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Pharmacist's Letter
Online Continuing Education and Webinars

Hormonal Contraceptive Selection

Volume 2019, Course No. 246
Self-Study Course #190246

Accreditation, Goals and Objectives

Course Accreditation Information, Goals and Objectives

Introduction

> Annabelle is a 20-year-old college student who is interested in starting birth control. She knows there are a lot of different types to choose from and is wondering if you could go over them with her. You ask her if she has any medical conditions or if she is taking any medications, since this can impact the type of birth control she could use. She tells you that she has no medical conditions and does not take any medications.
>
> Do you find all the different hormonal contraceptive product choices overwhelming? How do you help patients navigate their options? What more can you do? What information do you need to help you feel more confident in your ability to explain the different options available and make recommendations?

Unintended pregnancy accounts for about 50% of all pregnancies, and costs the U.S. an estimated 11.1 billion dollars each year.[1,2] Unfortunately, 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 U.S. 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 a person wants to get pregnant at some point in the future, but not at the time it actually occurs. Unwanted refers to a scenario where a person 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. However, about one in five unintended pregnancies is estimated to be caused by the discontinuation of oral contraceptives and issues with adherence.[7] One study found that some of the most common reasons patients are nonadherent to their oral contraceptives include traveling without their pill pack, forgetting to take the pills, and being unable to get a new refill in time for the beginning of a new cycle.[7]

When it comes to hormonal contraceptives, pharmacists play a huge role in helping to educate patients on adherence, navigate cost concerns, and ensure patients have refills in time. In a survey of over 1,200 patients aged 18 to 49 years, 60% of patients who weren't currently using a highly effective contraceptive method (e.g., hormonal contraception) said they would be more likely to use oral contraceptives if they were available over the counter.[8] Leading medical groups, such as the American Medical Association, American College of Obstetricians and Gynecologists, and the American Academy of Family Physicians, have endorsed making oral contraceptives available over the counter.[3,9,10] However, aside from emergency oral contraceptives, hormonal contraceptives continue to be available by prescription only.

Despite the lack of over-the-counter (OTC) availability of non-emergency hormonal contraceptives, some states are taking action to increase access by getting pharmacists involved. A survey of over 2,000 pharmacists in the United States identified that 85% were interested in providing hormonal contraception.[11] Pharmacists have shown that they can efficiently and effectively screen and help patients with the selection of hormonal contraceptive products.[12] Some states, such as Oregon, California, Utah, and West Virginia, allow appropriately trained pharmacists to provide certain hormonal contraceptives (as defined by state law) to patients under a standing order. In addition to being trained, depending on the state, pharmacists may need to utilize a state-approved protocol or algorithm when offering this service to ensure patients are screened for contraindications or precautions. There's also usually an age restriction; for example, the service may only be available for patients age 18 and older.[13,14] You can find out more about the states that currently have regulations allowing pharmacists to prescribe contraceptives at the National Alliance of State Pharmacy Associations website. Keep in mind that pharmacists may also be able to prescribe/initiate hormonal contraceptives via collaborative practice agreements, even if their state doesn't currently have a statewide protocol to do so.

> What are the different contraceptive products available? Which of these are hormonal? Which of the hormonal options can patients self-administer?
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> Self-administered hormonal contraceptives include the oral pills, transdermal patch, and the vaginal ring. The intramuscular depot injection (Depo-Provera) is typically given by a healthcare professional; however, the subcutaneous

Intramuscular depot injection (*Depo-Provera*) is typically given by a healthcare professional; however, the subcutaneous version (*Depo-SubQ Provera 104*) may be self-administered by patients who are appropriately trained. States may limit pharmacist prescribing of self-administered hormonal contraceptives to just some of these or include all of them. For example, in Oregon and California, pharmacists can prescribe the oral pills, transdermal patch, vaginal ring, and depot injection.[15,16] In Utah and West Virginia, legislation specifies that pharmacists can prescribe the pill, patch, and ring.[17,18]

Oral Contraceptives

Oral contraceptives include those that have a combination of estrogen and progestin (combined oral contraceptives, or COC) and those that contain progestin only. Take time to understand the differences between these products so that you can feel comfortable recommending (and in some states prescribing) them to patients.

Combined Oral Contraceptives (COCs)

You begin by explaining combined hormonal contraceptive options to Annabelle. After discussing the pill, patch, and vaginal ring, she expresses interest in trying the pill first. What are the different combinations of combined oral hormonal contraceptives available? Why might a prescriber choose one regimen over another? How can you help guide patients and prescribers on navigating these different options?

COCs were initially developed to closely mimic the menstrual cycle and provide predictable monthly bleeding. In addition to the contraceptive effects, COCs can help treat acne, hirsutism (abnormal hair growth), dysmenorrhea (painful menstruation), and endometriosis. Consider all agents in this class equally efficacious, preventing over 99% of pregnancies with perfect use.[19,20] With typical use, up to 8% of users may become pregnant.[20]

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. COCs can help treat this condition by slowing the growth of the endometrial tissue. To learn more about endometriosis and other reproductive health issues in female patients, review our CE, *Women's Reproductive Health*.

The most commonly used estrogen component in COCs is ethinyl estradiol. Doses range from 10 to 50 mcg. Estradiol valerate is another type of estrogen found in COCs. Estradiol valerate is converted to the naturally occurring estrogen, estradiol. Estradiol valerate is available as a multiphasic product in combination with the progestin dienogest (*Natazia*) at doses of 1 mg, 2 mg, and 3 mg. It was hoped that using a product which gets converted to a natural estrogen would decrease the incidence of adverse effects, but tell patients this hasn't been proven yet.[21,22]

There are a variety of progestins that are used in COCs.[23] 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.[24] The contraceptive effects of the various synthetic progestins are mediated by the progestin's activity on progesterone receptors in the reproductive tissue, while the side effects are often due to the progestin's activity on other steroid receptors.[25] 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 Combined Oral Contraceptives[20,23]

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

What are the different types of progestins you encounter most often? How does the type (i.e., generation) of progestin impact the effects experienced by patients? When is it better to use one progestin over another?

"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.[23,25] 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. For example, since second-generation progestins bind with higher affinity to androgen receptors than other progestins, they have more androgenic effects which can cause acne, abnormal hair growth (hirsutism), dyslipidemia, and weight gain.[25] "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.[26] 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.[27]

The third-generation progestins and drospirenone are associated with a possible increased risk of nonfatal venous thromboembolism in comparison to the older progestins.[28,29] This risk has yet to be proven by prospective, randomized controlled trials, and use of these progestins

comparison to the older progestins.[30] This risk has yet to be proven by prospective, randomized controlled trials, and use of these progestins is considered medically acceptable.[30] Thromboembolism is one of the major, but rare adverse effects associated with COCs in general. This risk is thought to be caused by the estrogenic activity on the coagulation cascade. When COCs were first developed, they had much higher doses of ethinyl estradiol than we see today (greater than 50 mcg). The risk for VTE is lower with the doses of estrogen currently available when compared to the higher doses used in the past. While there are certain patients who are at higher risk for thromboembolism with COC use (e.g., smoker, older age, obese), the risk of thromboembolism is usually less than that incurred by pregnancy.[20] For example, the relative risk of VTE with COC use ranges from two to six compared to non-users of COCs.[31,32] This equates to about 3 to 12 new cases per 10,000 women per year versus 1 to 5 new cases per 10,000 women per year in the general population.[33] In comparison, risk of VTE during pregnancy ranges from about 5 to 20 new cases per 10,000 women per year.[31,33] This risk goes up even more post-pregnancy to 40 to 65 new cases per 10,000 women per year.[33,34] The small increase in the risk of VTE in users of COCs, which prevents pregnancy, must be considered in the context of the greater risk of VTE in patients who are pregnant or have recently given birth.[34] Despite this small risk, it's important to use the lowest effective and tolerated dose of ethinyl estradiol. Generally, a patient shouldn't need a product with more than 30 mcg of ethinyl estradiol.[35]

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.[20,28] 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	

Within the COC category, there are 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 (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.[36,37] They also may be more confusing to use when handling a missed dose compared to monophasic products.

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.[20] Both extended- and continuous-cycle COCs are useful for patients with menstrual-related difficulties or those who prefer not to have monthly bleeding. These regimens can reduce symptoms of hormone withdrawal, dysmenorrhea, heavy bleeding, and help with severe premenstrual symptoms. Keep in mind that to avoid monthly bleeding, patients can also use traditional monophasic COCs by continuing to take active pills throughout the hormone-free interval. This may be a more cost-effective approach. However, they may run into insurance issues when trying to get refills if the Rx isn't written to take the active pills continuously. It's also worth noting that the long-term effects of this added hormone exposure aren't fully understood.[38,39] Taking oral contraceptives continuously will expose patients to one additional month of estrogen and progestin in the course of one year, increasing lifetime hormone exposure. Although the significance of this observation is not known, it's not thought to be harmful. Be aware that some patients may prefer to have periodic withdrawal bleeding as reassurance that they are not pregnant.

Become familiar with the different types of estrogen and progestin 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*.

Are there any reasons to use a multiphasic COC over a monophasic COC? When is it best to use an extended- or continuous-cycle regimen? Why would you use a higher dose of estrogen? Review the tables below for answers to these questions.

Available Monophasic COC Regimens		
Estrogen	**Progestin**	**Product Selection Considerations**
Ethinyl estradiol 20 mcg	• Levonorgestrel 0.1 mg • Norethindrone acetate 1 mg • Levonorgestrel 0.15 mg • Norgestrel 0.3 mg • Norethindrone acetate 1.5 mg • Desogestrel 0.15 mg • Drospirenone 3 mg	• Ethinyl estradiol 20 mcg monophasic regimens are a good starting dose for patients who want to use a COC[37,40,41] • May cause more breakthrough bleeding than higher doses of ethinyl estradiol in some patients[40] • Consider higher doses of estrogen (30 mcg of ethinyl estradiol or more) for patients taking CYP 3A4 enzyme inducers • May be useful for patients who experience bothersome breakthrough bleeding on lower doses of ethinyl estradiol[40] • Products with drospirenone can be considered for patients concerned with gaining weight[42,43] • The brand *Safyral* contains folate in addition to ethinyl estradiol and drospirenone; it may be cheaper for patients to take a different COC and add folate supplementation
Ethinyl estradiol 35 mcg	• Ethynodiol diacetate 1 mg • Norgestimate 0.25 mg	• Consider higher doses of estrogen (30 mcg of ethinyl estradiol or more) for patients taking

	• Norethindrone 0.4 mg • Norethindrone 0.5 mg • Norethindrone 1 mg	CYP 3A4 enzyme inducers • May be useful for patients who experience bothersome breakthrough bleeding on lower doses of ethinyl estradiol[40]
Ethinyl estradiol 50 mcg	• Norgestrel 0.5 mg • Ethynodiol diacetate 1 mg	• Consider higher doses of estrogen (30 mcg of ethinyl estradiol or more) for patients taking CYP 3A4 enzyme inducers • Avoid in obese patients and smokers

Available Multiphasic COC Regimens		
Estrogen	**Progestin**	**Product Selection Considerations**
Ethinyl estradiol 10 to 20 mcg	• Desogestrel 0.15 mg	• Multiphasic COCs haven't been found to be better at preventing side effects than monophasic pills[36,37,41] • Patients interested in COCs should be initiated on monophasic pills due more safety data and easier instructions if a dose is missed
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 3 mg	• Dienogest 2 to 3 mg	

Available Extended- and Continuous-Cycle Regimens		
Estrogen	**Progestin**	**Product Selection Considerations**
Ethinyl Estradiol 10 mcg x 26 days	• Norethindrone acetate 1 mg x 24 days	• Fewer placebo days may mean fewer symptoms from hormone withdrawal • Low dose of ethinyl estradiol may result in breakthrough bleeding
Ethinyl Estradiol 20 mcg x 24 days	• Norethindrone acetate 1 mg x 24 days • Drospirenone 3 mg x 24 days	• Fewer placebo days may mean fewer symptoms from hormone withdrawal • The brand *Beyaz* contains folate in addition to ethinyl estradiol and drospirenone; it may be cheaper for patients to take another COC and add folate supplementation, if needed
Ethinyl Estradiol 25 mcg x 24 days	• Norethindrone 0.8 mg x 24 days	• Fewer placebo days may mean fewer symptoms from hormone withdrawal
Ethinyl Estradiol 20 mcg x 84 days, then 10 mcg x 7 days	• Levonorgestrel 0.1 mg x 84 days	• Three-month cycles • Reduces symptoms of hormone withdrawal; consider for females with severe premenstrual symptoms, dysmenorrhea, or heavy bleeding • Consider using in obese patients to improve efficacy
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, 25 mcg x 21 days, 30 mcg x 21 days, then 10 mcg x 7 days	• Levonorgestrel 0.1 mg x 84 days	
Ethinyl Estradiol 20 mcg all days, no break	• Levonorgestrel 90 mcg all days	• Consider as an option for patients who do not want any monthly bleeding at all • Consider using in obese patients to improve efficacy

How should an Rx be entered into the pharmacy dispensing system if a patient is supposed to take a monophasic 21-day active pill/7-day inactive pill product continuously?

The days' supply for this product should be entered as a 21-day supply, so that the insurance will not reject the Rx when the patient attempts to get it refilled. If the insurance will not accept a 21-day supply because they think it should be a 28-day supply product, then switching to a product with 21 active pills and no inactive pills may be an option.

Progestin-Only Pills

Progestin-only pills, or "minipills," are another oral hormonal contraceptive option. The progestin-only pill is an attractive option for patients who can't take estrogen. The progestin-only pill generally results in less bleeding during menstruation, but more breakthrough bleeding compared to combined hormonal contraception.[20]

The progestin-only pill is available as norethindrone 350 mcg (*Camila*, *Jencycla*, etc) taken once a day. This is much less progestin than what is contained in COCs. While it 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 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. 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 48 hours. Because there is less room for error with the progestin-only pill, efficacy with typical use may be problematic.[20] Irregular and unpredictable menstrual bleeding is the most common adverse effect. Educate patients in advance that this can occur, as this is the most common reason that patients stop using progestin-only products.[44]

Use our patient education handout, *What I Need to Know About Missed Birth Control Doses* to help counsel patients on the importance of adherence to COCs and the progestin-only pill. Also, for more background information on important counseling points for patients taking hormonal contraception, take our CE, *Hormonal Contraceptive Counseling*.

Transdermal Patch

The transdermal patch is a combined hormonal contraceptive (CHC) available in the U.S. (*Xulane*) and Canada (*Evra*) that 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.[33,45] Norelgestromin is the active form of the progestin, norgestimate. Some patients like the patch because they only need to remember to change it weekly as opposed to taking a daily pill. This leads to a higher compliance rate.[46] 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.[47] This may be because it has a higher exposure to estrogen over time compared to some of the other combined hormonal agents. However, the clinical significance of this higher exposure is unknown.[48] Make sure patients know of potential side effects before starting. Counsel patients to place the patch on their upper arm, stomach, back, or buttock where it won't be rubbed by tight clothing.[33] They should consider rotating the application site with each new patch to reduce the risk of skin irritation. Recommend the use of a calendar to help patients remember when to change their patch and when to restart the four-week cycle. Let them know that their patch-free week is when they can expect to experience withdrawal bleeding. Keep in mind that the patch may not work as well in patients who weigh over 198 pounds (90 kg).[33]

Vaginal Ring

There are two different types of vaginal rings available. You are probably most familiar with the ethinyl estradiol/etonogestrel (*NuvaRing*) product, since this has been on the market for a while. It releases 15 mcg of ethinyl estradiol and 120 mcg of etonogestrel a day.[49] This ring is inserted for three weeks and then disposed of. A new ring is inserted one week later.

In contrast, the ethinyl estradiol/segesterone (*Annovera*) vaginal ring is reusable for up to one year (or 13 cycles). Similar to *NuvaRing*, there is an off week, but patients reinsert the same *Annovera* ring to start the next cycle. It releases 13 mcg of ethinyl estradiol and 150 mcg of segesterone a day.[50]

Let patients know that the ring has low estrogen exposure compared to the other available CHCs, so they may experience fewer estrogen-related side effects. However, the ring does lead to more localized issues. Counsel patients who are switching from the pill that the ring can cause more vaginal irritation and discharge.[51] Some patients may be concerned that the ring may be uncomfortable or may fall out. Reassure them that this happens in less than 5% of patients.[52]

Products considered to be CHCs include the oral pills previously discussed (COCs) and non-oral dosage forms such as the transdermal patch and vaginal ring. All of these products contain a combination of estrogen and progestin.

Depot Injection

Another type of hormonal contraceptive is the depot injection, medroxyprogesterone acetate. This progestin-only hormonal contraceptive 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). Tell patients the subcutaneous injection causes less injection pain compared to the intramuscular shot but that the progestin-related adverse effects are similar.[53] However, since the subcutaneous injection is available as a brand drug only, insurance companies may only cover the intramuscular injection which has a generic.

Around one in four female patients have used the depot injection for contraception. Unfortunately, almost half stop using it, mainly due to side effects and changes in menstrual cycle.[47] Like other progestin-only products, patients can experience spotting and breakthrough bleeding initially, but after one year many patients stop having periods. While this can be a concern for some patients, others may see it as a benefit.[19] Patients may worry about weight gain with medroxyprogesterone. Let them know that after five years, they can expect about an average weight gain of five pounds.[54]

Warn patients ahead of time that it may take longer to get pregnant after stopping the depot injection because of prolonged amenorrhea and anovulation after the last injection.[54,55] Injectable medroxyprogesterone can also decrease bone mineral density, so it may not be the best choice in patients at risk for osteoporosis.[54] Most of the bone loss occurs during the first two years of therapy. Make sure all patients receiving medroxyprogesterone get enough calcium and vitamin D.

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.[56] 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.[56] So most studies looking at the return to fertility evaluate the conception rates at twelve months following discontinuation of the contraceptive method.[56] The 12-month conception rates reported after discontinuing various forms of contraception are:[55,56]

- 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 done with caution.[56]

Test your hormonal contraceptive knowledge:

What is one of the biggest counseling points to keep in mind for the progestin-only pill?

Let patients know that with progestin-only pill, it's very important to take the pill at the same time each day. If it is taken more than three hours late, patients should use backup contraception for 48 hours.

In which patients should the patch be avoided?

The patch should be avoided in patients who weigh over 198 pounds (90 kg) because it might not work as well.

How can you advise a patient who is worried about using the vaginal ring because they are concerned that it might fall out often?

You can reassure the patient that this happens in less than 5% of patients.

What side effect with medroxyprogesterone depot injections would you discuss with a patient?

Let patients know that they may experience breakthrough bleeding initially, but this usually goes away with time. Also let them know that it might take longer for them to get pregnant after stopping this medication, when compared to other hormonal contraceptives
.

For more information on other methods of contraception, such as implants, intrauterine devices, and barrier methods, check out our CE, *Helping Patients Navigate Contraceptive Options*. Also, to learn about how contraceptives work to prevent pregnancy review our CE, *Pharmacology of Hormonal Contraceptives*.

Use of Hormonal Contraceptives with Select Conditions

Recall that your 20-year-old patient Annabelle had no medical conditions and was taking no medications. In this case, the selection of hormonal contraception comes down to patient preference. In general, beginning with a monophasic COC that has a low dose of estrogen (e.g., 20 mcg) is a good place to start with most patients like Annabelle.

However, what if she suffered from migraines? Was a 36-year-old obese smoker? Had epilepsy that was being treated with carbamazepine? In these scenarios, it's important to use the U.S. Medical Eligibility Criteria discussed below to help

guide the selection of the most appropriate contraceptive.

When helping a patient select a birth control option, especially a hormonal contraceptive, it's important to know about their medical conditions. Some conditions increase the risk for adverse effects or can decrease the efficacy of some hormonal contraceptives. Know which conditions hormonal contraceptives should be avoided in or used with caution. The Centers for Disease Control and Prevention (CDC) has an easy-to-read chart to help you make these decisions. The Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use (U.S. MEC) includes over 50 conditions with recommendations for initiation and continued use of CHCs, the progestin-only pill, the depot injection, implant, and IUDs.[57] Each contraceptive option will include one of the following recommendations:

- Category 1: No restriction (method can be used)
- Category 2: Advantages generally outweigh theoretical or proven risks
- Category 3: Theoretical or proven risks usually outweigh the advantages
- Category 4: Unacceptable health risk (method not to be used)

The U.S. MEC is meant to be used alongside the U.S. Selected Practice Recommendations for Contraceptive Use (U.S. SPR) to help guide clinicians on how to use these contraceptive methods effectively. U.S. SPR includes information on what clinical information is needed before method initiation, what routine follow-up is recommended, and how to manage common problems with each method.[58] It's important to be familiar with these documents and know where to find updated copies on the CDC website. States that allow for pharmacist prescribing of hormonal contraceptives may either require or recommend that the most current U.S. MEC be used by pharmacists.

We will discuss some of the more common conditions/scenarios addressed in the U.S. MEC. The focus will be on the use of self-administered hormonal contraceptive therapy and the depot injection in patients with these conditions. For a more comprehensive list of conditions and additional contraceptive options, such as the implant and IUDs, refer to the U.S. MEC.

States that allow appropriately trained pharmacists to prescribe hormonal contraceptives often require that pharmacists have patients fill out a self-assessment form. These forms require patients to answer questions regarding their potential for being pregnant, medical conditions, medication history, etc, to help guide the selection of the most appropriate contraceptive. Self-assessment forms are often used in conjunction with an algorithm, that will guide the pharmacist in making decisions based on how patients respond to the self-assessment form. For example, in the state of Maryland, pharmacists must provide patients with a self-assessment form, and use an algorithm to help guide them to either refer the patient, or to go ahead and prescribe a contraceptive.

Bariatric Surgery[19,57]

A history of bariatric surgery can lead to a decreased absorption of COCs and the progestin-only pill if the procedure is considered to be malabsorptive. Some types of bariatric surgery lead to a decreased absorptive capacity of the GI tract which causes malabsorption. These surgeries include bilopancreatic diversion and Roux-en-Y. Restrictive surgeries, such as gastric binding and sleeve gastrectomy, don't cause malabsorption. For malabsorptive procedures, oral contraceptives should be avoided and instead the patch, ring, or injection can be selected or prescribed. Oral contraceptives are considered Category 3 for use with a history of malabsorptive bariatric surgeries. Make sure to find out what type of bariatric surgery the patient has had before making a recommendation. Restrictive surgeries are Category 1 for use with all hormonal contraceptives.

Breast Cancer[19,57]

Patients who currently have breast cancer or who had a past history of breast cancer shouldn't use hormonal contraceptives. This is a Category 3 (past history) and 4 (current) recommendation. For patients who have a family history of breast cancer or a history of a benign breast disease, there are no restrictions (Category 1) for using hormonal contraceptives.

Patient Characteristics That Increase the Risk of Venous Thromboembolism (VTE)[19,57]

There are certain patient characteristics that increase the risk of VTE when CHCs are used. These include smoking, being obese, age 35 or older, and having had recent major surgery.

For patients who smoke, if they are under the age of 35 they can use CHCs (Category 2), the progestin-only pill (Category 1), or the injection (Category 1). However, ethinyl estradiol should be at a dose of less than 50 mcg. If a patient is 35 or older and smokes they should NOT use CHCs (Category 3 or 4, depending on how many cigarettes per day), but can use the progestin-only pill (Category 1) or the injection (Category 1).

For patients who are obese (BMI 30 kg/m^2 or more) they can use CHCs (Category 2), the progestin-only pill (Category 1), and the injection (Category 1 or 2, depending on the patient's age). However, ethinyl estradiol should also be at a dose of less than 50 mcg. Although not specified in the U.S. MEC, use of the CHC patch in patients who weigh over 198 pounds (90 kg) should be avoided because the efficacy might be reduced.[33]

When looking at the U.S. MEC recommendations for age, be aware that CHCs are a Category 1 recommendation for patients under 40 years of age, but change to Category 2 for patients 40 and older.

Patients who have had recent major surgery (or have one scheduled in the future) resulting in prolonged immobility should definitely NOT use CHCs (Category 4), but can use the progestin-only pill and the depot injection (Category 2 for both). Patients who have had a recent major surgery (or have one scheduled in the future) that did NOT result in prolonged immobility can use CHCs (Category 2). The challenge is in determining what is considered major surgery and prolonged immobility. There is no uniform definition for either, but typically a major general surgery is any kind of abdominal or thoracic surgery that lasts for more than 30 minutes and requires general anesthesia.[59] Also considered to be major surgeries are lower extremity orthopedic surgeries, such as hip or knee replacements, which often pose the greatest risk for VTE. Prolonged immobility is harder to define. It can mean anything from a long car or plane ride, to being immobile for two to three weeks after surgery. To help provide perspective, consider a study that found that 15% of patients on bed rest before death for less than one week had a VTE at autopsy. This incidence increased to 80% in patients who were in bed for longer than one week.[59]

While some of these characteristics like age and obesity still allow for the use of hormonal contraceptives, be aware that the more of these characteristics a patient has, the higher the risk for VTE. So if for example you have a patient who is 25, a smoker, obese, and has a major

characteristics a patient has, the higher the risk for VTE. So if, for example you have a patient who is 25, a smoker, obese, and has a major surgery scheduled that is not likely to result in prolonged immobilization, you might want to assess this patient more closely. Generally speaking, if you have a patient who has multiple conditions that are Category 2 for a particular hormonal contraceptive, clinical judgment and shared decision making with the patient should be utilized to help determine the best therapy.

> Some experts suggest using a high-dose estrogen COC for patients who are obese because of questions of efficacy. However, others suggest that it's not prudent to routinely prescribe high-dose COCs to heavier patients, especially because they are at higher risk of VTE. Instead, recommend decreasing or eliminating the pill-free interval for obese patients, rather than prescribing or recommending pills with the higher dose of hormones.[60]

Conditions Treated by Antiepileptics or Antiretrovirals[19,57]

Some drugs can induce the CYP450 hepatic enzymes that metabolize hormonal contraceptives and cause them to be less effective. Anticonvulsants such as phenytoin, carbamazepine, barbiturates, primidone, topiramate, and oxcarbazepine are Category 3 for CHCs and the progestin-only pill, so these contraceptive options should be avoided if possible. However, if a patient is on lamotrigine, although CHCs are still Category 3 (because estrogen decreases lamotrigine levels by about 50%), the progestin-only pill is Category 1 and can be used.[61] The protease inhibitor fosamprenavir does significantly interact with CHCs (Category 3). The progestin-only pill and the depot injection can be used in patients on this drug (Category 2).

Depression[19,57]

Depression may be adversely affected by progestins. Although the U.S. MEC indicates Category 1 for all hormonal contraceptive products, be aware that progestins can exacerbate depression. Consider avoiding injectable progestin since this is long-acting and can be more difficult to discontinue if depression is exacerbated.[60]

Diabetes[19,57]

Hormonal contraceptives may impair glucose control and carbohydrate metabolism. They are Category 2 for most patients with type 1 or type 2 diabetes. However, CHCs (Category 3/4) and the injection (Category 3) are NOT recommended for patients who have diabetes with nephropathy, retinopathy, neuropathy, or some other vascular disease or those who have had diabetes for over 20 years. The progestin-only pill (Category 2) can be used instead in these patients.

Ischemic Heart Disease or Stroke[19,57]

Ischemic heart disease, either current or a history of, and a history of stroke requires cautious use of hormonal contraceptives due to the increased risk of blood clotting which can result in a cardiac event or stroke. CHCs are not recommended at all (Category 4) and neither is the injection (Category 3). The progestin-only pill can be initiated (Category 2), but shouldn't be continued (Category 3) if ischemic heart disease symptoms worsen.

Patients who don't have ischemic heart disease, but have multiple risk factors for it (i.e., older age, smoking, diabetes, dyslipidemia, and hypertension), also require close evaluation. CHCs should be avoided in these patients (Category 3/4) and so should the injection (Category 3). The progestin-only pill can be used (Category 2).

High Blood Pressure or High Cholesterol[19,57]

Estrogen can raise blood pressure and may increase the risk of cardiovascular events in patients with hypertension. The CDC recommends measuring blood pressure prior to initiating a hormonal contraceptive. Patients who have hypertension that is controlled should not take CHCs (Category 3), but can take the progestin-only pill (Category 1) or receive the depot injection (Category 2). These categories remain the same if the patient's blood pressure is slightly elevated with a systolic BP of 140 to 159 mmHg and diastolic BP of 90 to 99. Any blood pressures above this results in mostly the same recommendations, but different categories. CHCs move to Category 4, the progestin-only pill to Category 2, and the depot injection moves to being not recommended at Category 3. Keep in mind that if a patient does have hypertension that is controlled on antihypertensives, some prescribers may be okay with a patient being on a CHC along with close monitoring.

Estrogen can increase triglyceride levels and progestins can increase LDL. This can be more problematic in a patient who has hyperlipidemia. The 2010 U.S. MEC assigned a Category 2 for all hormonal contraceptives; however, CHCs could have been Category 3 depending on the type and severity of hyperlipidemia and the presence of other cardiac risk factors. Any mention of hyperlipidemia on its own has since been removed from the updated 2016 U.S. MEC. According to the WHO Medical Eligibility Criteria for Contraceptive Use, generally a patient with hyperlipidemia can use a CHC if the patient doesn't have any other known cardiovascular risk factors or a severe genetic lipid disorder (i.e., homozygous or heterozygous familial hypercholesterolemia) that significantly increases the lifetime risk of cardiovascular disease.[62]

History of VTE[19,57]

Patients who have had a VTE, such as a deep vein thrombosis (DVT) or pulmonary embolism (PE) might already be at an increased risk for having another VTE. Estrogen can increase coagulability, which can be problematic in these patients. Generally, CHCs should not be used in patients with a history of VTE, even if it was an acute episode. All other hormonal contraceptives are Category 2. Those with a family history of VTE can use CHCs (Category 2) or any of the other hormonal contraceptives.

Liver Disease[19,57]

You may see some patient assessment questionnaires that ask about whether or not the patient has hepatitis, liver disease, liver cancer, gall bladder disease, and/or jaundice. Some patients who have acute cases of hepatitis, liver cancer, cirrhosis, a history of gall bladder disease, and cholestasis (a reduction or stoppage of bile flow) may have to avoid CHCs since they contain estrogen. The estrogen found in CHCs can cause mild inhibition of bilirubin excretion (leading to jaundice) and cholestasis that may lead to liver injury. Estrogen-containing CHCs have also been found to slightly increase the risk of gall bladder disease and have been linked to liver tumors. Also, liver impairment in general can result in poor metabolism of hormones, which can decrease efficacy. If a patient does have any of these liver issues, make sure to investigate further and use the details outlined in the U.S. MEC to help decide whether or not CHCs are okay to use.[63]

Migraines[19,57]

Migraines

Estrogen-containing contraceptives can increase the risk of stroke in patients who have migraine headaches with aura (light sensitivity, numbness, sick to stomach, lose sight or have other vision problems, etc). Patients who suffer from migraines with aura shouldn't use CHCs (Category 4). Patients who have migraines without aura can use CHCs, but discontinuation may be necessary if migraines are exacerbated. The progestin-only pill may be preferred in these patients.

Postpartum and Breastfeeding[19,57]

Patients remain in a hypercoagulable state for many weeks after childbirth. In addition to increasing the risk of VTE, estrogen also can decrease milk production. This is a larger issue in the first few weeks of breastfeeding, while milk production is being established. Progestin-only contraceptives may be helpful during breastfeeding because they increase the quality and duration of lactation.[64] Regardless of whether or not a patient is breastfeeding, if they are less than 21 days postpartum they shouldn't use CHCs (Category 4), but can use the progestin-only pill or the depot injection (Category 1 for non-breastfeeding patients or 2 for breastfeeding patients). If the patient is more than 21 days postpartum, knowing whether or not they are breastfeeding is important since there are different recommendations for each. Below is a summary:

- Breastfeeding
    - 21 to less than 30 days postpartum: CHCs are Category 3 while all other hormonal contraceptives are Category 2.
    - 30 to 42 days postpartum: CHCs are Category 3 if the patient has other risk factors for VTE, otherwise they are Category 2 and can be used. All other hormonal contraceptives are Category 1, regardless of VTE risk factors.
    - Beyond 42 days postpartum: Any hormonal contraceptive can be used, but CHCs have a slightly higher risk and are Category 2.
- Non-breastfeeding
    - 21 to 42 days postpartum: CHCs are Category 3 if the patient has other risk factors for VTE, otherwise they are Category 2 and can be used. All other hormonal contraceptives are Category 1, regardless of VTE risk factors.
    - Beyond 42 days postpartum: Any hormonal contraceptive can be used (all are Category 1).

Rheumatoid Arthritis (RA)[19,57]

Estrogens and progestins can affect control of RA. The injection can also increase the risk of fractures, which patients who use long-term corticosteroids for their RA are already at risk for. The preference is to use the progestin-only pill in patients who have RA and are on steroid therapy (Category 1), but they can also use CHCs (Category 2). The injection should be used cautiously in patients on long-term steroid treatment (Category 2/3).

Systemic Lupus Erythematosus (SLE)[19,57]

Patients with SLE who have a positive or unknown antiphospholipid antibody test shouldn't use any hormonal contraceptive. This is because the presence of antiphospholipid antibodies increases the risk of ischemic heart disease, stroke, and VTE. Using a hormonal contraceptive can further elevate this risk.

Managing Side Effects with Therapy Adjustments

> Annabelle has been taking a monophasic COC consisting of ethinyl estradiol 20 mcg and levonorgestrel 0.1 mg for the past 4 months. She tells you she has always had issues with acne, but that her acne has recently become more bothersome. Would you recommend a change to her oral contraceptive? Why or why not? If so, what other therapy would you recommend instead?

As discussed previously, side effects with hormonal contraceptive use are usually attributed to having too much or too little estrogen or progestin. You can help manage side effects by recommending a product to switch to or prescribing a different product if your state law allows it.

> What are the side effects with too much or too little estrogen, progestin, and androgen exposure? Take a moment to recall this information and think about how you might adjust a patient's therapy in response to bothersome effects.
>
> Too much estrogen can cause nausea, breast tenderness, headache, bloating, melasma, and increased blood pressure. Too much progestin can cause breast tenderness, headache, fatigue, and mood changes. Too much androgen can cause weight gain, acne, hirsutism, and dyslipidemia.
>
> On the other hand, too little estrogen can cause early or mid-cycle breakthrough bleeding. Too little progestin can cause late-cycle breakthrough bleeding.

Managing Side Effects of Hormonal Contraceptives	
Side Effect	Therapy Adjustment Options[49,62,65,66]
Acne	• Switch to a COC with a 3rd generation progestin, drospirenone, or dienogest since they have less androgenic activity • Switch to a product with a higher estrogen dose • Move to an extended- or continuous-cycle regimen

Breakthrough Bleeding	• First, make sure the patient has been adherent to their therapy for at least the first three months and that there are no drug interactions
	• Second, determine if the bleeding occurs early- or mid-cycle versus late-cycle
	  ◦ Early- or mid-cycle: Switch to a higher estrogen dose
	  ◦ Late-cycle: Switch to a 2nd generation progestin since

	these are more potent, or increase the progestin dose
Endometriosis-related menstrual pain	• Consider a continuous-cycle regimen
Menstruation-related problems (anemia, menorrhagia, bloating, dysmenorrhea, endometriosis, menstrual headache)	• Consider a continuous- or extended-cycle regimen
Migraines	• Stop estrogen-containing contraceptive and switch to a progestin-only contraceptive
Too Much Androgen: Increased appetite, weight gain, acne, oily skin, hirsutism, dyslipidemia	• Switch to a progestin with less androgenic activity such as 3rd generation progestins, drospirenone, or dienogest
Too Much Estrogen: Nausea, breast tenderness, melasma (grey-brown patches on the face), increased blood pressure, headache, bloating	• Switch to a lower-dose estrogen product but avoid the patch since it gives a higher estrogen exposure • Consider the vaginal ring because it has the lowest estrogen exposure • Consider a product with drospirenone if bloating is a particular problem
Too Much Progestin: Headache, breast tenderness, fatigue, changes in mood	• Switch to a progestin with less activity at progesterone receptors, such as drospirenone or a 1st generation progestin

Test your hormonal contraceptive knowledge:

Which side effects might lead you to suggest extended- or continuous-cycle hormonal contraceptive therapy?

- *Acne*
- *Endometriosis-related menstrual pain*
- *Menstruation-related problems such as dysmenorrhea, endometriosis, bloating, or menstrual headache*

Which side effect warrants stopping estrogen-containing contraceptives?
Migraines

The Bottom Line

Pharmacists are being asked to get more involved with hormonal contraceptive therapy recommendations for patients. There are several different hormonal contraceptive options available, so it's important for pharmacists to be familiar with what's available, when certain products should be used or avoided, and how to adjust therapy in response to side effects. By learning this information and knowing how to apply it, pharmacists will be able to participate in recommending and prescribing hormonal contraceptive products (where allowed by state law).

Quiz Questions

Question #1

How do the different types of estrogen used in combined oral contraceptives compare?

- a. Estradiol valerate comes in the same doses as ethinyl estradiol.
- b. Estradiol valerate is associated with fewer side effects than ethinyl estradiol.
- c. Ethinyl estradiol gets converted to a naturally occurring estrogen, while estradiol valerate does not.
- d. Ethinyl estradiol comes in single and multiphasic products, while estradiol valerate is only available in a multiphasic product.

Question #2

Which progestin has the lowest risk of causing an exacerbation of acne or hirsutism?

- a. Drospirenone
- b. Levonorgestrel
- c. Norethindrone
- d. Norgestrel

Question #3

Which progestin would be most likely to cause breakthrough bleeding?

- a. Desogestrel
- b. Ethynodiol diacetate
- c. Levonorgestrel
- d. Norgestimate

Question #4

What would be a reason to consider using an oral contraceptive with more than 30 mcg of ethinyl estradiol?

- a. Obesity
- b. Smoking
- c. Concomitant use of a CYP 3A4 inducer
- d. Concomitant use of a P-glycoprotein substrate

Question #5

How are monophasic oral contraceptives different from multiphasic?

- a. They have more straightforward instructions for missed doses.
- b. They have an increased risk of causing side effects.
- c. They are not as readily available.
- d. They are more effective.

Question #6

What would be the best option for a patient who is interested in contraception and also wants to stop monthly bleeding due to severe dysmenorrhea and heavy bleeding?

- a. Monophasic pill taken as directed on the packaging
- b. Monophasic pill taken continuously
- c. Multiphasic pill taken as directed on the packaging
- d. Multiphasic pill taken continuously

Question #7

Samantha is a 30-year-old female patient who suffers from migraine headaches with aura. Which hormonal contraceptive therapy would be most appropriate for her to use?

- a. Vaginal ring
- b. Transdermal patch
- c. Norethindrone 350 mcg
- d. Ethinyl estradiol 50 mcg/norethindrone 1 mg pill

Question #8

Alissa is a 24-year-old female patient who takes topiramate for epilepsy. According to the U.S. MEC, which hormonal contraceptive therapy would be most appropriate to recommend for Alissa?

- a. Combined oral contraceptive pill
- b. Depot injection
- c. Progestin-only pill
- d. Vaginal ring

Question #9

Jennifer is a 21-year-old female patient who began taking ethinyl estradiol 20 mcg/levonorgestrel 0.1 mg three months ago. She reports that she doesn't feel like herself lately and has been feeling more fatigued and moody. Which therapy would be the best option to recommend the patient be switched to?

- a. Transdermal patch
- b. Medroxyprogesterone depot injection
- c. Estradiol valerate 1 to 3 mg/dienogest 2 to 3 mg
- d. Ethinyl estradiol 20 mcg/norethindrone acetate 1 mg

Question #10

Courtney is a 19-year-old female patient with a history of depression who recently started using the hormonal patch. She reports that she has been experiencing very uncomfortable bloating and nausea. She states that she wants to stop the patch and try something different. What would be the best recommendation?

- a. Vaginal ring
- b. Depot injection
- c. Norethindrone 350 mcg
- d. Ethinyl estradiol 35 mcg/ethynodiol diacetate 1 mg

Submit your answers

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Hormonal Contraceptive Selection
(19-246)

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, as well as manage adverse effects related to different products. Pharmacists are playing an even bigger role in helping patients with contraceptive selection in states that allow pharmacists to prescribe hormonal contraceptive products

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

Goals and Objectives: The goal of this application-based activity is to help pharmacists in all settings recommend or prescribe hormonal contraceptives for patients.

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

1. Compare different types of hormonal contraceptives.
2. Choose the most appropriate combined hormonal contraceptive regimen for a patient.
3. Assess a patient for conditions that may impact hormonal contraceptive selection.
4. Recommend a hormonal contraceptive based on other interacting meds a patient is taking.
5. Identify alternative options for patients with side effects from their hormonal contraceptive.

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Date of Release
September 1, 2019

Date of Expiration
August 31, 2021

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