Pharmacist's Letter
Online Continuing Education and Webinars

Pharmacology of Hormonal Contraceptives

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Accreditation, Goals and Objectives

Course Accreditation Information, Goals and Objectives

> Katie is a 23-year-old patient who is picking up a prescription for an oral combined hormonal contraceptive. She has been taking the same medication for the past six months and admits that she has missed some days here and there. She knows it's important not to miss any days but she doesn't really know why. She wonders how this medication works anyway. How would you explain this to Katie? What are some other forms of hormonal contraceptives and how do they work?

Introduction

Unintended pregnancy accounts for about 50% of all pregnancies, and costs the U.S. an estimated 11.1 billion dollars each year.[1,2] Over the past several years, the rate of unintended pregnancies hasn't substantially changed.[2,3] This is concerning because individuals with unintended pregnancies might be more likely to smoke or drink alcohol during pregnancy, have depression, and use less prenatal care.[4] Reducing the rate of unintended pregnancies is a national public health goal. In fact, an objective of the Department of Health and Human Services' Healthy People 2020 campaign is to reduce unintended pregnancy by 10% by 2020.[5]

> An unintended pregnancy can be categorized as either a mistimed or unwanted pregnancy. Mistimed refers to a scenario where an individual wants to get pregnant at some point in the future, but not at the time it actually occurs. Unwanted refers to a scenario where an individual does not want to get pregnant at any point in the future, but gets pregnant anyway. An intended pregnancy is considered to be desired at the time it occurred.[6]

There are several reasons for the high rate of unintended pregnancies, including cost and access to contraceptive methods.[3] Even when reversible contraceptive methods are used, about 12% of females still have unintended pregnancies.[5] Hormonal contraceptives are a popular reversible contraceptive method and can be very effective, if used correctly. Pharmacists play a huge role in helping to educate patients on the different hormonal contraceptives available and how they work so that patients can make informed decisions when choosing a contraceptive method.

> Appropriately trained pharmacists are able to prescribe some hormonal contraceptive products in some states, with many additional states looking to pass similar legislation.[7]

Menstrual Cycle

In order to understand how hormonal contraceptives work, it's important to first understand the menstrual cycle. The menstrual cycle usually begins by the time a patient turns twelve but can start as early as eight years old and as late as 15.[8] Menstruation lasts until menopause, usually around age 50.[9] The menstrual cycle can be divided into three phases: follicular (preovulatory), ovulatory, and luteal (postovulatory). The follicular phase begins with day one of the menstrual cycle, which coincides with the first day of menstrual bleeding. This phase lasts about 12 to 14 days for most, and ends with the ovulatory phase where a mature egg (ovum) is released from an ovary. The time after ovulation is referred to as the luteal phase which usually lasts around 14 days. The average menstrual cycle length is 28 days. But this can range from 21 to 40 days.[9]

Hormones secreted by the hypothalamus, anterior pituitary gland, and the ovaries are what drive the menstrual cycle. The hypothalamus secretes gonadotropin-releasing hormone (GnRH) in pulses. GnRH works on the anterior pituitary gland to stimulate the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH are responsible for the development and release of a mature ovum.[9]

> What are the different phases of the menstrual cycle? What is happening during each of these phases? How do hormonal contraceptives interrupt the normal menstrual cycle to prevent pregnancy?

Follicular Phase

Day one of the follicular phase (and day one of the menstrual cycle) begins with menstruation.[9] During menstruation, the endometrial lining that grows in preparation for a fertilized egg sloughs off if fertilization doesn't occur. At the same time that the endometrial lining is shedding, FSH

levels rise slightly. FSH promotes the growth of follicles. Follicles grow in the ovaries and are responsible for releasing a mature egg during ovulation. They also secrete estrogen and progesterone. Between days five and seven of the follicular phase, one follicle becomes dominant. The dominant follicle begins secreting increasing levels of estrogen and progesterone. Estrogen serves as negative feedback to tell the hypothalamus to decrease its release of GnRH which ultimately leads to less FSH being released from the anterior pituitary gland. This causes atresia (degeneration) of the other non-dominant follicles since they need FSH to continue growing. Towards the second half of the follicular phase, estrogen levels continue to increase. Estrogen stops the menstrual flow from the previous cycle and triggers thickening of the endometrial lining to prepare for implantation of a fertilized egg. Estrogen is also responsible for producing thin, watery cervical mucus which helps makes it easier for sperm to move.[9]

Ovulation Phase

Eventually, high levels of estrogen cause a surge of LH to be released.[9] LH causes the final stages of follicular maturation and ovulation. This LH surge occurs about 28 to 32 hours before a follicle ruptures. It is a good predictor for ovulation and is what's measured in ovulation kits. Ovulation occurs when the dominant follicle ruptures and releases an egg into the fallopian tube. Egg fertilization is most successful when sexual intercourse takes place from a couple of days before ovulation, to the day of ovulation.[9] Shortly after the LH surge, estrogen levels begin to drop.

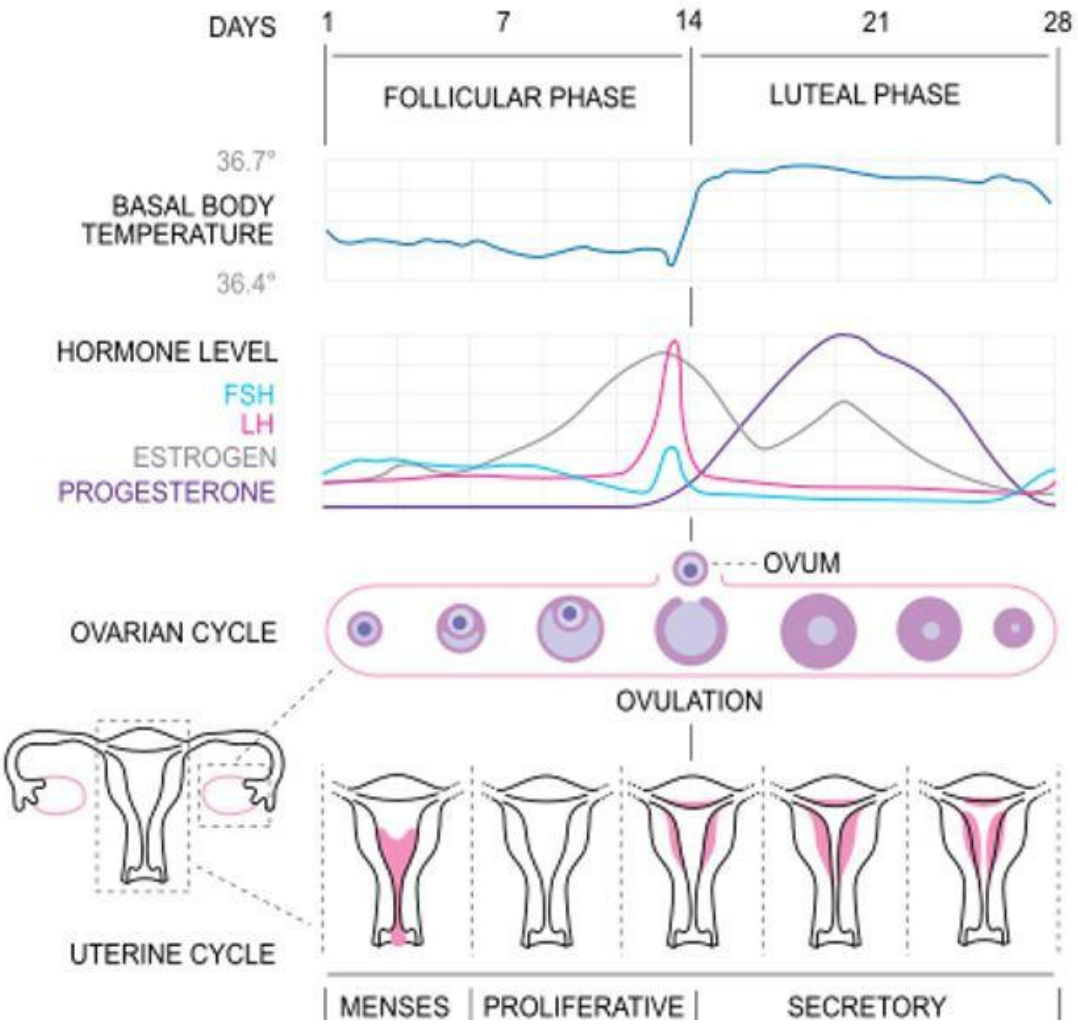
Luteal Phase

The ruptured dominant follicle eventually turns into the corpus luteum.[9] The corpus luteum is a temporary hormone-producing structure that releases progesterone in increasing quantities. It also secretes smaller amounts of estrogen and androgen. Progesterone helps to maintain the endometrial lining and it inhibits the release of GnRH, preventing the development of any new follicles. Progesterone also thickens the cervical mucus, making it harder for sperm and bacteria to enter the uterus. If egg fertilization doesn't occur, the corpus luteum degenerates and levels of progesterone and estrogen fall. The decrease in progesterone levels causes shedding of the endometrial lining and menstruation. The decrease in estrogen and progesterone also removes the negative feedback on the release of GnRH which allows FSH levels to start to rise again. The cycle then begins once again.[9]

If a patient starts taking a combined hormonal contraceptive pill containing estrogen and progestin during the luteal phase, what would happen?

The menstrual cycle would be disrupted. The removal of the endogenous hormones as a result of degeneration of the corpus luteum would be cancelled out by the introduction of exogenous hormones in the form of the oral contraceptive. The presence of exogenous estrogen and progestin will result in continued negative feedback on the hypothalamus. This means less GnRH release, which results in less FSH and LH. Without adequate levels of FSH and LH the menstrual cycle is unable to progress to the follicular phase and ultimately to ovulation. Ovulation is thus prevented.

The Menstrual Cycle[10]



> Which hormones are most dominant during the various phases of the menstrual cycle? How do the levels of these hormones impact what happens during the menstrual cycle?

Hormones Used in Contraceptives

> What are the different kinds of hormonal contraceptives available? What types of hormones do they contain and in what dosage forms are they available? How do these hormones work to prevent pregnancy?

Hormonal contraceptives come in a variety of different presentations. They could be categorized into combination hormonal contraceptives (CHCs) and progestin-only hormonal contraceptives. CHCs are available as an oral pill, transdermal patch, and vaginal ring. Progestin-only contraceptives are available as an oral pill, injection (both intramuscular and subcutaneous), and implant. Additionally, some intrauterine devices (IUDs) contain progestin.

Combined Hormonal Contraceptives

CHCs have several mechanisms of action which aren't all fully understood. However, it's generally believed that their contraceptive effect is primarily via prevention of ovulation.[11] Ovulation is prevented by suppression of the FSH and LH hormones. Combining estrogen and progestin helps prevent ovulation more consistently than either alone. Progestin is thought to have the most pronounced effect on decreasing GnRH release from the hypothalamus, at least when first starting a CHC. Estrogen also appears to contribute to a decrease in GnRH release, but only after using CHCs for a prolonged period of time. Estrogen can also work directly on the anterior pituitary gland to decrease FSH release, which negatively impacts follicular development. Progestins are thought to be responsible for inhibiting the estrogen-induced LH surge, which is responsible for triggering follicular rupture. Although prevention of ovulation is the main mechanism by which CHCs work, changes to the cervical mucus are also thought to contribute to the contraceptive effect of CHCs.[12] Specifically, progestins can cause thickening of the cervical mucus, which makes it more difficult for sperm to enter the uterus and fertilize an egg.[11]

Estrogens

The most commonly used estrogen component in CHCs is ethinyl estradiol. Doses range from 10 to 50 mcg in combined oral contraceptives (COC). The patch releases 35 mcg of ethinyl estradiol per day while the ring releases 13 mcg (*Annovera*) or 15 mcg per day (*NuvaRing*). Estradiol is a natural form of estrogen found in the body. However, when administered orally, it undergoes extensive first-pass metabolism.[11] Adding an ethinyl group (two carbons bonded by a triple bond) to the estradiol molecule increases the potency and makes it more resistant to first-pass metabolism.[11]

Estradiol valerate is another type of estrogen found in COCs. Estradiol valerate is converted in the body to the naturally occurring estradiol. It was hoped that using a product that gets converted to a natural estrogen would decrease the incidence of adverse effects, but this has yet to be proven.[13,14]

Progestins

There are a variety of synthetic progestins that are used in CHCs.[15] The different progestins all have a high affinity for the progesterone receptors, but differ in their affinity for other receptors, such as androgen and glucocorticoid receptors.[16] The contraceptive effects of the various synthetic progestins are mediated by the progestin's activity on the progesterone receptors in the reproductive tissue. On the other hand, many of the side effects of a progestin are due to its activity on other steroid receptors.[17] Based on these affinities and the general timing of when a synthetic progestin was developed, progestins may be categorized into different generations.

Progestins Available in CHCs[9,15]

Progestin Class	Name
First-generation	• Norethindrone • Norethindrone acetate • Ethynodiol diacetate
Second-generation	• Norgestrel • Levonorgestrel
Third-generation	• Norgestimate • Desogestrel
Other	• Drospirenone • Dienogest • Segesterone

"First-" generation progestins include norethindrone and norethindrone acetate. These progestins have affinity for androgen receptors, in addition to progesterone receptors. However, they bind with lower affinity to progesterone and androgen receptors when compared to second-generation progestins. "Second-" generation progestins include levonorgestrel and norgestrel. They are thought to cause less breakthrough bleeding and spotting than the first-generation progestins because they have a higher affinity for progesterone receptors.[15,17] While this difference in affinity for receptor binding does not impact efficacy of the products containing these progestins, it may impact the frequency of side effects. Since second-generation progestins bind with higher affinity to androgen receptors than other progestins, they have more androgenic effects, such as acne, abnormal hair growth (hirsutism), dyslipidemia, and weight gain.[17] "Third-" generation progestins include desogestrel and norgestimate.

Third-generation progestins don't have much activity on the androgen receptors and are therefore associated with less androgenic side effects.[18] Other newer progestins, such as drospirenone and dienogest, have been designed to bind primarily to progesterone receptors with little to no affinity for other steroid receptors. They may even have some antiandrogenic effects.[19]

Common side effects of COCs are caused by excessive or deficient amounts of estrogen or progestin, and the extent of activity of progestin on androgen receptors.[9,20] Based on the predominant symptoms a patient is experiencing, the estrogen or progestin content can be adjusted. For example, in a patient complaining of excessive breast tenderness, a COC with less estrogen can be considered.

Hormone	Too Much	Too Little
Estrogen	Nausea, breast tenderness, headache, bloating, increased blood pressure, melasma (grey-brown patches on the face)	Spotting, breakthrough bleeding early/mid-cycle
Progestin	Breast tenderness, headache, fatigue, mood changes	Breakthrough bleeding late cycle
Androgen	Weight gain, acne, hirsutism, ↑ LDL, ↓ HDL	

Combinations of Estrogens and Progestins

As previously mentioned, CHCs are available as a transdermal patch, vaginal ring, and COCs. The transdermal patch releases 35 mcg of ethinyl estradiol and 150 (U.S.) or 200 mcg (Canada) of norelgestromin daily for three weeks followed by a patch-free week.[21,22] Norelgestromin is the active form of the third-generation progestin, norgestimate. While around one in ten females use the patch, almost half stop using it, primarily because they are not satisfied with it or due to side effects.[23] This may be because the patch provides a higher exposure to estrogen over time compared to the other combined hormonal agents.[24,25]

The vaginal ring releases either 13 mcg (*Annovera*) or 15 mcg (*NuvaRing*) of ethinyl estradiol and 150 mcg of segesterone (*Annovera*) or 120 mcg of etonogestrel (*NuvaRing*) daily for three weeks followed by a ring-free week.[26,27] Etonogestrel is the active metabolite of the third-generation progestin, desogestrel.[25] In contrast to the transdermal patch, the ring provides lower estrogen exposure compared to the other available CHCs, so patients may experience fewer estrogen-related side effects.[25]

COCs come in a variety of different combinations of estrogens and progestins. COCs are available as monophasic, biphasic, triphasic, and quadriphasic formulations, as well as extended- and continuous-cycle formulations. Monophasic COCs are the most common and contain the same amounts of estrogen and progestin for 21 days, typically followed by a seven-day hormone-free interval to mimic a 28-day menstrual cycle (unless it's an extended-cycle regimen). The multiphasic formulations have different amounts of estrogen and progestin typically throughout 21 days, and are also typically followed by a seven-day hormone-free interval. Multiphasic pills were developed in an attempt to better mimic the levels of estrogen and progesterone during the menstrual cycle. However, these pills don't necessarily decrease side effects.[28,29]

The traditional seven-day hormone-free interval was initially designed to mimic the monthly menstrual cycle and to reassure patients that they were not pregnant.[30] This was thought to increase the acceptability of COCs when they were first released into the market.[31] However, the bleeding that occurs is not due to normal physiology.[31] You have probably heard the term "withdrawal bleeding," but what does this really mean? Recall that during the follicular phase of the menstrual cycle, estrogen is responsible for building up and thickening the endometrial lining in preparation for implantation. When using a CHC, the progestin cancels out the effects of the estrogen on the endometrial lining. But during the seven-day hormone-free interval, follicular development can take place during the hormone-free interval due to rising levels of FSH and LH in the absence of exogenous estrogen and progestin. Essentially, the hormone-free interval mimics the first seven days of the follicular phase of the menstrual cycle. Because of this, it's very important that patients do not skip any days of active pills beyond the seven-day hormone-free interval because of the risk of ovulating early. Unopposed endogenous estrogen released by the growing follicles during the seven-day hormone-free interval leads to some thickening of the endometrial lining (although not to the same extent as non-users of CHCs). At the end of that month's cycle, progesterone levels drop at the beginning of the hormone-free interval due to withdrawal of the active pills. This causes "withdrawal bleeding."[31]

Since there is no physiological need to have withdrawal bleeding, and since the hormone-free interval may cause undesirable side effects due to hormone withdrawal, extended-and continuous-cycle regimens have been developed.[32] Extended-cycle regimens provide more days of hormones, with some products providing up to 84 days of hormone-containing pills followed by a seven day hormone-free interval. Continuous-cycle regimens involve taking hormone-containing pills daily throughout the year, with no hormone-free interval.[9] Monophasic COCs can be turned into continuous-cycle regimens by skipping the hormone-free interval week and starting a new pack right away. Both extended- and continuous-cycle COCs are useful for patients with menstrual-related difficulties, such as dysmenorrhea (painful menstruation) or heavy bleeding, or those who prefer not to have monthly bleeding. Extended- and continuous-cycle COCs might help improve contraceptive efficacy in obese patients. Obesity can impact the pharmacokinetics of COCs in many different ways including half-life, time to steady state, bioavailability, clearance, etc.[33] Although the evidence regarding a decrease in efficacy of COCs in obese patients is conflicting, based on pharmacokinetic parameters, it may be better to recommend extended- or continuous-cycle regimens in these patients.[33,34,35,36]

Become familiar with the different types of estrogen and progestin COC combinations. For a detailed chart that includes the various estrogens and progestins and their accompanying doses, along with brand names and manufacturers, refer to our chart, *Comparison of Oral Contraceptives and Non-Oral Alternatives*. To learn more about when to recommend one product over another, review our CE, *Hormonal Contraceptive Selection*.

Combinations of Estrogens and Progestins in COCs		
Type of Regimen	**Estrogen**	**Progestin**
	Ethinyl estradiol 20 mcg	• Levonorgestrel 0.1 mg • Norethindrone acetate 1 mg
	Ethinyl estradiol 30 mcg	• Levonorgestrel 0.15 mg • Norgestrel 0.3 mg • Norethindrone acetate 1.5 mg • Desogestrel 0.15 mg

Monophasic		• Desogestrel 0.15 mg • Drospirenone 3 mg
	Ethinyl estradiol 35 mcg	• Ethynodiol diacetate 1 mg • Norgestimate 0.25 mg • Norethindrone 0.4 mg • Norethindrone 0.5 mg • Norethindrone 1 mg
	Ethinyl estradiol 50 mcg	• Norgestrel 0.5 mg • Ethynodiol diacetate 1 mg
Multiphasic	Ethinyl estradiol 10 to 20 mcg	• Desogestrel 0.15 mg
	Ethinyl estradiol 35 mcg	• Norethindrone acetate 0.5 to 1 mg • Norgestimate 0.18 to 0.25 mg
	Ethinyl estradiol 20 to 35 mcg	• Norethindrone acetate 1 mg
	Ethinyl estradiol 25 mcg	• Norgestimate 0.18 to 0.25 mg • Desogestrel 0.1 to 0.15 mg
	Ethinyl estradiol 30 to 40 mcg	• Levonorgestrel 0.05 to 0.125 mg
	Estradiol valerate 1 to 3mg	• Dienogest 2 to 3 mg
Extended-cycle	Ethinyl estradiol 10 mcg x 26 days	• Norethindrone acetate 1 mg x 24 days
	Ethinyl estradiol 20 mcg x 24 days	• Norethindrone acetate 1 mg x 24 days • Drospirenone 3 mg x 24 days
	Ethinyl estradiol 20 mcg x 84 days then 10 mcg x 7 days	• Levonorgestrel 0.1 mg x 84 days
	Ethinyl estradiol 30 mcg x 84 days	• Levonorgestrel 0.15 mg x 84 days
	Ethinyl estradiol 30 mcg x 84 days then 10 mcg x 7 days	• Levonorgestrel 0.1 mg x 84 days
	Ethinyl estradiol 20 mcg x 42 days, then 25 mcg x 21 days, then 30 mcg x 21 days, then 10 mcg x 7 days	• Levonorgestrel 0.1 mg x 84 days
Continuous-cycle	Ethinyl estradiol 20 mcg all days, no break	• Levonorgestrel 90 mcg all days

What are the different combinations of estrogen and progestin that you see most often with COCs that you dispense? How do you keep all of the different COCs straight?

Progestin-only Contraceptives

Progestin-only contraceptives include progestin-only pills, the depot medroxyprogesterone injection (DMPA), the implant, the levonorgestrel-containing IUD, and emergency contraceptives. Progestins have several mechanisms of action, but the primary actions that help prevent pregnancy are the partial suppression of ovulation and the alteration of the cervical mucus.[12] As previously discussed, progestins inhibit the release of GnRH from the hypothalamus and suppress the LH surge that is needed for ovulation. Without the presence of estrogen to help suppress ovulation, patients are more likely to ovulate while taking progestin-only contraceptives. In fact, the progestin-only pill and the implant block ovulation in only 60% to 80% of cycles.[11] So, the activity on the cervical mucus becomes very important with progestin-only contraceptives.

Progestins create an undesirable environment for sperm motility by decreasing the volume of cervical mucus and increasing cervical mucus viscosity.

Progestin-only contraceptives can also cause changes in the endometrium. Progesterone causes atrophy of the endometrium, which leads to endometrial thinning and an environment that is not welcoming to implantation.[9,12] Despite these actions on the endometrium, it hasn't been proven that progestins prevent pregnancy by inhibiting implantation.[12,37] Current evidence shows that the primary mechanisms of progestins are to stop or disrupt ovulation and prevent the sperm from fertilizing an egg. So, when taking progestin-only contraceptives there should be no fertilized egg to prevent it from attaching to the uterine lining in the first place.[37]

Patients may experience irregular bleeding while taking progestin-only contraceptives more often than with CHCs. There are several potential causes for this irregular bleeding. One contributing factor can be the fact that ovulation can still occur in some patients. As with the normal menstrual cycle, the dominant follicle releases endogenous hormones and this can disrupt the ability of the progestin-only contraceptive to suppress bleeding.[38] Other potential reasons for irregular bleeding could be due to the activity of progestins on the endometrial blood vessels; however, these mechanisms aren't clearly understood.[38]

Progestin-Only Pills

The only available progestin-only pill is norethindrone 350 mcg (*Micronor*, *Jencycla*, etc) taken once a day. This is a much lower dose than what is contained in COCs, which is part of the reason why the progestin-only pill doesn't prevent ovulation as consistently as COCs.[12] While the progestin-only pill is dispensed in four-week packs like most COCs, educate patients that there are no "free" weeks and each pill contains active medication. In other words, a pill will be taken every day with no breaks. This is important to keep in mind because the packaging of these products looks very similar to COCs that have a week of inactive pills. Counsel patients starting the progestin-only pill to take ALL pills in their pack and to start a new pack right after finishing the previous pack. Since the progestin-only pill has such a short half-life, it's also important to let patients know to take the pill at the same time each day; otherwise, the cervical mucus could start to thin, allowing sperm to be more mobile.[39] Tell your patients that taking it more than three hours late can increase the risk of pregnancy. If the progestin-only pill is taken more than three hours late, patients should use backup contraception for at least 48 hours. Because there is less room for error with the progestin-only pill, efficacy with typical use may be reduced in comparison to COCs.[9]

Depot Medroxyprogesterone

Depot medroxyprogesterone, or DMPA, is available as either a subcutaneous (*Depo-subQ Provera 104*) or intramuscular (*Depo-Provera*) injection that is administered every three months. The subcutaneous product contains less progestin (104 mg/0.65 mL) than the intramuscular shot (150 mg/mL). Unlike the progestin-only pill and implant, DMPA is able to achieve higher progestin concentrations which results in more consistent prevention of ovulation.[11] Consistent and sustained exposure to medroxyprogesterone blocks the LH surge. DMPA prevents ovulation so well that patients may even continue to be anovulatory after discontinuing DMPA. For this reason, the prescribing information for DMPA products includes a precaution that it may take longer for patients to get pregnant after discontinuing the injections.[40,41] The median time to conception from the first skipped dose of DMPA is ten months.[9] But you can tell patients that most individuals get pregnant within a year after stopping DMPA.[9]

Like other progestin-only products, patients can experience spotting and breakthrough bleeding initially. But after one year of using DMPA many patients stop having periods. In fact, after twelve months of therapy, 55% of patients reported amenorrhea.[9]

DMPA can potentially cause bone loss, which prompted the U.S. Food and Drug Administration (FDA) to issue a black box warning in 2004.[9] This bone loss seems to be greater with increasing duration of use. The reason bone loss is seen in DMPA but not the other progestin-only contraceptives is thought to be because of the more complete suppression of ovulation. This means there is less endogenous ovarian estrogen production than what you would see with the progestin-only pill or implant. Estrogen protects against bone loss by facilitating vitamin D-related intestinal calcium absorption and suppressing bone resorption.[42] Another potential contributing mechanism for bone loss observed with DMPA is the activity of medroxyprogesterone on glucocorticoid receptors.[43] Medroxyprogesterone has affinity for glucocorticoid receptors and has been found to act as a glucocorticoid receptor agonist in animal models.[43] Glucocorticoids used at high doses for a long period of time have negative effects on bone formation.

Patients may be concerned with the return to fertility after using contraceptives. You can let patients know that although some contraceptive methods can be associated with a slight delay in fertility, this is not sustained in the long term.[44] The average time for a couple to conceive in the general population is six months and this can take up to twelve months for some couples.[44] Most studies looking at the return to fertility evaluate the conception rates at twelve months following discontinuation of the contraceptive method.[44] The 12-month conception rates reported after discontinuing various forms of contraception are:[44,45]

- Progestin-only Pill - 95%
- COCs - 72% to 94%
- Natural Family Planning - 92%
- IUDs - 71% to 92%
- Condoms - 91%
- Progestin Implant - 77% to 81%
- Depot Medroxyprogesterone - 68% to 78%

Be aware that there are no head-to-head trials comparing return to fertility as a primary outcome, so any comparisons you make from this info should be made with caution.[44]

Progestin Implant

The progestin implant contains 68 mg of etonogestrel (*Nexplanon*).[9] It is a single four-centimeter long rod that is inserted (by a trained professional) subdermally, just under the skin of the inner upper arm. Etonogestrel is the same progestin used in one of the vaginal ring contraceptive products (*NuvaRing*), and it is the active metabolite of desogestrel, a third-generation progestin. The implant releases much smaller amounts of progestin when compared to CHCs, with 60 to 70 mcg released daily for the first month, followed by 35 to 45 mcg daily

through the first year, 30 to 40 mcg daily through the second year, and ending with 25 to 30 mcg daily through the third year.[46] The implant is approved for use for up to three years. As with the progestin-only pill, partial ovulation suppression is observed with the implant due to its low dose, so thickening of the cervical mucus is important for inhibiting sperm penetration.[12] Since there are no adherence issues with the implant, efficacy with both perfect and imperfect use is over 99%.[9]

Levonorgestrel-containing IUD

Some IUDs release low doses of the progestin levonorgestrel (*Kyleena*, *Liletta*, *Mirena*, and *Skyla*). IUDs, also known as intrauterine systems, are T-shaped and must be inserted into the uterine cavity by a trained clinician. They have several possible mechanisms for preventing pregnancy including inhibiting sperm migration, and damaging the ovum or disrupting its transport. The IUDs that release levonorgestrel have additional mechanisms of action such as thickening of the cervical mucus and changes to the endometrium.[9,12] For more information on IUDs and other nonhormonal methods of contraception, review our CE, *Helping Patients Navigate Contraceptive Options*.

When helping patients pick a hormonal contraceptive that fits their preferences and lifestyle, it's important to understand how effective different methods of contraception are with perfect use and typical use. Most hormonal contraceptive options are close to 99% effective when used perfectly, which means using the method consistently and correctly according to instructions. Unfortunately, with patient typical use, efficacy decreases as the average person doesn't always use methods correctly or consistently. Compare these rates to the rates of other non-hormonal contraceptive methods, such as condom use and spermicide use.

Estimated Efficacy Rates for Contraceptive Methods[47,48,49]

	Perfect Use	Typical Use
Implant	>99%	>99%
IUD	>99%	>99%
DMPA	>99%	94%
Oral Contraceptives	99%	91%
Patch	99%	91%
Ring	99%	91%
Male Condom	98%	82%
Withdrawal	96%	78%
Female Condom	95%	79%
Diaphragm	94%	88%
Sponge (has never given birth)	91%	88%
Spermicide	82%	72%
Sponge (has given birth)	80%	76%

Emergency Contraception

> A patient comes into your pharmacy and requests to speak to the pharmacist. You make your way over to her and see that she's holding an emergency contraceptive product. She's wondering how this works. How would you advise this patient?

Emergency contraception is used by around one in ten females.[23] The first available method was called the "Yuzpe" regimen. This consisted of taking 100 mcg ethinyl estradiol plus 1 mg norgestrel or 0.5 mg levonorgestrel, repeated twelve hours later.[50] To illustrate, this would be the equivalent of two pills containing ethinyl estradiol 50 mcg/norgestrel 0.5 mg or five pills containing ethinyl estradiol 20 mcg/levonorgestrel 0.1 mg. Because of the high dose of estrogen, the Yuzpe regimen has more side effects than progestin-only emergency contraception, such as vomiting, and has been shown to be less effective than other emergency contraception regimens.[50] This method has fallen out of favor with the availability of better tolerated and more effective methods.

Levonorgestrel is an emergency contraceptive that can be obtained without a prescription. It is available as a 1.5 mg single dose (*Plan B One-Step, Next Choice One Dose, My Way,* etc) and is approved for OTC use in patients of any age. Levonorgestrel's primary function as an emergency contraceptive is to inhibit or delay ovulation.[9] Levonorgestrel may also impair sperm transport and inhibit fertilization through changes to the cervical mucus.[51] There is no data to support that levonorgestrel prevents an already fertilized egg from implanting into the endometrium.[9] Since levonorgestrel exerts its emergency contraceptive effect mainly by inhibiting ovulation, it is most effective when taken before the LH surge, which usually occurs about 28 to 32 hours before ovulation.[9,51] Levonorgestrel appears to lose its inhibitory effect once luteinizing hormone levels start to increase.

> The World Health Organization defines pregnancy as beginning with implantation.[37] According to this definition, preventing a fertilized egg from implanting would be preventing pregnancy. However, there is a belief that human life begins with fertilization. Based on this belief, preventing a fertilized egg from implanting can be seen as a problem for some individuals. Although there's no data to support that levonorgestrel prevents an already fertilized egg from implanting, some people may still be worried about the possibility of implantation prevention. Regardless of your beliefs, it's important to understand the available evidence and be able to share this information with patients. Each patient should be able to make an informed decision that's best for them, based on the facts and their personal beliefs.

Recognize that levonorgestrel won't work as an emergency contraceptive if ovulation has already occurred, so the sooner levonorgestrel is taken the more effective it is. There is only a limited period of time during the menstrual cycle that unprotected sex can lead to pregnancy. Since sperm can live for a maximum of five days in the female reproductive tract, the highest-risk fertile period spans from five days before ovulation to the day of ovulation.[51,52] Fertilization must take place 12 to 24 hours after ovulation because after that time, the egg rapidly deteriorates.[51] Expect that levonorgestrel will prevent about 95% of pregnancies if taken within the first 24 hours. This drops to 50% of pregnancies when used within 72 hours of unprotected intercourse or contraceptive failure.[53] Levonorgestrel emergency contraceptives are approved for use within 72 hours of

72 hours of unprotected intercourse or contraceptive failure. Levonorgestrel emergency contraceptives are approved for use within 72 hours of unprotected intercourse or contraceptive failure.

Ulipristal (*Ella*) is another kind of emergency contraceptive, and is only available with an Rx. It is a hormone modulator versus a traditional hormone. Ulipristal is a selective progesterone receptor modulator that has agonist and antagonist properties. Ulipristal has a direct inhibitory effect on follicular development and release of an egg. Unlike levonorgestrel, ulipristal can delay follicle rupture even when luteinizing hormone levels have started to rise, which may provide an extra couple days of coverage.[51] Ulipristal can be given up to five days after unprotected sex or contraceptive failure.

CDC recently published a recommendation in the U.S. Selected Practice Recommendations (U.S. SPR) for Contraceptive Use regarding when to start regular hormonal contraception after using ulipristal.[54] There is theoretical concern, which is backed up by at least one pharmacodynamic study, that hormonal contraceptives can interfere with the ability of ulipristal to delay ovulation.[55] The interaction is thought to be due to the agonist/antagonist properties of ulipristal. This issue doesn't exist with levonorgestrel emergency contraception, since levonorgestrel is a progesterone receptor agonist.[56] The clinical significance of the interaction with ulipristal and regular hormonal contraception hasn't been proven, but experts and CDC recommend to wait at least five days after taking ulipristal before initiating short-acting hormonal contraceptives (pill, patch, ring).[54] Initiating the injection, implant, and IUDs can be considered at the time of ulipristal use (if being given in a clinic setting) as long as the risk of not starting a regular long-acting hormonal contraception outweighs the risk of decreased efficacy.[54]

For more information on emergency contraception, including the use of copper IUDs, drug interactions, patient weight considerations, and more, check out our chart, *Emergency Contraception: FAQs*.

> How do the different types of progestin-only contraceptives work to prevent pregnancy? What unique features or considerations do each of these formulations have?

Noncontraceptive Benefits of Hormonal Contraception

> Stephanie is a 20-year-old female who comes to your pharmacy complaining of extremely bad menstrual cramps. She is wondering if there is anything stronger than ibuprofen or naproxen that she can get over the counter. You explain that there are other kinds of pain relievers but that ibuprofen or naproxen are probably the best options. Stephanie continues to tell you that she heard birth control can help with bad cramps and asks if that's true. What can you share with Stephanie about the noncontraceptive benefits of birth control?

Many patients are unaware of the noncontraceptive benefits of hormonal contraceptives.[57] Hormonal contraceptives have been found to provide a large number of health benefits including helping with disorders of the menstrual cycle (irregularities, dysmenorrhea, premenstrual symptoms, etc), protecting against various cancers, treating acne, and providing symptom relief from endometriosis. Know which hormonal contraceptives have the mechanisms to provide these noncontraceptive benefits so that you can help patients select the most appropriate therapy.

> For more background information on reproductive issues that hormonal contraceptives can help out with, check out our CE, *Women's Reproductive Health*.

Menstrual Cycle Disorders

Dysmenorrhea, or painful menstruation, is very common, affecting up to 90% of menstruating patients.[58] It is caused by uterine contractions which are triggered by prostaglandins produced by the endometrium. COCs have been found to decrease uterine prostaglandin production and reduce painful menstruation in 70% to 80% of patients.[58] Although COCs have the most data for their ability to decrease dysmenorrhea, any hormonal contraceptive that leads to a reduction or elimination of menstruation is thought to have similar positive benefits.

Irregular menstrual cycles, which can have a number of causes, such as anovulation or irregular ovulation, can be made regular or at least more predictable with CHCs.[58] Counsel patients with irregular bleeding that with CHCs it's possible to continue to experience unscheduled spotting or light bleeding during the first three to six months of therapy. Let them know that this is a common side effect seen with any patient, not just those who had irregular bleeding to begin with. Since ovulation can be inhibited in up to 50% of patients taking the progestin-only pill or using the implant, these might not be the best options for patients hoping to correct their unpredictable bleeding patterns. These products can continue to cause unpredictable bleeding. DMPA on the other hand can lead to a complete elimination of bleeding which some patients may not want.[58]

Heavy uterine bleeding can lead to iron deficiency anemia if it's left untreated.[58] Up to 30% of patients seek treatment for this disorder. While some patients with excessive bleeding may eventually require surgery, hormonal contraceptives or the levonorgestrel-releasing IUD are good first-line options for most. CHCs are able to help reduce bleeding and by doing so can improve heavy uterine bleeding. For example, COCs can help reduce menstrual blood loss by 40% to 50%.[58] This reduction is even more pronounced with extended- and continuous-cycle regimens that can reduce overall bleeding days or even achieve amenorrhea. Progestin-only products can be used for patients in whom CHC or IUD use wouldn't be appropriate.[58]

Premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) can occur in the week or two prior to menses. PMS involves mild mood disturbances and physical symptoms while PMDD is a more severe form of PMS. PMDD, unlike PMS, is characterized by severe mood disorders that adversely impact well-being and social interactions.[59] The approach that appears to be the most helpful with both psychological and physical symptoms of PMS and PMDD is an extended- or continuous-cycle CHC regimen.[58] Some COCs even have FDA-approval for the treatment of PMDD (*Yaz*, *Gianvi*, etc [ethinyl estradiol 20 mcg and drospirenone 3 mg for 24 days]).[60]

Endometriosis

Endometriosis is a condition where the endometrial tissue (the tissue that lines the uterus) grows on the outside of the uterus in other areas of the body, such as the abdomen, the outer surface of the uterus, etc. This condition can lead to severe pelvic pain. Pelvic pain associated with endometriosis can be decreased with CHCs and progestin-only therapies including the levonorgestrel-releasing IUD.[58,61] Similar to dysmenorrhea unrelated to endometriosis, any hormonal contraceptive product that can reduce or eliminate menstruation may be able to help improve pelvic pain with endometriosis. Hormonal contraceptives also can contribute to symptom relief by decreasing the growth of the irregular endometrial tissue. For more information on pharmacologic therapies used for endometriosis, check out our chart, *Drug Treatment for*

Endometriosis.

Treatment of Acne

The hormone-producing bodies of the menstrual cycle, which include the follicles and corpus luteum, secrete androgen in addition to estrogen and progesterone. All COCs have the potential to improve androgen-related effects, such as acne and hirsutism, by suppressing the formation of these hormone-producing bodies.[58] They also increase levels of sex hormone binding globulin, a protein which binds to free androgen and decreases circulating levels.[58] COCs containing progestins that have antiandrogen effects, such as drospirenone and dienogest, may have even more beneficial effects on acne. In fact, some of these products even have approval for the treatment of acne (*Yaz*, *Gianvi*, etc [ethinyl estradiol 20 mcg and drospirenone 3 mg for 24 days]).[60] CHCs that bypass first-pass metabolism, such as the patch and vaginal ring, have less effect on sex hormone binding globulin. So they might not be the best choices for helping with acne. Progesterone-only products are not typically considered effective for acne.[58]

Reduction of Cancer Risk

While there is concern of a small increased risk of breast cancer with CHCs, they may have protective effects against endometrial and ovarian cancers.[9,58] There is up to a 50% reduced risk of endometrial cancer among patients who have used COCs compared to those who have never used COCs.[9,58] This reduction in risk was seen with both long-term and short-term use.[58] There is limited data on lower doses of COCs, the patch, and the vaginal ring; however, this protective effect is likely to exist in all CHCs based on the mechanism of action.[58] Since progestins stabilize the endometrial lining by preventing additional tissue growth, any progestin-containing product, including progestin-only contraceptives, has the potential to be protective against endometrial cancer.

COCs also have been found to protect against ovarian cancer by preventing ovulation.[58] Although there is less evidence for the other CHC formulations, it's possible that any product that prevents ovulation will have similar protective effects. There is some evidence that DMPA, which completely blocks ovulation, can also protect against ovarian cancer.[62]

The Bottom Line

Hormonal contraceptives prevent pregnancy in a number of different ways. They also can help treat other conditions unrelated to contraception. Understanding how hormonal contraceptives work can help pharmacists better care for their patients. Knowing about noncontraceptive benefits allows pharmacists to recommend or select the product that is most appropriate considering a patient's unique comorbidities or issues. Pharmacists will be better prepared to counsel and educate patients by having a good understanding of how hormonal contraceptives work.

For more information on counseling patients taking hormonal contraceptives, take our CE, *Hormonal Contraceptive Counseling*.

Quiz Questions

Question #1

What happens during the luteal phase of the menstrual cycle?

- a. Discontinuation of menstruation
- b. Production of a thin, watery cervical mucus
- c. Increase in estrogen levels until a mature follicle develops
- d. Formation of a temporary hormone-producing structure

Question #2

During which phase of the menstrual cycle does menstruation end?

- a. Luteal
- b. Uterine
- c. Ovulation
- d. Follicular

Question #3

Which hormone has the most direct impact on sperm motility during the follicular phase?

- a. LH
- b. FSH
- c. Estrogen
- d. Progesterone

Question #4

What do the corpus luteum and dominant follicle have in common?

- a. They develop prior to ovulation.
- b. They are hormone-producing bodies.
- c. When stimulated by GnRH, they rupture.

d. When they degenerate, it's a sign of pregnancy.

Question #5

Which hormone surges about 28 to 32 hours before ovulation?

a. LH

b. FSH

c. Estrogen

d. Progesterone

Question #6

Which dosage form are combined hormonal contraceptives available in?

a. Injection

b. Implant

c. Vaginal cream

d. Vaginal ring

Question #7

What is one way that combined hormonal contraceptives are thought to prevent pregnancy?

a. They thin cervical mucus.

b. They decrease FSH release.

c. They stimulate an LH surge.

d. They promote follicular rupture.

Question #8

Why is it most important for patients using combined oral contraceptives to begin taking active pills again immediately after the 7-day hormone-free interval?

a. To prevent the risk of ovulating early

b. To bring an end to the luteal phase

c. To allow the cervical mucus to thicken again

d. To stop the bleeding caused by hormone withdrawal

Question #9

Which progestin is used in the progestin implant?

a. Desogestrel

b. Etonogestrel

c. Medroxyprogesterone acetate

d. Norethindrone

Question #10

Which hormonal contraceptive would you recommend to help improve acne symptoms in a 20-year-old patient interested in preventing pregnancy?

a. Combined oral pill

b. Transdermal patch

c. Progestin-only pill

d. Depot injection

Submit your answers

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Pharmacology of Hormonal Contraceptives
(19-248)

Needs: Unintended pregnancies account for about 50% of all pregnancies in the U.S and cost an estimated 11.1 billion dollars each year. With the wide variety of contraceptives available, pharmacists need to be able to help patients choose the best option for them. Understanding how hormonal contraceptives work is the first step to helping patients navigate their options.

Target Learners: This activity is intended for pharmacists in any practice setting. There are no prerequisites.

Goals and Objectives: The goal of this activity is to help pharmacists in all settings develop a better knowledge base of how hormonal contraceptives work so that they can assist patients with product selection and education.

Upon completion of this course, the learner will be able to:

1. Discuss the 3 different phases of the menstrual cycle.
2. Identify the predominant hormone(s) for each phase of the menstrual cycle.
3. List the different types of hormonal contraceptives.
4. Explain how hormonal contraceptives prevent pregnancy.
5. Recognize 3 noncontraceptive uses of hormonal contraceptives.

Director of Continuing Education and Continuing Medical Education

Tammie Armeni, RPh, PharmD
Editor, Senior Director of Continuing Education & Content Management
Pharmacist's Letter & Prescriber's Letter
Nurse's Letter & Natural Medicines

Principal Author

Flora Harp, PharmD
Assistant Editor
Pharmacist's Letter & Prescriber's Letter

Expert Reviewer(s)

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Annie Ottney, PharmD, BCPS
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