PHARMACIST CE:

Review of Pharmacologic Contraceptive Options and Clinical Considerations for Use

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According to the most recently available data, nearly half of all pregnancies that have occurred in the United States (U.S.) are defined as unintended.[1] Unintended pregnancies include those pregnancies that are either unwanted or mistimed, and studies have found that children born from such circumstances are not only more likely to arrive prematurely, but they are also more likely to die within their first year of life.[2] Additionally, children of mothers with unintended pregnancies are more likely to suffer physical abuse, cigarette smoke exposure, substance abuse, and other forms of neglect when compared to those children born from mothers with timed and expected conception.[2] With higher instances of abuse and neglect, children of mothers with unintended pregnancies tend to rely more on social systems, such as welfare and social services, which can pose a societal strain and perpetuate multigenerational health disparities.

In response, the Office of Disease Prevention and Health listed decreasing the number of unintended pregnancies in the U.S. to be a national priority in 2010 when it compiled its Healthy People 2020 initiative.[3] The use of contraceptives, in particular hormonal contraceptives, is central to this task.[4,5] Despite this, many women still struggle with having adequate AZaccess to these necessary therapeutics.[6] In fact, recent surveys suggest that, of those women who have tried hormonal contraceptives at least once in their lifetime, at least 29% of them had trouble either obtaining an initial prescription or getting refills.[7] This was primarily due to lack of transportation, limited and inconvenient clinic hours, or lack of a clinic itself. In contrast, a very small percentage of women (4%) listed issues with having access to a pharmacy.

In an effort to increase access to hormonal contraceptives, multiple states have passed legislation to allow licensed pharmacists to autonomously prescribe some hormonal contraceptives. States where pharmacists currently have this prescriptive authority include California, Colorado, Hawaii, Idaho, Maryland, New Mexico, Oregon, Utah, and West Virginia, along with the District of Columbia.[8] It might be anticipated that other states will follow suit and pass similar legislation in the near future. As such, it is pivotal that practicing pharmacists feel comfortable stepping into this expanded role. In states where pharmacist contraceptive prescribing already occurs, a recent study found that most pharmacists felt comfortable with recall of contraceptive adverse effects and appropriate dosing regimens.[9] However, few pharmacists felt confident in their ability to find a contraceptive that is tailored to a specific patient's needs, taking into consideration a patient's medical conditions and prior adverse effects. In an attempt to decrease this knowledge gap

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Learning Objectives

- Describe the two phases of the menstrual cycle including the key hormones involved
- Determine which prescription contraceptive options are safe for a specific patient utilizing the CDC Medical Eligibility Criteria chart
- Compare and contrast available prescription contraceptives taking into consideration route of administration, duration of action, effectiveness, and safety
- Apply knowledge regarding properties of estrogen and progestins to customize a patient's hormonal contraceptive regimen when adverse effects are experienced
- Identify serious adverse effects of hormonal contraception using the ACHES acronym

and increase pharmacist confidence in providing recommendations for initiation and modification of contraceptive therapy, this continuing education will provide a review of menstrual physiology, screening tactics to identify women eligible for hormonal contraceptive use, therapeutic considerations for different prescription contraceptive options, and strategies to address and mitigate adverse effects. Of note, emergency contraception and barrier methods (like condoms, diaphragm, cervical cap, and spermicides) are not discussed in this review but are important to consider when providing comprehensive contraception care for patients—it is recommended to review these topics on your own if a refresher is needed.

Menstrual Cycle Overview

A general knowledge of the physiology of the menstrual cycle and the hormones involved is required to understand the mechanism of action for the various contraceptive agents and to be able to appropriately modify and adjust contraceptive therapy when needed. The menstrual cycle duration is defined as the time between the first day of one period and the first day of the following period.[10] On average, the menstrual cycle is 28 days in length, but this will vary from woman to woman with a normal range of 21 to 40 days. Menstrual cycles that are shorter or longer than this range might be due to an underlying disorder, and women should be referred to their medical provider for further evaluation.

The menstrual cycle can be divided into two phases: the follicular (preovulatory) phase and the luteal (postovulatory) phase.[10] Ovulation occurs between these two phases and is typically around day 14 of the cycle. The follicular phase begins on the first day of the menstrual cycle and is characterized by rising levels of follicle stimulating hormone (FSH). This hormone is responsible for stimulating the growth of a group of ovarian follicles with ultimately one follicle becoming dominant. Ovarian follicles produce estradiol and progesterone, and estradiol promotes growth of the uterine endometrium in preparation for implantation. The sustained elevated levels of estradiol trigger the pituitary gland to release high levels of luteinizing hormone (LH), known as the LH surge. Luteinizing hormone is responsible for catalyzing the final steps of follicular maturation, rupture, and release of the oocyte. The ovulation process typically occurs shortly (10 to 16 hours) after the peak of the LH surge. As a result, conception is most likely to occur when intercourse takes place from two days prior to ovulation to the day of ovulation. After the follicle ruptures, it is called the corpus luteum, and the luteal phase has begun. The corpus luteum secretes progesterone and estradiol. Progesterone production during the luteal phase is essential for maintaining the endometrial lining should pregnancy occur. If fertilization and implantation do not occur, then the corpus luteum will degenerate, and progesterone and estradiol levels will decline. The decline in these hormones leads to shedding of the endometrial lining and a rise in FSH levels for the beginning of the next cycle.

TABLE 1. Risk categories from U.S. Medical Eligibility Criteria for Contraceptive Use

Category 1	No restriction (method can be used)
Category 2	Advantages generally outweigh risks (method can be used, but careful follow-up might be required).
Category 3	Risks generally outweigh the advantages. (method not recommended unless other more appropriate methods are not available or acceptable).
Category 4	Unacceptable health risk (method not to be used)

Table adapted from CDC U.S. MEC[17]

Health and History of Screening

Prior to initiating contraception, it is essential that an accurate past and present medical and medication history is obtained from the patient to assist in selecting contraception that will be safe and effective. The medication history should include prescription drugs, nonprescription drugs, herbals, and supplements. In states where pharmacist-prescribed birth control legislation is enacted, standard self-screening tools have been developed by state pharmacy associations to assist pharmacists with collecting pertinent information from a patient.[11-14] Patients should be asked about the presence or history of specific medical conditions that can be impacted by contraceptive drug therapy, including but not limited to: diabetes, migraine, hypertension, hyperlipidemia, cardiovascular (CV) disease, venous thromboembolism (VTE), tobacco use, cancer, liver disease, immunological disorders, seizures, human immunodeficiency virus, and other infections.[15] While not required prior to initiating or for continuing birth control, pharmacists should discuss the importance of routine women's health screenings at regular intervals and refer patients to other healthcare providers as needed. This includes pap smears, sexually transmitted infection testing, and breast examinations.[16] Pharmacists are also positioned to promote other preventative healthcare services, such as administration of human papillomavirus (HPV) vaccination.

Once an accurate past and present medical history is obtained, pharmacists should determine which contraceptive options a patient is medically eligible for. The Centers for Disease Control and Prevention (CDC) has published evidence-based guidance in this area in its "U.S. Medical Eligibility Criteria for Contraceptive Use" report.[17] This guidance document provides recommendations that focus on the safety of initiating or continuing six different types of contraceptive methods (copper intrauterine device [IUD], levonorgestrel IUD, implant, depot medroxyprogesterone acetate [DMPA], progestin-only pill [POP], and combined hormonal contraceptives [CHC]) based on the presence of certain medical conditions, characteristics, and concurrent medications. It is crucial that pharmacists are skilled in using and interpreting the CDC Medical Eligibility Criteria (MEC) as a tool to guide their clinical decision making with regard to contraceptives.

The MEC summary table includes medical conditions, patient characteristics,

TABLE 2. Summary of Contraceptive Options[10,19,24-25,28,30-35,39-43,48-49,52-53]

Contraceptive Category	Drugs	Dosing Considerations	Effectiveness		Clinical Pearls
			Typical Use	Perfect Use	
Non-Hormonal					
Copper IUD	Paragard®	• Needs to be inserted by clinician • Lasts up to 10 years	99.2%	>99%	• Heavy menstrual bleeding • Cost-effective in long-term • Patient counseling should include PAINS acronym
Progestin-Only					
Pill	Norethindrone Drospirenone	• Norethindrone has 3-hour window for missed dose • Drospirenone has 24-hour window for missed dose • No placebo pills	91-93%	>99%	• Common oral option used in breastfeeding women • Irregular menses and breakthrough bleeding common
IUD	Kyleena® Liletta® Mirena® Skyla® (all contain LNG)	• Need to be inserted by clinician • Kyleena® - lasts 5 years • Liletta® - lasts 6 years • Mirena® - lasts 5 years • Skyla® - lasts 3 years	>99%	>99%	• Lighter or reduced bleeding • Cost effective in long-term • Patient counseling should include PAINS acronym
Injection	Depo-Provera® (DMPA)	• Administered every 3 months IM or SQ » IM is clinician-administered only » SQ can be self-administered or clinician-administered • Duration of use should be limited to 2 years	93-94%	>99%	• More weight gain • Bone loss limits duration of use • Delayed return to fertility
Implant	Nexplanon® (ENG)	• Need to be inserted by clinician • Lasts 3 years	>99%	>99%	• Bleeding can be unpredictable—some women will have heavier bleeding and some will achieve amenorrhea
Combined Hormonal					
Pill	Many (consider estrogen and progestin components when assessing a specific product)	• Monophasic and multiphasic options • Extended use dosing is an option • Number of placebo pills can be variable (3 days or 7 days) depending on drug	91-93%	>99%	• Medication adherence is critical to prevent pregnancy • Given number of available products with varying hormone levels and progestin generation, can be more easily tailored to specific patient • Higher risk of thrombotic events • Important to assess medical eligibility prior to using CHC
Patch	Xulane® (norelgestromin+ EE) Twirla® (LNG+EE)	• New patch is applied weekly • Extended use dosing is an option • Application sites should be rotated	91-93%	>99%	• Higher systemic estrogen exposure • Contraindicated if BMI>30 kg/m2 • Important to assess medical eligibility prior to using CHC
Ring	NuvaRing® (ENG+EE) Annovera® (SGA+EE)	• Ring is kept in place for 3 continuous weeks and then removed • Each NuvaRing® system is for single use; Annovera® system can be used for 13 cycles	91-93%	>99%	• Avoid if history of toxic shock syndrome • Important to assess medical eligibility prior to using CHC

Abbreviations: IUD, intrauterine device; LNG, levonorgestrel; DMPA, depot medroxyprogesterone acetate; IM, intramuscular; SQ, subcutaneous; ENG, etonorgestrel; CHC, combined hormonal contraceptive; EE, ethinyl estradiol; SGA, segesterone acetate

and concurrent medications as rows and includes the six different types of contraceptive methods mentioned above as columns.[18] Within each method, there are two subheadings: I and C, where I represents initiation of the contraceptive method and C represents continuation of the contraceptive method. Each cell represents the intersection of a particular contraceptive option and a specific medical condition or characteristic, and is assigned to one of four categories (Table 1). Category 1 indicates that there are no restrictions to using the contraceptive method for that condition while category 4 indicates that the contraceptive method should be avoided for that condition due to unacceptable health risk. Categories 2 and 3 require more clinical judgment in weighing the benefits and risks and might require closer patient follow-up. For example, if we use the table to consider what options would be appropriate for a patient who experiences migraine with aura, we see that all contraceptive methods are assigned a category 1 except for combined hormonal contraceptives, which is assigned a category 4. The categories are the same for both initiation and continuation in this example. This indicates that an IUD, DMPA, implant, or POP would be safe to use, but CHCs, including combined oral contraceptives, vaginal ring, and patch, should be avoided.

It is important to note that this tool is intended to assess safety and does not address efficacy or patient preferences. Therefore, it is important to collect additional information to assist in tailoring a contraceptive regimen for an individual patient. For example, patients should be asked about their primary purpose for using contraception, as not all patients use contraception solely for preventing pregnancy. Clinicians should also determine whether a patient is sexually active, in order to provide appropriate patient education. Other pertinent information might include the patient's desired family planning, prior experiences with contraception (if any), and preference for dosage form.

Overview of Contraceptives and Therapeutic Considerations

In this section, we provide an overview of three types of prescription contraceptives—non-hormonal, progestin-only, and combined hormonal contraceptives—and the drugs that are included in each of these categories. Table 2 highlights key information for each. The medical eligibility category; patient preferences; and drug properties, including effectiveness, can be collectively evaluated to determine an ideal contraceptive option for a specific patient.

Non-Hormonal Contraceptives

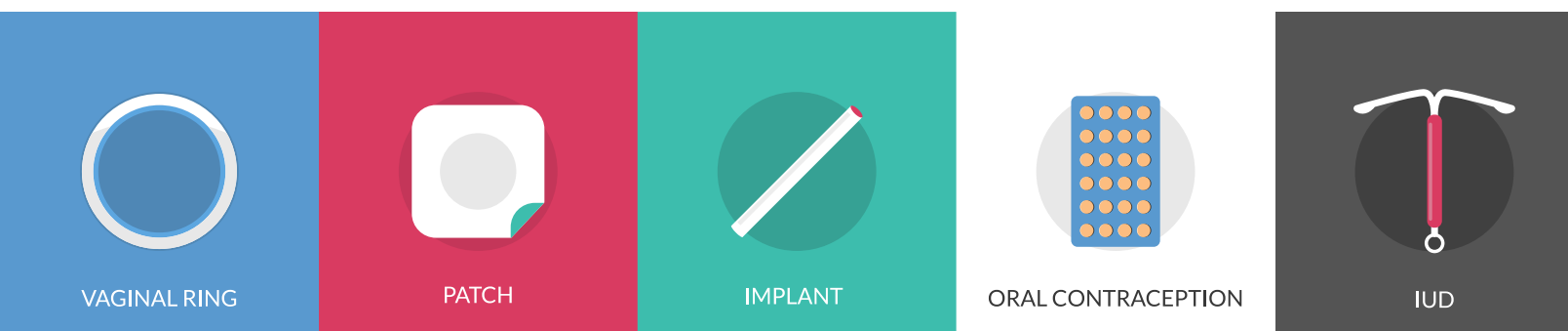
Copper Intrauterine Device - The copper IUD, Paragard®, is the only non-hormonal prescription contraceptive currently available in the U.S. It was the first IUD to come to market and can last up to 10 years once in place in the uterus.[19] The copper coil IUD achieves its contraceptive effects by acting as a foreign body in the uterus. It is also believed to inhibit fertilization through its toxic effects on sperm and the endometrial lining, and takes effect almost immediately after insertion.[20]

Due to its copper content, Paragard® might not be the best option for women who have Wilson's disease or other syndromes that impair absorption of elemental copper.[19] Women who use it are more likely to experience heavier menstruation and increased dysmenorrhea and thus the device might not be the best option for women with anemia or those who already have long periods and heavy menstrual flow. The copper IUD should be considered for women who prefer or need to avoid all hormonal contraceptive options. Adverse effects and monitoring considerations for all IUDs are further discussed in the levonorgestrel IUD section.

On-Demand Vaginal pH Regulator - The U.S. Food and Drug Administration (FDA) recently approved a contraceptive vaginal gel, Phexxi™, which contains lactic acid, citric acid, and potassium bitartrate. This product is anticipated to be available in the U.S. in the fall of 2020, along with a telemedicine support system to assist women with access to the product.[21] This contraceptive is intended to be used on demand and works by maintaining the acidic vaginal pH in the range of 3.5 to 4.5, which directly impacts sperm motility.[22] The recommended dosing is to administer 5 grams vaginally up to 1 hour prior to vaginal intercourse and is supplied as a single-use, pre-filled applicator. In an open-label, single-arm, multicenter trial, the 7-cycle pregnancy rate was 13.7% (101 pregnancies in 1,183 patients during 4,769 cycles).[22] This on-demand option appears to be less effective than other contraceptive methods, and its place in therapy is currently unknown. However, it might be a desirable non-hormonal option for women who might not have otherwise used contraception.

Progestin-Only Contraceptives

Progestins act as contraceptives via multiple mechanisms of action. The primary mechanism of action is to prevent or delay ovulation via inhibition of LH release from the pituitary gland.[10] This is accomplished by negative feedback from excess progestin levels. With blunted levels of LH, the surge in LH that usually causes ovulation is either absent or delayed. In the case of delayed ovulation, it is thought that this would cause a mistiming with



when viable sperm would be available for conception. Secondary mechanisms of action include thickening of the cervical mucus, atrophy of the endometrium, and decreased motility of an ovum in fallopian tubes, all of which make it harder for ovulation or proper fertilization to occur.

Contraceptives consisting solely of progestins are available as pills (norethindrone, drospirenone), IUDs (levonorgestrel), implant (etonogestrel), and injection (medroxyprogesterone acetate). Both the IUDs and the implant available are commonly referred to as LARCs (long acting reversible contraceptives). In general, progestin-only contraceptives are good options for women who need to avoid estrogen (e.g., because they are breastfeeding, have a history of VTE, or have a high CV risk). They are also preferred when a patient desires a long-acting reversible option.

Progestin-Only Pills (POPs) - Pills that contain only progestin are often referred to as "mini-pills" or POPs. Until June 2019, the only approved POP in the U.S. was norethindrone. The norethindrone-containing POP should be taken once daily and must be taken as close as possible to the same time each day in order to ensure efficacy. If a dose is taken even three hours from its usual time, it is considered a missed dose and a back-up method (such as a barrier method) should be used for the next 48 hours to prevent pregnancy.[23,24] It is important that women are informed that there is no placebo or "sugar pill" week with this option; the contraceptive is taken continuously. In 2019, the FDA approved a new progestin-only oral option containing drospirenone.[25] This new POP is the first and only POP with a 24-hour missed-pill window, which is in contrast to the norethindrone-containing POP. The drospirenone-containing POP is supplied as a 28-day pack with 24 days of active tablets and four days of placebo. In general, POPs might be considered for women who cannot take estrogen. POPs are commonly used in the postpartum period by breastfeeding women, because they have been shown to have a positive or neutral effect on lactation, in contrast to estrogens.[26] There is no delay in return to fertility with POPs, which is in contrast to other progestin-only options discussed later. This might be due in part to the fact that an estimated 40% of women still experience ovulation while on POPs. In this case, the secondary effects of the progestins are thought to contribute to a greater degree of contraceptive effectiveness.[23,27] However, the combination of continued ovulation with decreased fallopian motility caused by progestin creates higher risks for ectopic pregnancy.

Injection - The injectable form of progestin, also known as Depo-Provera® or DMPA, consists of crystalline medroxyprogesterone acetate in an aqueous suspension and is available in 150 mg/mL strength in either vials or prefilled syringes.[28] The injection can be administered intramuscularly or subcutaneously. The intramuscular option must be administered in a clinic setting, whereas the subcutaneous option can be administered in the clinic or self-administered by the patient at home. The DMPA injection ideally should be given within the first 5 to 7 days of a woman's menstrual period. If given outside of this time frame, a reliable form of back-up contraception should be used for the first week after the injection is given. One dose lasts 13 weeks (3 months) and does not need to be adjusted for weight, making it a good option for women who are considered overweight or obese. If a woman misses one of her injections, there is a two-week "grace period" in which no back-up contraception is needed. Long-term use of DMPA, defined as two years or longer, is warned against in the package labeling, due to a propensity for it to cause hypoestrogenism, which can lead to loss in bone mineral density. The manufacturer warns that such bone loss might not be completely reversible and that DMPA should only be used long-term when other contraceptive options cannot be considered. Furthermore, DMPA causes a prolonged delay in return to fertility following cessation of its use. On average, return to fertility can take anywhere from 14 weeks to 22 months.[23,29] As such, DMPA might not be a good option for women trying to conceive in the near future, as well as those with a history of bone-related comorbidities or fractures. However, the DMPA injection might be preferred for women who do not want to take a medication daily and wish to avoid more invasive options like the implant or the IUD discussed later.

Implant - The progestin implant is a small, flexible rod containing etonogestrel that is inserted subdermally by a specially trained clinician into the inner side of the non-dominant upper arm. The Nexplanon® implant is designed to release etonogestrel over a period of three years.[30] Of note, Nexplanon® has replaced an older version of the implant, Implanon®. This newer version of the implant contains barium sulfate so that it can be located by imaging if displaced.

The timing of implant insertion depends on the woman's recent contraceptive history, and the package insert should be reviewed for more specific details on this topic.[30] Once inserted, the patient should be able to feel the implant in the arm at all times. Patients should be counseled that, if at any point they can no longer feel the implant, they need to contact their provider, because there is a chance that the implant might have migrated or been improperly placed, increasing risk for pregnancy to occur. The implant has not been studied in women whose weight is greater than 130% of their ideal body weight and thus might not be the best option for those who are overweight or obese. In regard to return of fertility after implant removal, most women are able to become pregnant within the year following the device's removal.

Women who struggle to adhere to pills, rings, or patches might benefit from using the implant if they can tolerate the insertion process. One of the most common side effects seen is change in menstrual bleeding, which could include either amenorrhea or increased flow.[30] Overall, most women experienced infrequent bleeding, defined as less than three bleeding or spotting episodes over a 90-day time period. However, bleeding that was prolonged, defined as lasting 14 days or more over a 90-day time period, was also fairly common. It is suggested that whatever changes a woman experiences within the first 90 days of use of Nexplanon® will predict what she will see for the duration of use.

Intrauterine Devices (IUDs) - The four levonorgestrel-containing IUDs are

Kyleena®, Liletta®, Mirena®, and Skyla® and were designed to help reduce heavy menstrual bleeding that is observed with Paragard® users.[23, 31-34] While all four of the hormonal IUDs share the same active ingredient, they do vary slightly in their suggested population of use, length of duration, and concentration of hormone released.[35]

It is best to consider desired duration of action, potential for systemic side effects, and cost/insurance coverage when helping a patient decide which IUD is best for them. The duration of use ranges from 3 years (Skyla®) to 6 years (Liletta®) and the amount of hormone released per day is variable, with Skyla® having the lowest amount of hormone released per day and Mirena® and Liletta® having the greatest amount of hormone released per day.[31-34] For women with barriers to accessing IUDs due to cost, it might be worth considering patient-assistance programs. For Liletta® in particular, the manufacturer has partnered with Medicines360, a nonprofit pharmaceutical company, to provide the IUD at a more affordable cost.[36]

One important consideration for all IUDs is that a trained clinician must insert the device, which could mean higher up-front costs for their use. However, it has been demonstrated that IUDs are the most cost-effective hormonal contraceptive for use over time.[37] Once an IUD is inserted, women should be re-evaluated in four to six weeks to ensure the IUD is properly placed.[31-34] Women should also be educated on warning signs that should prompt medical attention. Warning signs can be recalled by the "PAINS" acronym: Period is late; Abdominal pain or pain with intercourse; Infection, abnormal or odorous vaginal discharge; Not feeling well, fevers, chills; String missing, shortened or longer.[35] If any of these signs or symptoms are present, they necessitate a referral to a provider. There is no significant delay in fertility seen following removal of an IUD.[10,35]

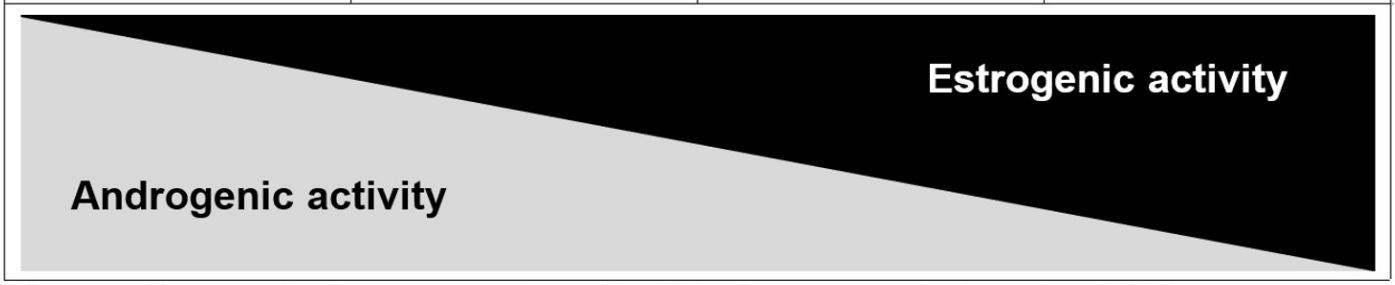
IUDs are a good option for women who desire a highly effective and long-acting contraceptive, but struggle with routine adherence to a pill, patch, or ring contraceptive regimen. Additionally, IUDs might be preferred for women who have barriers to accessing a pharmacy to obtain refills.

Combined Hormonal Contraceptives

Combined hormonal contraceptives (CHCs) have a synthetic estrogen component in addition to a progestin component. In the U.S., ethinyl estradiol (EE), mestranol, and estradiol valerate are the three estrogens used, with EE being the most commonly seen in combination contraceptives.[35,38] Ethinyl estradiol doses range from 10 to 50 mcg depending on the combined contraceptive with typical doses in the range of 20 to 35 mcg.[10] There are currently eleven synthetic progestins used in contraceptives in the U.S.. They are categorized according to generation, ranging from first generation to fourth generation. As generation increases, androgenic properties decrease, and estrogenic properties increase (Figure 1). This is important to consider as it can impact effects of the contraceptive beyond pregnancy prevention. For example, patients with acne or hirsutism would benefit from a contraceptive with less androgenic properties. In this case, a third or fourth generation progestin would be preferred over a first or second generation progestin. Of note, drospirenone actually displays antiandrogenic properties as well as antimineralocorticoid effects, which can be helpful for women who experience side effects like bloating as a result of excess estrogen. The progestin component in combined hormonal contraceptives exerts the same mechanism of action as it does in progestin-only options. The estrogen component also contributes through negative feedback on FSH levels, which over time hinders normal follicle development to further impede ovulation and halt formation of the corpus luteum.[27] The sex hormone-binding globulin (SHBG), which binds free androgens in the body, is also increased by estrogen, which might be one reason some CHC formulations have indications for acne and hirsutism treatment.[4] Estrogen can also

FIGURE 1. Progestin Generations[10,35,40]

1st Generation	2nd Generation	3rd Generation	4th Generation
Norethindrone	Levonorgestrel	Desogestrel	Drospirenone
Norethindrone acetate	Norgestrel	Etonogestrel	Dienogest
Ethynodiol diacetate		Norgestimate	
		Norelgestromin	



As progestin generation increases, androgrenic activity decreases and estrogenic activity increases.

TABLE 3. Therapy Modifications for Combined Oral Contraceptives Based on Adverse Effects[10,35,40,56]

Adverse Effect	*Reason*	*Therapy Modification*
Early breakthrough bleeding (first half of cycle)	Insufficient estrogen	Increase estrogenic activity
Late breakthrough bleeding (second half of cycle)	Insufficient progestin	Increase progestin
Nausea/vomiting	Excess estrogen	Decrease estrogenic activity
Cyclical weight gain		
Bloating		
Fluid retention		
Breast tenderness		
Headache		
Acne, oily skin	Excess progestin*	Decrease androgenic activity
Hirsutism		
Depression	Excess progestin	Decrease progestin
Non-cyclical weight gain		

**Indicates androgen excess specifically*

help to prevent breakthrough bleeding that occurs early on in the cycle.

One of the most important factors when considering use of a CHC is to assess risk associated with exogenous estrogen use. This is where the MEC chart from the CDC can be extremely valuable. Combined hormonal contraceptives were originally developed as pills but are now available in other dosage forms, including an intravaginal ring and transdermal patch. Of note, seven days of back-up contraception are needed if it has been more than five days since the patient's last menses at the time of CHC initiation.[39]

Combined Oral Contraceptives - We cannot cover all available combined oral contraceptives (COCs) in this review, but a foundational understanding of the estrogen and progestin components that make up the various combined OCs can help in clinical decision-making. Most COCs contain 21 days of active pills and seven days of inactive or placebo pills; however, some pill packs offer 24 days of active pills and only four days of placebo in order to reduce hormone withdrawal and menses duration. Some formulations might contain iron in the hormone-free week, which might be helpful for iron-deficiency anemia. There is also a chewable form of combined OC available that can be used if a woman has trouble swallowing pills.

COCs are available in monophasic or multiphasic dosing regimens. With multiphasic (biphasic, triphasic, quadriphasic) formulations, the hormone levels in each pill fluctuate according to which week of the pill pack the patient is taking.[40] In contrast, monophasic formulations have consistent hormone levels throughout the month. Biphasic options contain two phases of varying hormone levels. Triphasic formulations include varying doses in each of the three weeks of hormonal tablets. Typically, the progestin dose increases with each week. However, estrophasic formulations are now available, where the estrogen level increases instead. Quadriphasic regimens are the newest formulations of COCs and have changing levels of both estrogen and progestin throughout the cycle.[41-43] Multiphasic options are marketed as being more physiologically similar to a woman's natural hormones during a menstrual cycle and are therefore thought to decrease adverse effects and improve cycle control. However, in two 2011 Cochrane reviews, there was insufficient evidence to conclude that multiphasic options improve effectiveness, discontinuation rates, or bleeding patterns.[44,45] Because of a lack of evidence suggesting a benefit of multiphasic options over monophasic options, it is suggested to start with a monophasic formulation in women who are initiating COCs.

As a pharmacist, it is important to note which COCs can be taken in an "extended-use" manner. An extended-use regimen is where a patient takes active hormonal contraception continuously beyond 21 days without a hormone-free interval.[40] For example, a woman could take the active tablets of a COC daily for 3 months followed by a 7-day hormone-free interval. This option might be preferred by women who desire to reduce the number of menstrual periods and the adverse effects secondary to estrogen withdrawal. There are some COCs that are specifically supplied in an extended-use regimen (i.e., contain 84 active tablets and 7 placebo tablets). Monophasic combined OCs can also be used in an extended-use manner by skipping the placebo pills and beginning the next pack. Extended-use dosing should be avoided with multiphasic formulations because of the fluctuating levels of estrogen and progestin, as this could lead to adverse effects. Of note, risk of breakthrough bleeding might be higher with extended-

use dosing for the first 3 to 6 cycles, but this decreases over time.[46] When starting a COC, there are 3 initiation methods that can be considered.[40] One is the "Sunday method," in which the woman begins the first pill in the pack on the Sunday following her most recent menses. There is also the "first day" or "same day" start, in which the woman simply starts the COC on the first day of her menses cycle. Finally, there is the "quick start," where the woman takes the first dose of the COC in the prescriber's office or as soon as she picks up the medication from the pharmacy.[47] Regardless of the method chosen, it is recommended that a back-up contraceptive be used for the first 7 days after starting an oral contraceptive if it has been more than 5 days since the start of menses. If it has been less than 5 days since the start of menses, backup contraception is not warranted.[39]

One of the major issues with oral contraceptives is adherence, with women frequently forgetting doses, being late to take doses, or missing doses due to sickness such as vomiting or diarrhea. It is important that women be counseled on what to do should a missed dose occur. If one tablet is missed or late, the woman should take the missed dose as soon as possible, which might mean taking two pills in one day, and then continue the pack as normal afterwards.[40] No back-up contraceptive is needed. If two or more consecutive tablets are missed, the woman should take one of the missed tablets and then discard the rest that were forgotten. She should then continue the rest of the pack as scheduled and use a back-up method for 7 days. If the missed dose occurs in the last week of a pill pack, she should finish the rest of the active tablets, omit the hormonal free interval of the pack and begin a new pack altogether. If at any point in a pack cycle, she misses two or more pills and has unprotected sexual intercourse within 5 days of forgetting a pill, she should consider emergency contraception. It is important to note that missed doses for progestin-only pills are handled differently (refer to progestin-only pill section above). If routine difficulty with adherence is a concern, other contraceptive options discussed in this review should be considered.

Pharmacists can play a key role in assisting women in selecting a COC, either directly (in states where pharmacist-prescribed birth control is allowed) or indirectly (by working with the woman's prescriber). The number of available COCs can be overwhelming, but a general starting place for selecting a COC is to choose a monophasic option that includes 20-30 mcg of ethinyl estradiol and a second-generation progestin like levonorgestrel. Pharmacists can then use their knowledge of the estrogen and progestin components in COCs along with patient preferences to tailor the regimen to that specific patient. For example, a patient who desires acne control might be initiated on a COC that includes a fourth generation progestin instead. Once the initial therapy has been chosen, it is possible that the woman will experience side effects from the COC, and she should be counseled accordingly. The management of adverse effects is discussed in greater detail in a later section.

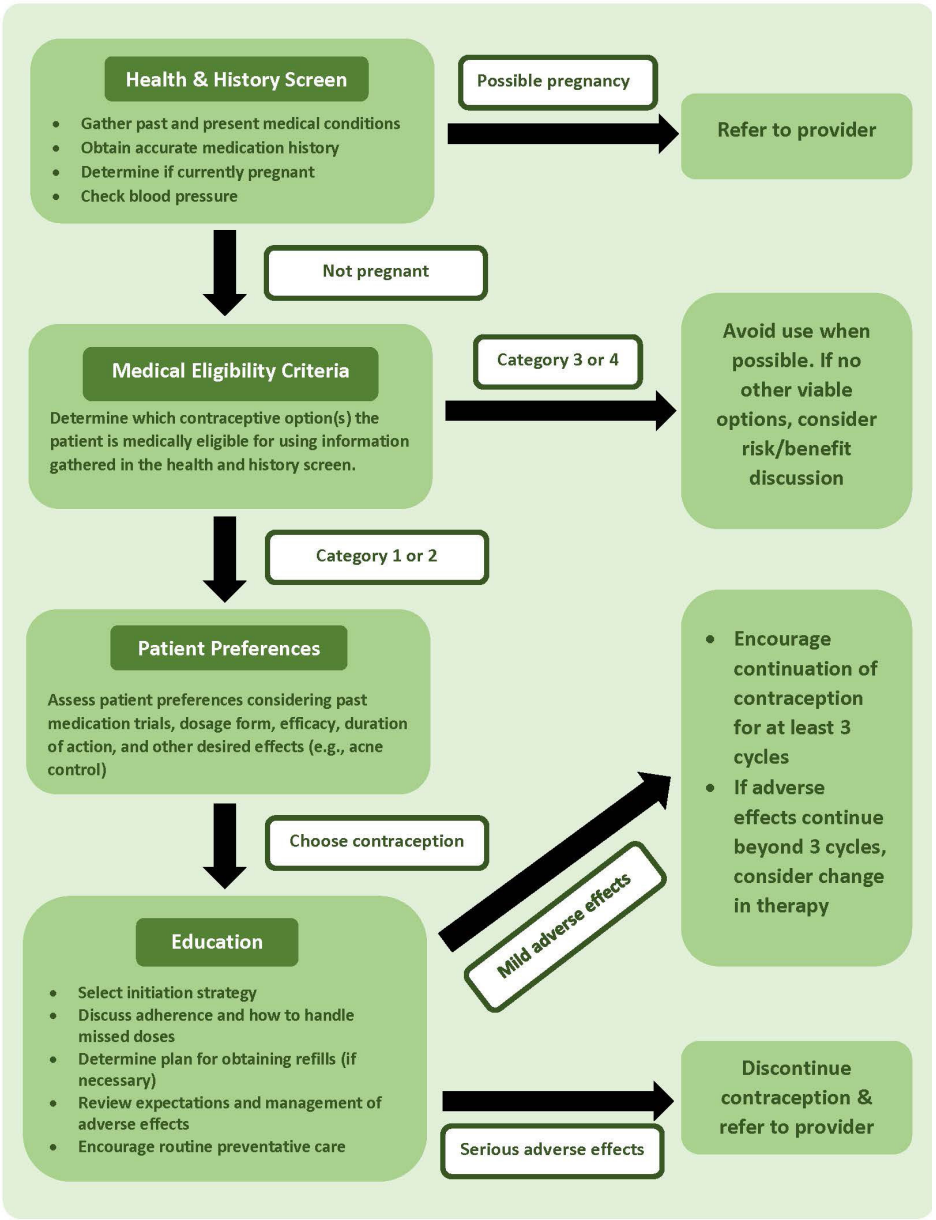
Transdermal Contraceptive Patches - There are two brands of transdermal contraceptive patches available for use currently: Xulane®, which contains 6 mg of norelgestromin and 0.75 mg of EE; and Twirla®, which contains 2.6 mg of levonorgestrel and 2.3 mg of EE.[48,49] The transdermal patch works the same way as COCs to prevent pregnancy; however, they might be more convenient for women who find daily adherence to a medication challenging. During a single 4-week cycle, a new patch is applied to the upper outer arm, abdomen, buttock, or back at the start of each week, during weeks 1-3. The previous week's patch is also removed at the beginning of these weeks and thrown away with the two adhesive sides put together. For week 4 of the cycle, the patient has a 1-week hormone-free interval during which no patch is worn. Patches can be kept on while swimming and showering, but should never be cut, damaged, or exposed to extreme heat.

The same methods for initiation of oral contraceptives apply to the transdermal patches. If a woman is switching from an oral contraceptive to the patch, she should finish her most recent pack of pills, wait for the 7-day withdrawal period to occur, and then begin the first patch on the day when she would normally begin her next pill pack.[48,49] No back-up contraception is needed if the patch is started within 7 days of stopping the pill.

When applying the patch, the upper outer arm, abdomen, buttock, or back can be used, and sites should be rotated weekly in order to avoid irritation. Women should be counseled to check the patch every day in order to ensure all the edges are still adhered to the skin. If the patch for some reason falls off, no back-up contraceptive is needed unless it is off for longer than 1 day, in which case back-up would be needed for a period of at least 7 days. If the patient forgets to remove a patch, the specific action that needs to be taken will depend on which week of the cycle it is. Pharmacists can refer to the package insert to provide education should this occur. The patch can be used in an extended-use fashion similar to the COC. Instead of the 7-day hormone-free interval during which the patch would be off, the patient could immediately apply the next patch. A common approach is for the patient to continue applying a new patch weekly for 12 weeks, followed by a 1-week hormone-free interval for menses to occur. However, other regimens have also been studied and well-tolerated.[50]

Women with a body mass index (BMI) greater than 30 kg/m^2 and women with venous thromboembolism (VTE) risk factors should generally avoid the patch as a first option. Both patches are only approved for women with BMI less than 30 kg/m^2 due to the possibility of altered pharmacokinetics and decreased efficacy in this population. Of note, a 2016 Cochrane Review was conducted that evaluated the efficacy of hormonal contraceptives in overweight and obese women and did not find an association between effectiveness of hormonal contraceptives and BMI or weight.[51] However, the quality of the studies that included the patch were considered to be low or very low. Of note, package labeling for contraceptive patches includes a warning stating that women who use the patch might be exposed to 60% greater estrogen levels than what is seen with combined COC use, potentially increasing risk for VTE.[48,49] If other contraceptive options are not available or appropriate for a patient with the aforementioned characteristics, then the

FIGURE 2. General Process for Initiating Contraception



contraceptive patch could be considered with discussion of risks and benefits.

Intravaginal Contraceptive Rings - NuvaRing® and Annovera® are the two intravaginal contraceptive ring systems available for use, both containing a progestin and estrogen component.[52,53] The NuvaRing® system is a colorless ring containing etonogestrel and EE, while Annovera® is an opaque white ring containing segesterone acetate and EE. Of note, neither ring contains latex.

Regardless of whether NuvaRing® or Annovera® is used, one ring is meant to be placed into the vagina and remain there for a continuous 3-week time period.[52,53] At the end of the third week of use, the ring is removed by hooking the index finger under the rim of the ring, grasping firmly with both the index and middle finger and pulling. This is then followed by a ring-free week during which bleeding occurs due to hormone withdrawal. Following the 7-day hormone-free interval, the woman is ready for the next 3-week cycle of use. It is important that, each month, the ring is inserted on the same day of the week and around the same time of the day as the last ring was inserted. This helps maintain more consistent drug levels in the body to reduce risk of pregnancy.

Each NuvaRing® is for single use and should be disposed of after each month.[52] In contrast, Annovera® is a reusable ring, and after week 3 of each cycle can be washed with mild soap and water, patted dry, and then kept in its case during the ring-free period.[53] When it is time to start a new cycle, the Annovera® ring should be once again cleaned prior to insertion. Annovera® is designed to last for thirteen 28-day cycles, which is equivalent to one year of use. Since Annovera® is reusable, it does not require routine access to a pharmacy for refills, making it a potentially good option for those women who live in rural areas or who frequently travel. It also might be an ideal option for those women who wish to use a contraceptive method that allows them to reduce their impact on the environment. Both intravaginal ring options might be preferred for women who wish to avoid taking a medication daily and wish to avoid LARCs like the IUD and implant. Of note, Annovera® is a new, branded product which is important to consider from a cost perspective. Extended-use dosing has been studied with NuvaRing®, but not with the Annovera® ring.[54] If extended-use dosing is used with NuvaRing®, the patient would insert a ring that is then left in place for 3 weeks. After 3 weeks, the ring is removed, and a new ring is inserted. The hormone-free interval is skipped.

If a woman is not on hormonal contraception prior to beginning NuvaRing®, it is ideal to insert the ring on the first day of her most recent menses. It is okay to begin using the ring after day one of menses, however a reliable form of back-up contraceptive should be used for 7 days.[52] When starting on Annovera®, it is recommended the ring be inserted anywhere between days 2 and 5 of menses and back-up only used if insertion occurs outside of this range.[53] Accidental expulsion of either ring might occur during the 3-week cycle and the package insert should be reviewed for how to counsel a patient on how to manage if this occurs.

There have been some studies that suggest the risk of toxic shock syndrome (TSS) with use of an intravaginal contraceptive system; thus, women with a history of TSS might want to

consider other options.[52,53] Neither ring is compatible with douching; however, spermicides, tampons, and antifungal creams can be used concomitantly. Due to the nature of insertion, women who are prone to vaginal irritation or tears might not be good candidates for transdermal ring systems. NuvaRing® should be kept in a refrigerator prior to dispensing to the patient[52] but can be kept at room temperature afterwards for up to 4 months.[55] Annovera®, on the other hand, should always be stored at room temperature.[53]

Management of Adverse Effects

Discontinuation of contraception is common, and adverse effects have been the most commonly reported reason for discontinuation.[55] Pharmacists can play a key role in providing appropriate counseling to women regarding adverse effects when contraception is initiated. Furthermore, pharmacists can provide recommendations for how to appropriately adjust contraception after identifying and assessing adverse effects that women experience while on contraception.

When contraception is initiated, patients should be informed about what adverse effects would be considered serious and require drug discontinuation. A common acronym that can be used to remember serious adverse effects for hormonal contraception is ACHES: abdominal pain, chest pain, headaches (severe), eye problems, and severe leg pain.[35] If a patient is experiencing any of these symptoms, she should stop contraception immediately and seek medical attention, as these symptoms could be indicative of a thrombotic event like myocardial infarction, stroke, pulmonary embolism, or deep vein thrombosis.

Common side effects include headache, nausea, vomiting, breakthrough bleeding or spotting, bloating, weight gain, and mood changes. Upon initiation of a contraceptive, women should be counseled that it can take 2 to 3 cycles for their bodies to adjust to the new drug.[35] Many side effects occur early and then dissipate with continued use. Therefore, it is recommended that no changes are made to the contraceptive regimen for at least 2 to 3 months after it is initiated, or a new change is made (unless a serious adverse effect occurs that requires immediate discontinuation).

Adverse effects that occur beyond the adjustment period can usually be attributed to an excess or insufficiency of the estrogen or progestin activity in the current contraceptive. Table 3 summarizes some common adverse effects and how to adjust the estrogen or progestin activity to mitigate the adverse effect. Estrogenic activity can be modified by either changing the dose of the estradiol component or by switching the progestin component to a different generation progestin (Figure 1). Similarly, if the progestin component needs to be modified, both the dose and the androgenicity of the progestin should be considered.

Conclusion

Access to and appropriate use of contraception is critical for prevention of unintended pregnancies. Given the number of available contraceptive options, each with its own unique considerations, pharmacists can play a key role in ensuring safe and effective use of contraception. Figure 2 outlines a general process for pharmacists to consider when prescribing contraception and/or providing recommendations to another healthcare provider who is prescribing contraception. As pharmacists are the most accessible healthcare providers and pharmacist-driven services continue to expand, it is essential that we are confident in our ability to provide women with high-quality care in regard to contraceptive use.

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Assessment Questions

For the assessment questions, you will need to access the CDC Medical Eligibility Criteria for Contraceptive Use chart (www.cdc.gov/reproductivehealth/contraception/pdf/summary-chart-us-medical-eligibility-criteria_508tagged.pdf)

1. Choose the correct statement regarding the menstrual cycle:
   a. The follicular phase begins around day 14 of each menstrual cycle
   b. High levels of estradiol triggers menses to occur
   c. All women have a menstrual cycle that is 30 days in length
   d. The "LH surge" is responsible for catalyzing the final steps for ovulation to occur

2. **True or False:** According to the CDC Medical Eligibility Criteria for contraceptive use, a woman who has mild compensated cirrhosis should avoid use of combined hormonal contraceptives given their category 4 rating.
   a. True
   b. False

3. What is the category designation for the contraceptive patch in a woman with high risk for recurrent venous thromboembolism according to the CDC MEC?
   a. Category 1
   b. Category 2
   c. Category 3
   d. Category 4

4. **True or False:** Prior to starting a woman on an oral contraceptive, the pharmacist must ensure a pap smear and STI screening has been completed within the past year.
   a. True
   b. False

5. Choose the correct statement regarding intrauterine devices (IUDs):
   a. Active pelvic inflammatory disease is category 4 for initiation of IUDs
   b. Hormonal IUDs available in the US contain desogestrel or levonorgestrel
   c. The copper IUD was designed to decrease heavy menstrual flow
   d. All IUDs are effective at preventing pregnancy for at least 5 years

6. **True or False:** A patient has been taking a combined hormonal contraceptive containing ethinyl estradiol 20 mcg/

norethindrone acetate 1 mg for the past 4 months and never misses doses. The patient has been experiencing breakthrough bleeding 1 week after the end of menses. This is most likely due to insufficient progestin.
   a. True
   b. False

7. Choose the correct statement regarding progestin-only contraceptives:
   a. Women should avoid all progestin-only contraceptives until they are at least 4-6 weeks postpartum and no longer breastfeeding
   b. The acronym "LARC" refers to IUDs, the implant, and the injection
   c. The Depo-Provera® injection should be administered every 3 months
   d. The Nexplanon® implant provide continuous pregnancy prevention for up to 5 years

8. **True or False:** The duration of Depo-Provera® use should be limited to 2 years unless other contraceptive options are inadequate.
   a. True
   b. False

9. Choose the correct statement regarding combined hormonal contraceptives (CHCs):
   a. Ethinyl estradiol doses in combined oral contraceptives typically range from 10-80 mcg
   b. CHC dosage forms include the pill, the patch, and the ring
   c. CHCs should always be initiated on the first Sunday following most recent menses
   d. The ring should be replaced once weekly for 3 weeks, followed by a 1-week hormone free period

10. **True or False:** When considering extended-use dosing, it is recommended to use multiphasic over monophasic combined oral contraceptive formulations.
   a. True
   b. False

11. **True or False:** A woman who has recently started a new oral contraceptive and is experiencing some mild breast tenderness should be advised to continue her therapy for at least 3 months.
   a. True
   b. False

12. A woman has been taking ethinyl estradiol 35 mcg/norethindrone 1 mg for the past 6 months. She complains that she has had significant bloating and fluid retention since beginning the medication that has not subsided. She is not interested in switching to a non-oral option. Which modification is the best option to address her side effects?
   a. Change to ethinyl estradiol 35 mcg/norgestimate 0.18 mg
   b. Change to ethinyl estradiol 20 mcg/norethindrone 1 mg
   c. Change to ethinyl estradiol 35 mcg/norethindrone 0.5 mg
   d. No modification necessary. Patient should be counseled to trial medication for 1 year before switching

13. Given the following options, choose which adverse effects would require referral to a doctor and advised discontinuation of treatment of a woman's hormonal contraceptive regimen:
   a. Abdominal pain
   b. Chest pain
   c. Blind spots in field of vision
   d. Severe leg pain
   e. All of the above

14. JK is a 38yo female who was recently diagnosed with breast cancer. She was previously prescribed Junel Fe 1.5/30 (combined hormonal contraceptive) for pregnancy prevention. However, her oncologist told her she must discontinue this immediately. JK is extremely concerned about the additional stress a pregnancy may put on her body right now and is wondering how to most effectively prevent pregnancy during this difficult time. Which of the following recommendation(s) is most appropriate for JK? Hint – you may need to check the CDC Medical Eligibility Criteria chart.
   a. Depot medroxyprogesterone acetate injection
   b. Levonorgestrel intrauterine device
   c. Copper intrauterine device
   d. Transdermal patch
   e. Progestin implant

15. A 26-year old patient gave birth to her son 6 weeks ago and is currently breastfeeding. Prior to pregnancy, the patient took norethindrone (progestin-only pill) which she tolerated well. However, she does report that she often forgot to take doses which is how she got pregnant. Her past medical history is significant for migraines with aura. She states that she has no desire to become pregnant again any time soon. Which contraceptive options should be offered to the patient? Hint – you may need to check the CDC Medical Eligibility Criteria chart.
   a. Combined oral contraceptive and copper IUD
   b. Progestin-only pill and transdermal patch
   c. Levonorgestrel IUD and vaginal ring
   d. Progestin implant and combined oral contraceptive
   e. Levonorgestrel IUD and progestin implant

16. Did the activity meet the stated learning objectives? (if you answer no, please email sarahs@pswi.org to explain)
   a. Yes
   b. No

17. On a scale of 1 – 10 (1-no impact; 10-strong impact), please rate how this program will impact the medication therapy management outcomes or safety of your patients.

18. On a scale of 1 – 10 (1-did not enhance; 10-greatly enhanced), please rate how this program enhanced your competence in the clinical areas covered.

19. On a scale of 1 – 10 (1-did not help; 10-great help), please rate how this program helped to build your management and leadership skills.

20. How useful was the educational material?
   a. Very useful
   b. Somewhat useful
   c. Not useful

21. How effective were the learning methods used for this activity?
   a. Very effective
   b. Somewhat effective
   c. Not effective

22. Learning assessment questions were appropriate.
   a. Yes
   b. No

23. Were the authors free from bias?
   a. Yes
   b. No

24. If you answered "no" to question 23, please comment (email info@pswi.org).

25. Please indicate the amount of time it took you to read the article and complete the assessment questions.

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November/December 2020
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10) a b
11) a b
12) a b c d
13 a b c d e
14) a b c d e
15) a b c d e
16) a b
17)_____
18)_____
19)_____
20) a b c
21) a b c
22) a b
23) a b
24)_____
25)_____

Name_____Designation (RPh, PharmD, etc.)_____

CPE Monitor #_____ DOB (MMDDYY)_____

Preferred Mailing Address_____

City_____State_____ Zip _____

Is this your home ☐ or work ☐ address?

ONLINE EDUCATION

PSW Online CE offerings include:

- PSW Online CE
- Pharmacist Only Journal CE
- Pharmacist & Technician Journal CE
- Technician Only Journal CE

LECTURE PANDA

How to Claim CE:

- Click the desired Online CE link from the list.
- You will be directed to LecturePanda to complete registration and claim your CE.
- You will need to know your NABP ID in order to register (If you don't know your NABP ID, you can look it up on their website).
- Please make sure to use your "key email" address associated with your PSW account. (Not sure what email that is, check your profile)
- Once you have completed the assessment quiz and evaluation survey, you will be able to claim your CE credit to ACPE. Your credit should show up in your NABP Monitor within 24 hours

Once you have claimed your CE, your credits will appear in CPE Monitor within 24 hours. We strongly recommend you review your CPE Monitor portal quarterly.