for cardiovascular events, women should have their blood pressure checked prior to initiating oral contraceptives, as well as periodically throughout oral contraceptive use. If significant elevations in blood pressure are noted, oral contraceptives should be discontinued.
- *Venous thromboembolism:* It is believed that the estrogen component of COCs stimulates enhanced hepatic production of clotting factors. Contraceptive users at greatest risk for the development of venous thromboembolism include those who are obese, smoke, have hypertension, have diabetes complicated by end-organ damage, are immobile, have experienced recent trauma or surgery, or have a history of prior thromboembolism.

  In general, progestin-only contraceptives are preferred for women who are at increased risk of cardiovascular or thromboembolic complications, including women with a prior history of thromboembolic disease.

- *Gallbladder disease:* In women with preexisting gallstones, low-dose estrogen-containing oral contraceptives may enhance the potential for the development of symptomatic gallbladder disease and may worsen existing gallbladder disease. COCs containing estrogen should be used with caution in patients with a history of gallbladder disease.
- *Hepatic tumors:* Long-term use of high-dose oral contraceptives has been associated with the development of benign liver tumors. Because even benign liver tumors may pose significant risk to the patient, oral contraceptives should be discontinued if liver enlargement is noted on physical examination. In cases of hepatoma (malignancy), the use of COCs is contraindicated.
- *Cervical cancer:* There appears to be an increased risk for the development of cervical cancer among long-term users of oral contraceptives.

❖ **Adverse Effects of Oral Contraceptives**

Common complaints with COCs include headaches, nausea, vomiting, mastalgia, and weight gain. Between 30% and 50% of women complain of breakthrough bleeding or spotting when oral contraceptives are initiated. These side effects tend to resolve by the third or fourth cycle. Many of the side effects of COCs may be minimized by adjusting the estrogen or progestin content of the preparation.

❖ **Drug Interactions with Oral Contraceptives**

EE is metabolized in the liver primarily via cytochrome P-450 (CYP450) 3A4. When reviewing drug interactions of oral contraceptives, *clinicians should be aware of the many drugs that may potentially interact with contraceptives—especially those that may reduce the effectiveness of contraceptives.*

2. Progestin-Only Pill (Minipill)

The minipill is devoid of some of the nuisance side effects caused by estrogen (e.g., headaches, chloasma). More importantly, estrogen-mediated hypertension and clotting factor changes will be avoided. Minipills also have noncontraceptive benefits, including decreased dysmenorrhea and bleeding and possible protection against pelvic inflammatory disease (PID) and endometrial cancer. Women may also choose them because they are not estrogen containing and fertility returns rapidly after discontinuation.

These products have also been found safe to use in women who are nursing, so they are a viable option for women who breast-feed and desire hormonal contraception. In such patients, it should not be initiated until 6 weeks postpartum. Spotting does not subside in some women, and this is a common cause for discontinuation. These products should be taken at the same time every day, and there is no pill free or hormone-free period.

B. HORMONAL NONORAL CONTRACEPTIVES

As an alternative to oral contraceptive pills, which must be taken daily in order to reliably prevent pregnancy, nonoral contraceptives in the form of transdermal, transvaginal, and injectable preparations are available and offer patients safe and effective alternatives to the pills for prevention of pregnancy. These formulations also do not require daily administration, making them more convenient than the pill formulations.

1. Contraceptive Patch

The contraceptive patch (Ortho Evra) contains 6 mg of norelgestromin and 750 mcg of EE. It was originally formulated to transdermally deliver 150 mcg of norelgestromin and 20 mcg of EE daily into the systemic circulation. The patch is a 1.75-inch square with rounded corners and is beige and thin. One patch is applied each week for three consecutive weeks for a total of three patches used, followed by 1 week with no patch. Then this cycle is repeated. Menses should begin during the patch-free week. The contraceptive patch may be worn on the buttock, abdomen, upper torso, or upper outer arm. The patch should not be applied to the breasts to prevent direct administration of estradiol to the breast tissue.

The patch may be started using the quick, Sunday, or day 1 start method.

2. Contraceptive Ring

The contraceptive ring (NuvaRing) delivers 120 mcg of etonogestrel and 15 mcg of EE daily through the vaginal mucosa for the prevention of ovulation. The ring is flexible, transparent, and has a diameter of just over 2 inches. The ring is inserted vaginally and kept in place for 3 weeks in a row. After 3 weeks, the ring is removed for 1 week, and then a new ring is inserted.

The contraceptive vaginal ring should be inserted anytime during the first 5 days of the menstrual cycle or inserted using the quick start method.

3. Injectable Medroxyprogesterone Acetate

Depo-Provera is a progestin-only, injectable contraceptive that contains depot medroxyprogesterone acetate. Depo-Provera is administered intramuscularly as a 150-mg injection once every 3 months. Package inserts instruct the patient to begin the injectable MPA methods in the first 5 days of her menses.

An advantage of Depo-Provera is that it provides an estrogen-free method of contraception. Depo-Provera is extremely effective in preventing pregnancy. However, the incidence of menstrual irregularities (including amenorrhea) and weight gain appears to be much greater than that seen with COCs. The use of Depo-Provera also has been demonstrated to result in significant loss of bone mineral

density. It is important to note that on discontinuation of Depo-Provera, the return of fertility can be delayed by approximately 10 to 12 months (range 4–31 months).

4. Subdermal Implant

The contraceptive implant (Nexplanon) contains 68 mg of etonogestrel in a single, thin, radiopaque, rod. The rod is inserted subdermally in the upper inner arm using a needle and a local anesthetic. Once inserted, the implant is effective for up to 3 years. Nexplanon should be inserted during the first 5 days of menses, and no backup contraception is required. A small incision is required to remove the implant.

C. INTRAUTERINE DEVICE (IUD) AND INTRAUTERINE SYSTEM (IUS) (Long-Acting Reversible Contraception (LARC))

The ParaGard T 380A *(copper)* IUD has a polyethylene body that is wound with copper wire. Once inserted, the copper IUD may be left in place for 10 years. The Mirena, Skyla, Kyleena, and Liletta IUSs also have polyethylene bodies, with *levonorgestrel* reservoirs in the vertical stem of the T that provide levonorgestrel daily. Mirena and Kyleena are effective for 5 years. Skyla and Liletta are effective for 3 years.

Possible mechanisms of action for copper IUDs include prevention of fertilization and implantation and the copper interfering with sperm transport, viability, or number. The levonorgestrel IUS is believed to work by thickening the cervical mucus, preventing sperm from entering the uterus, altering the endometrial lining, preventing ovulation, and altering sperm activity.

Contraindications to the use of progestin-containing LARC products include (a) known or suspected pregnancy, (b) hepatic tumors or active liver disease, (c) undiagnosed abnormal genital bleeding, (d) known or suspected carcinoma of the breast or personal history of breast cancer, (e) history of thrombosis or thromboembolic disorders, and (f) hypersensitivity to any components of the products. Evaluation of the patient is essential because IUDs cannot be used in the following situations: (a) anatomically abnormal or distorted uterine cavity, (b) acute pelvic inflammatory disease (PID) or history of PID unless there has been a subsequent intrauterine pregnancy (c) postpartum endometritis or infected abortion in the past 3 months, (d) known or suspected uterine or cervical malignancy, (e) untreated acute cervicitis, (f) previously inserted IUD still in place, (g) increased susceptibility to pelvic infections, and (h) Wilson disease (Paragard T 380A only).

The most common adverse effects are abdominal/pelvic cramping, abnormal uterine bleeding, and expulsion of the device. Other side effects seen are ectopic pregnancy, sepsis, PID, embedment of the device, uterine or cervical perforation, and ovarian cysts.

D. OTHER NONHORMONAL CONTRACEPTION

⇨ Barrier Contraceptives

Although barrier contraceptives are associated with far fewer adverse effects compared with hormonal contraceptives, their efficacy is highly user-dependent and are associated with much higher unintended pregnancy rates than hormonal contraceptives.

1. Diaphragms and Cervical Caps

Diaphragms and cervical caps are dome-shaped rubber caps that provide barrier protection during intercourse. Both diaphragms and cervical caps require fitting by a health care professional. Diaphragms or cervical caps typically can be placed over the cervix as much as 6 hours prior to intercourse. They must be left in place for at least 6 hours after intercourse before they can be removed. Diaphragms should not be left in place longer than 24 hours, and smaller cervical caps should not be left in place longer than 48 hours owing to the risk of toxic shock syndrome (TSS). Diaphragms and cervical caps are used along with spermicides to prevent pregnancy.

2. Spermicides

Nonoxynol-9, a surfactant that destroys the cell membranes of sperm, is the most commonly used spermicide. Nonoxynol-9 is available in a variety of forms, including a cream, foam, film, gel, suppository, and tablet. Spermicides may be used alone, with a barrier method, or adjunctively with other forms of contraceptives to provide additional protection against unwanted pregnancy. To be used most effectively, spermicides must be placed in the vagina not more than 1 hour prior to sexual intercourse, and they must come in contact with the cervix.

3. Condoms

Condoms, which are available for both male and female use, act as physical barriers to prevent sperm from coming into contact with ova. Condoms are easy to use, available without a prescription, and inexpensive. Most condoms are made of latex. When used correctly, condoms can be very effective in prevention of unwanted pregnancy.

4. Sponge

The Today sponge is a small, pillow-shaped polyurethane sponge impregnated with nonoxynol-9. It is an over-the counter barrier contraceptive that has been shown to be generally less effective at preventing pregnancy than diaphragms. The sponge is moistened with water and then is inserted and placed over the cervix for up to 6 hours prior to sexual intercourse. The sponge then is left in place for at least 6 hours following intercourse. Although the sponge maintains efficacy for 24 hours (even if intercourse is repeated), as with diaphragms, the sponge should be removed after 24 hours owing to the risk of TSS.

E. EMERGENCY CONTRACEPTION

Emergency contraception (EC), also referred to as the morning-after pill, is postcoital contraception useful for women who did not use a contraceptive (e.g., forgot, were assaulted) or whose method failed (e.g., broken condom, missed pill).

Emergency contraceptive pills (ECPs) are available in a variety of formulations known as *progestin-only*, *Yuzpe*, and *selective progesterone receptor modulators*.

Currently, the one dose progestin-only (levonorgestrel 1.5 mg) ECPs are available over-the-counter to all ages. The one tablet should be taken within 72 hours of unprotected intercourse according the package labeling.

Progestin-only ECPs reduce the risk of pregnancy by a few potential mechanisms: preventing ovulation, preventing fertilization, or preventing implantation. The most common side effects with ECPs are nausea and vomiting.

As an alternative to progestin-only ECPs, regular COCs may be used as long as they contain levonorgestrel or norgestrel as the progestin. This is known as the Yuzpe method, which consists of high-dose progestin and high-dose estrogen. There are no marketed formulations of this method. Depending on the brand of COCs used, a differing number of pills are taken within 120 hours of unprotected intercourse as two separate doses 12 hours apart. Compared with progestin-only ECPs, the Yuzpe method is associated with higher incidence of nausea and vomiting, and patients may wish to take an antiemetic before each dose.

A newer ECP classified as an oral selective progesterone receptor modulator (SPRM), ulipristal acetate (ella), was approved for use in the United States. The 30-mg oral tablet should be taken within 120 hours of unprotected intercourse. It is available by prescription only. It has progesterone receptor antagonist and agonist effects; however, its main mechanism is through receptor antagonism at the uterus, cervix, hypothalamus, and ovaries, thus preventing ovulation even after the LH surge, which progestin-only ECPs may not do.