

Pharmacist's Letter
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Women's Reproductive Health

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Accreditation, Goals and Objectives



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Introduction



Candice is a 19-year-old female who comes to your pharmacy and requests to speak to the pharmacist. She notes that over the past six months she sometimes misses her period. She is wondering if there's anything she can do or take to help make her periods more regular. You ask her if she is currently taking any medications and she says no. You inquire as to whether or not anything significant has changed in her life. She mentions that about eight months ago she started training for a marathon. You ask if she has had an annual well-woman visit within the past year. Candice isn't sure what you are referring to.

What unique healthcare needs do women have? What preventative services should women receive to help meet these needs? How would you explain a well-woman visit to Candice? What are some common reproductive health problems women experience? What additional questions would you ask Candice to help figure out what might be going on?

From a global standpoint, women and girls are disadvantaged in many societies due to several sociocultural factors.¹ Therefore, women's health is of particular concern in several countries, including the U.S. Women's health refers to an area of healthcare that focuses on the treatment and diagnosis of diseases and conditions that affect a woman's physical and emotional well-being.² It includes many services that address women's health across the lifespan; including, preventative care and screenings, breast care, sexual health, reproductive health, pregnancy and childbirth, and infertility.

To help optimize women's health and address common concerns, the American College of Obstetricians and Gynecologists (ACOG) recommends that women receive an annual well-woman visit. This annual visit should include recommended screenings and tests, immunizations, and evaluation and counseling for a variety of topics such as contraception, reproductive health, sexual health, cardiovascular risk factors, fitness and nutrition, and breast self-examination.³

It's important to understand some of the unique healthcare problems women face to better meet their needs. Many women are faced with chronic disease states that directly impact their reproductive health. It is important to understand the distinct preventative healthcare needs these women face in order to stay healthy at each stage of the lifespan. For example, a woman with a coagulation disorder has many things to consider when determining contraception choices, preconception planning, pregnancy, and during the aging process that other patients do not have to worry about.

Pharmacists should understand these problems and needs as they get more involved in helping women make decisions about their reproductive health. For example, some states have either implemented, or are in the process of passing and implementing, legislation that allows pharmacists to prescribe hormonal contraceptives.⁴ By understanding the recommended preventative healthcare services for women and the common reproductive health problems impacting women, pharmacists will be better suited to help women make decisions about their reproductive health.

Annual Well-Woman Visit



ACOG recommends an annual well-woman visit for all females, with the first visit to the obstetrician-gynecologist starting between the ages of 13 and 15.⁵ Depending on the patient's age and potential risk factors, there are certain routine screenings, tests, and immunizations that are recommended during a well-woman visit.

History and Physical³

A history and physical are performed during the annual well-woman visit. A history should include obtaining information on family medical history, nutrition, physical activity, substance use, sexual practices, medical/surgical history, menstrual health, and reproductive health. As women get older, they should also be assessed for urinary and fecal incontinence since these problems happen more often as women age and are things women may be more reluctant to share. Patients 40 years of age and older should also be asked about menopausal symptoms.

The physical exam should include obtaining standard objective measures, such as height, weight, body mass index (BMI), pulse, and blood pressure. Abdominal exams are recommended regardless of age, and some patients may also be candidates for a pelvic exam. Pelvic exams are used to screen for specific conditions and/or to evaluate symptoms.⁶ A complete pelvic exam typically consists of a visual inspection of the external genitalia and an internal exam which involves a speculum examination of the vagina and cervix and a manual examination of the uterus and cervix.

There has been recent controversy regarding the true need for a complete pelvic exam. In 2014, the American College of Physicians advised doctors to stop performing routine pelvic exams as part of a physical.⁷ There is limited evidence on the usefulness of these exams, and some experts consider them to be time-consuming, expensive, and provoke fear, anxiety, and pain in women. The American Academy of Family Physicians also endorses against routine pelvic exams as part of screening.⁸ The U.S. Preventive Services Task Force (USPSTF) states that available evidence is insufficient to assess the balance of benefits and harms of conducting routine pelvic exams in asymptomatic, nonpregnant females.^{6,9}

However, ACOG continues to recommend routine pelvic exams for most patients starting at age 21, but acknowledges that limitations to the internal pelvic exam should be recognized.¹⁰ The guideline also recommends that performing routine pelvic examinations annually in patients that are asymptomatic should be a shared decision between the patient and healthcare provider.¹⁰ ACOG does point out that while an annual pelvic exam is logical, data to support the exact time frame or frequency is lacking.⁹

ACOG recommends a clinical breast examination be done every one to three years beginning at age 25 through age 39.¹¹ Starting at age 40, ACOG recommends this exam be done annually. A clinical breast exam involves a visual inspection of the breasts while sitting and lying down and palpation of the breasts and underarm to identify abnormalities or lumps. The National Comprehensive Cancer Network has similar recommendations as ACOG regarding clinical breast exams.¹²

Routine Screening Tests³

Sexually active patients who are 24 years of age and younger should be routinely tested for chlamydia and gonorrhea. All adults and adolescents from 13 to 64 should be tested at least once for HIV. Once a patient turns 21, cervical cancer screening should begin and be repeated every three years via Pap smear. A Pap test involves obtaining a sample of cervical cells, and is often done during a pelvic exam; however, it's not the same as a pelvic exam. It involves a woman lying on an exam table while a trained clinician inserts a speculum to widen the vagina in order to see the cervix. Then, cervical cells are gathered via speculum and this sample is sent to a lab to detect abnormal cells. Another method for cervical cancer screening involves using the relatively new human papilloma virus (HPV) screening test which is approved for use as a primary test in patients 25 years of age and older. Nearly all cases of cervical cancer are caused by HPV infection and this test is designed to detect high-risk types of HPV.¹³ Similar to the Pap test, the HPV screening test also requires a sample of cervical cells. ACOG recognizes the Food and Drug Administration (FDA) approved labeling of the HPV test and notes that the test can be considered as an alternative to the Pap test in patients 25 years of age and older.¹⁴ Due to limited evidence surrounding the overall impact and screening potential for the HPV test, Pap smears are still recommended as the gold standard for screening by ACOG as routine care in patients 25 to 29 years of age.

Both the Pap test and HPV test may be done together to decrease the chances of missing an abnormality. Known as the "HPV co-test," major professional organizations such as ACOG, USPSTF, and the American Cancer Society don't recommend this approach for women under the age of 30.¹⁵ However, for those who are 30 to 65 years of age, the HPV co-test is preferred, and when it is used, females only need to repeat the screening every five years instead of every three years. Patients 30 years of age and older can also get the Pap test alone (acceptable, but not preferred), which would need to be repeated every three years. Women older than 65 years of age don't need to continue screening if they have historically tested negative for HPV.

In addition to being screened for cervical cancer, women should also be screened for breast cancer with routine mammograms. A mammogram involves taking an x-ray of the breast to identify abnormalities. ACOG recommends **offering** a yearly or every other year mammogram to all patients starting at age 40 after counseling the patient on the uncertainty of additional benefits and harms. By age 50, mammograms should be recommended if the patient hasn't already begun receiving them, and they should continue until age 75. Similar to ACOG, the American Cancer Society says to **offer** yearly mammograms starting at age 40. But the American Cancer Society advises to start recommending yearly mammograms in patients who haven't started getting them yet at age 45, increasing to every two years starting at age 55.¹⁶ USPSTF advises that the decision to start mammograms before age 50 should be an individual one, and that starting at age 50 through 74, women should get screened once every 2 years.¹⁷

There is little evidence for continuing mammograms in patients who are 75 and older, but in general, screening should continue as long as women are in good health and want to continue receiving the screening.

Other routine screening tests that ACOG recommends during the annual well-woman visit for females over the age of 40 include:^{3,18}

- **Diabetes screening** - begin at age 45 and repeat every three years
- **Lipid profile** - begin at age 45 and repeat every five years
- **Colorectal screening** - begin at age 50 using one or a combination of the following methods:
 - Fecal occult blood testing - repeat yearly (does not replace sigmoidoscopy or colonoscopy but may be done in addition to one of these two tests)
 - Flexible sigmoidoscopy - repeat every five years
 - Colonoscopy - repeat every ten years
- **Hepatitis C screening** - complete once if born between 1945 and 1965 and unaware of their status
- **Bone mineral density screening** - begin at age 65 and repeat every two years in the absence of risk factors
- **Thyroid-stimulating hormone testing** - begin at age 50 and repeat every five years
- **Urinalysis** - begin at age 65 and repeat yearly

Summary of ACOG Recommendations for Routine Screening Tests ^{3,10,14,18}			
Test	Starting Age	Frequency	Notes
Breast Exam	25	Every 1 to 3 years	Clinical breast exams involve visual inspection and palpation of the breasts and underarm to identify abnormalities.
	40	Annually	
Pelvic Exam	21	Annually	May be reasonable to stop routine pelvic exams for patients who are age 65 and older, if the

			patient wouldn't be likely to intervene on conditions detected.
Pap Test	21	Every 3 years	Also known as a "Pap smear."
HPV Co-test	30	Every 5 years	Although not preferred, the Pap test can be used instead in patients who are age 30 and older and should be repeated every 3 years. Women older than age 65 don't need to continue screening if they have had negative results.
Mammogram	40 (offer) 50 (recommend)	Yearly or biennially	There's little evidence for continuing mammograms in patients who are 75 and older, but in general, screening should continue as long as women are in good health and want to continue receiving the screening.

Immunizations³

All pregnant patients should get the annual flu shot and a dose of the Tdap (tetanus, diphtheria, pertussis) vaccine with each pregnancy. Non-pregnant women should also receive the annual flu shot, in addition to the varicella vaccine for those with no evidence of immunity, MMR (measles, mumps, rubella) vaccine for those not previously immunized, and age-appropriate vaccines against diphtheria, pertussis, and tetanus. Anyone who has not received the Tdap vaccine should get it, regardless of the interval since the last tetanus and diphtheria toxoid-containing vaccine. They should then get Td booster doses every ten years. Additionally, females aged nine to 26 years old are recommended to receive the HPV vaccine. Patients 13 to 18 years old should also get the hepatitis B vaccine and the meningococcal conjugate vaccine if they haven't already. [Herpes zoster vaccine](#) is routinely recommended for patients age 50 years and older, while the [pneumococcal vaccine](#) should be routinely given to those who are age 65 and older. Pharmacists who are trained to immunize can play a vital role in ensuring women are up-to-date on vaccines indicated for their age and other medical conditions. For more details on vaccines recommended for certain age groups and conditions, refer to the [CDC immunization schedules](#).

Evaluation and Counseling³

Women should receive evaluation and counseling on sexuality, reproductive planning, psychosocial issues, cardiovascular risk factors, fitness and nutrition, and [tobacco](#) and substance use. An important topic for discussion with sexually active females is prevention of unwanted or unintended pregnancies. This usually involves a review of contraceptive options including hormonal and nonhormonal options. Preconception health should also be discussed, which refers to the health of women during their reproductive years.¹⁹ It involves taking steps to protect the health of a baby they might have sometime in the future. Preconception health is important regardless of whether a woman plans to become pregnant now, in the future, or ever. Since unplanned pregnancies account for half of the pregnancies in the U.S., women should be educated on healthy habits to make part of their daily lives.^{20,21} Understanding reproductive problems begins with obtaining a thorough medical history. Hormones are important for regulating menstruation, fertility, sex drive, and menopause. Hormonal imbalance, which can be caused by conditions such as polycystic ovarian syndrome or endometriosis, can lead to reproductive abnormalities, including menstruation-related issues, such as amenorrhea or irregular bleeding, or infertility. We will discuss some of these issues later.

Preconception Health



Paige is a 22-year-old patient who comes to your pharmacy interested in learning more about the contraceptive patch. She has been using birth control pills for the past couple of years but is wondering if it might be easier to switch to something she doesn't have to remember to take every day. You live in a state that allows you to prescribe hormonal contraceptives like the patch and oral pills. What steps should you take before prescribing anything to her? What additional questions do you want to ask her? What kind of information should you share with Paige about her preconception healthcare?

Preconception health is important for all women and men during their reproductive years.¹⁹ It includes deciding whether or not to have children in the future and then acting on that plan. During preconception, women may have varied goals, depending on when or if, they want to conceive. Regardless, steps should be taken to choose healthy habits. Prevention of pregnancy should be discussed if conception is not a current goal.¹⁹

It's recommended that all women develop a plan regarding their goals for conception. Goals should be reevaluated at the well-woman visit. A [checklist](#) from CDC is available to share with patients that can be used to help them develop and follow their plan. This checklist can also help patients develop talking points to discuss with their healthcare providers regarding their preconception healthcare.

Regardless of whether or not a woman is planning to get pregnant, she should take at least 400 mcg of folic acid daily.¹⁹ Folic acid is important for the creation of new cells in both mother and baby. Folic acid is specifically important for preventing major birth defects in the fetus' brain and spine if pregnancy does occur. Since about half of pregnancies in the U.S. are unplanned, it's important for all reproductive-aged women to get enough folic acid.^{20,21}

Using recreational drugs, binge drinking, and smoking are harmful to a patient's health and can cause serious birth defects if the patient has an unplanned pregnancy. An important part of preconception health is avoiding these detrimental habits.¹⁹ Cigarette smoke is considered to be a substance that can be toxic to the reproductive system. Women may also be exposed to toxic substances at work or home, such as fertilizers, pesticides, cleaning products, clothes that have been dry-cleaned, or paint.²² If exposed in high enough amounts, these substances can hurt the reproductive system and cause menstrual cycle irregularity, infertility, miscarriage, or birth defects.²³ Certain drugs can also be toxic and many of these are listed in the National Institute for Occupational Safety and Health (NIOSH) [list of hazardous drugs in healthcare settings](#). The first step to avoiding these substances is being aware that they can cause a problem. Advise women to seek non-toxic personal care and cleaning

to avoiding these substances is being aware that they can cause a problem. Advise women to seek non-toxic personal care and cleaning products, avoid tobacco products, check to make sure their dry-cleaner uses non-toxic products, hire licensed pest exterminators, and encourage patients to get information and training about hazardous substances in their workplace.²² You can [print brochures](#) with additional practical recommendations on how to avoid exposure to common toxic substances.

Being overweight or underweight can lead to reproductive problems. For example, overweight or obese women may be at higher risk for gynecological cancers. Both overweight and underweight women might have menstrual abnormalities. It also might be difficult for overweight and underweight women to conceive. Additionally, being overweight can also have implications on the efficacy of hormonal birth control. For example, the contraceptive patch might not work as well in women who weigh over 198 pounds (90 kg).²⁴ Regardless of whether a patient is overweight or underweight, it's important to encourage a long-term, healthy lifestyle approach rather than short-term changes. Many of the same lifestyle changes that help reduce cardiovascular risk can also help improve preconception health. Use our patient education handouts, [Tips for Getting to a Healthy Weight](#) and [How to Eat a Heart-Healthy Diet](#), to guide patients who want to improve their health.

For women who aren't interested in getting pregnant or who want to wait to get pregnant, contraception is an important topic to discuss. You can learn more about the different types of contraceptive options available by reviewing our CE, [Helping Patients Navigate Contraceptive Options](#). Being able to explain how hormonal contraceptives work to patients can help you educate them on why adherence is so important. Make sure that patients understand most contraceptive methods, with the exception of condoms, do not protect against sexually transmitted infections (STIs). In other words, protection against pregnancy does not necessarily mean protection against STIs.

Prior to initiating a combined hormonal contraceptive, [blood pressure should be measured](#). No additional testing is needed according to CDC.²⁵ Properly trained pharmacists who practice in states that allow for RPh prescribing of hormonal contraceptives should check the patient's blood pressure before initiating therapy. It is advised not to start combined hormonal contraceptives in patients with a blood pressure measured to be greater than 140 mmHg/90 mmHg, or in those who have been diagnosed with high blood pressure, even if its adequately controlled. Refer these patients to their primary care provider or OBGYN. Alternatively, you can consider a progestin-only option for these patients.

Prescribing pharmacists should also do the following before initiating a hormonal contraceptive:

- Conduct a review of conditions and risks that could pose as precautions or contraindications to the use of certain products.
 - Use the [Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use](#) (U.S. MEC) to ensure appropriateness of therapy.
- Assess pregnancy status in women to be reasonably certain that they are not pregnant.²⁵
 - Pharmacists can be reasonably certain that a female isn't pregnant if she has no signs or symptoms of pregnancy and meets any of the following criteria:
 - Has started her menstrual period less than or equal to seven days ago
 - Hasn't had sex since the start of her last normal period
 - Has correctly and consistently been using a reliable method of contraception
 - Has had a spontaneous abortion less than or equal to seven days ago
 - Is within four weeks postpartum
 - Is fully or nearly fully (>85% of feeds are breastfeeds) breastfeeding, amenorrheic, and less than six months postpartum
 - In situations where a patient has no signs or symptoms of pregnancy and doesn't meet any of the conditions listed above, the benefits of starting hormonal contraceptives likely exceed the risk. CDC recommends starting the chosen method of contraception (except for IUDs) and following up with a pregnancy test two to four weeks later.²⁵
- Stress the importance of seeing a qualified healthcare provider for an annual well-woman visit if the patient hasn't received one yet.
 - **Inform patients that receiving a prescription for a hormonal contraceptive is one small portion of what happens during an annual well-woman visit and that their consultation with the pharmacist is not meant to replace that visit.**

Patients who initiate hormonal contraceptives will need counseling on adherence, how to use the contraceptive, and what to do in the event of a missed dose. For more details on these counseling points and more, review our CE, [Hormonal Contraceptive Counseling](#).

Reproductive Health Problems



Reproductive health includes conditions that affect the functioning of the female reproductive system. Reproductive health problems can be caused by poor preconception health, genetics, environmental factors, or other unknown causes. Disorders of reproduction can have negative impacts on pregnancy and childbirth, fertility, and the menstrual cycle. Fortunately, many of these issues can be addressed with maintaining a healthy lifestyle and therapeutic interventions, such as hormonal contraceptives. For more details on the female menstrual cycle and some of the noncontraceptive benefits of hormonal contraceptives, including how they can help with some of these reproductive issues, take our CE, [Pharmacology of Hormonal Contraceptives](#).

Menstruation-Related Disorders

Think back to your patient Candice. She has been experiencing occasional missed periods over the past six months. She isn't taking any other meds and hasn't been sexually active. However, she did report that eight months ago she started to train for a marathon. What is this menstruation-related issue called and what could be the cause? What treatment options would you describe to Candice?

Before discussing some of the common menstruation-related issues women experience, it's important to review some definitions:^{26,27}

Amenorrhea - This term refers to the absence of menses. It can be described as either primary or secondary amenorrhea. Primary amenorrhea is the absence of menses by the age of 13 when there is no development of secondary sex characteristics, or by the age of 16 in the presence of secondary sex characteristics. Secondary amenorrhea is the absence of menses for three cycles or for six months in a previously menstruating woman.

Anovulatory Abnormal Uterine Bleeding - Abnormal, noncyclic uterine bleeding is most often caused by anovulation. When women do not ovulate, the normal secretion of progesterone doesn't occur which leads to estrogen acting on the endometrium unopposed.²⁸ Estrogen continues to cause the endometrial lining to thicken until it outgrows its blood supply and sloughs off incompletely. This leads to irregular and sometimes excessive bleeding.

Dysmenorrhea - Painful menstruation in the abdominal or pelvic region, also known as "cramps."

Menorrhagia - Heavy menstrual blood loss (usually greater than 60 to 80 mL per cycle) and/or prolonged menstrual bleeding (bleeding for greater than seven days). Keep in mind that in practice, measuring menstrual blood loss is difficult, and only 10% of women who perceive their menstrual bleeding to be heavy actually experience blood loss severe enough to be defined as menorrhagia.²⁹ Therefore, you may hear the term heavy uterine bleeding used instead.

Premenstrual Syndrome (PMS) - A number of different symptoms that occur in the week or two prior to menses and include mild mood disturbances such as anxiety, depression, irritability, anger, and physical symptoms such as bloating, breast tenderness, fatigue, muscle aches, and cramping.³⁰ These symptoms usually go away with the start of menses.

Premenstrual Dysphoric Disorder (PMDD) - PMDD is a much more severe form of PMS. Similar to PMS, PMDD begins the week or two before menses and usually goes away once menses begins. A set of defined criteria must be met in order for PMDD to be diagnosed. At a high level, patients must have at least five of the following symptoms:

- Depressed mood
- Anxiety
- Unstable or rapidly changing emotions
- Anger or irritability
- Decreased interest in activities
- Fatigue
- Difficulty concentrating
- Changes in appetite
- Sleep disturbance
- Feeling overwhelmed
- Physical symptoms (breast tenderness, bloating, muscle aches, etc)

At least one of these symptoms must be marked depression, anxiety, irritability, or unstable or rapidly changing emotions. Symptoms must also interfere with work and/or social relationships.

Amenorrhea²⁶

Primary amenorrhea occurs in less than 0.1% of the general population while secondary amenorrhea occurs in 0.7 to 5% of the general population. Amenorrhea can have a number of different causes which impacts how it gets treated. Assuming pregnancy has been ruled out (one of the most common causes of amenorrhea), assessing a patient for hypothalamic suppression, anovulation, hyperprolactinemia, ovarian failure, and uterine disorders can help identify a cause.

Any changes in the normal functioning of the hypothalamic-pituitary-ovarian-uterine axis can cause amenorrhea. The hypothalamus normally releases pulses of gonadotropin-releasing hormone (GnRH). These GnRH pulses stimulate the anterior pituitary gland to secrete follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH are responsible for ovarian follicle development and ovulation, respectively. The dominant follicle that eventually releases an egg during ovulation is a hormone-producing body which secretes estrogen, progesterone, and androgen. The estrogen secreted by the dominant follicle causes the endometrial lining to build up and thicken in preparation for implantation of a fertilized egg. Estrogen and progesterone also provide negative feedback to the hypothalamus and the anterior pituitary which decreases the production of FSH and LH. After ovulation, the dominant follicle turns into the corpus luteum, another hormone-producing body. If an egg goes unfertilized, the corpus luteum degenerates and the negative-feedback loop goes away, allowing the cycle to start all over again. The decline in progesterone levels caused by the degeneration of the corpus luteum causes sloughing of the endometrium which leads to menstruation.

One potential cause of amenorrhea is premature ovarian failure. This occurs when no viable follicles are in the ovaries. Premature ovarian failure is often caused by genetic anomalies. It causes amenorrhea because without viable follicles, the menstrual cycle is suspended.

Other causes for amenorrhea involve situations when normal secretion of FSH and LH by the pituitary gland is interrupted. Prolactin, a hormone that is responsible for stimulating milk production, is also secreted by the pituitary gland. Its presence initiates negative feedback on the hypothalamus, which reduces the secretion of GnRH, ultimately decreasing the production of FSH and LH. Conditions or situations that cause levels of prolactin to increase, such as hypothyroidism or certain medications (e.g., antipsychotics or verapamil), can cause amenorrhea. Other conditions that can directly affect the ability of the hypothalamus to secrete GnRH include anorexia, bulimia, intense exercise, and stress.

Treatment of amenorrhea depends on the cause. Desired outcomes of treatment are often to restore the menstrual cycle, preserve bone density and prevent bone loss, restore ovulation, and improve fertility. For example, bromocriptine can be used to normalize prolactin levels in cases where amenorrhea is caused by hyperprolactinemia. Dopamine naturally decreases secretion of prolactin in the body. By using a dopamine agonist such as bromocriptine, this natural process can be mimicked and prolactin levels can be decreased.

Anovulatory Abnormal Uterine Bleeding^{26,31}

What is polycystic ovarian syndrome (PCOS)? How can it impact a woman's reproductive health? How is PCOS treated and how do the various treatment options treat symptoms? If you currently have patients with PCOS that come to your pharmacy, what are usually their biggest concerns and/or desired treatment goals?

Anovulation can also cause amenorrhea, which demonstrates the overlap between the causes of these two disorders. Ovulation is required in order for the dominant follicle to turn into the corpus luteum. Without the corpus luteum, the right sequence of estrogen and progesterone production is disrupted and withdrawal may not occur. In the absence of progesterone withdrawal-induced endometrial shedding, unopposed estrogen allows the endometrium to continue to proliferate. This can lead to irregular bleeding, heavy bleeding, or no bleeding at all.

Polycystic ovarian syndrome (PCOS) is the most common cause of anovulation in women during their reproductive years. The prevalence of

PCOS varies depending on which diagnostic criteria are used, but it can be as high as 15% to 20%.³² Its cause isn't well understood, but genetics are generally thought to contribute to the development of PCOS. PCOS is a condition that is often characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovaries.³³ High levels of androgens can prevent ovulation and cause unwanted hair growth ([hirsutism](#)) and acne. Although not included in the diagnostic criteria, insulin resistance is often seen with PCOS and may contribute to hyperandrogenism by directly stimulating the ovarian production of androgens and inhibiting the synthesis of sex hormone binding globulin by the liver.^{32,34} Sex hormone binding globulin is a protein that binds to androgens and removes them from the circulation so that they can't exert their effects on androgen receptors.³³ In addition to anovulatory irregular bleeding, PCOS can also cause anovulatory amenorrhea or heavy uterine bleeding.

Patients can have multiple risk factors for anovulation. Other causes of anovulation include hyperprolactinemia, premature ovarian failure, stress, eating disorders, and hypothyroidism. As women get older, they may experience physiologic anovulatory cycles because of declining estrogen and progesterone levels.

Treatment goals for anovulatory abnormal uterine bleeding include control of excessive bleeding, restoring the natural menstrual cycle, and improving fertility. Like amenorrhea, treatment depends on the underlying cause.

Treatment options for anovulation due to PCOS include letrozole, clomiphene citrate, and metformin.^{32,35,36} Letrozole should be considered first-line for ovulation induction in women with PCOS. Letrozole appears to have a lower risk of multiple pregnancies when compared to clomiphene citrate; and it's considered more effective than metformin.³⁵ Clomiphene citrate and metformin are additional options, in cases where letrozole cannot be used (e.g., due to cost issues or contraindications). Lifestyle modifications, such as weight loss, smoking cessation, and physical activity, can also help improve symptoms of PCOS. For example, weight loss can help lower circulating levels of androgen, cause spontaneous resumption of menses, and improve pregnancy rates.^{32,35} Metformin can be particularly useful in addition to lifestyle changes for the treatment of weight, hormonal, and metabolic outcomes associated with PCOS.³⁵

COCs are recommended in patients with PCOS to provide predictable menstrual cycles and for the management of hyperandrogenism.^{35,36} Women with PCOS who experience effects from high androgen levels (i.e., acne and hirsutism) might benefit specifically from COCs containing progestins with antiandrogen activity (e.g., drospirenone), but more data is needed.³⁷ For patients who experience anovulatory abnormal uterine bleeding due to a reason other than PCOS, progestin-only therapies may be helpful (depot medroxyprogesterone acetate, megestrol acetate, or norethindrone acetate, levonorgestrel-releasing intrauterine device [IUD]). However, data is lacking on the use of progestin-only therapies to help treat anovulatory abnormal uterine bleeding caused by PCOS. Generally, progestin-only therapies for PCOS should be considered as an alternative in the presence of a contraindication to estrogen-containing therapies.³²

Refer to our CE course, [Hormonal Contraceptive Selection](#), for an overview of the different hormonal contraceptives available, including additional information on the types of progestins used in COCs and their relative androgen activity.

Heavy Uterine Bleeding²⁶

Heavy uterine bleeding can be seen in high rates in women with [coagulation disorders](#) such as von Willebrand's disease or platelet dysfunction. Other causes of heavy uterine bleeding include hypothyroidism, fibroids, endometrial polyps, gynecological cancers, and adenomyosis (when endometrial tissue grows into the uterine wall). In addition to presenting with heavy and/or prolonged blood flow, women may also have signs of fatigue, lightheadedness, and tachycardia.

Treatment goals include reducing menstrual blood flow. COCs can be useful with a 40% to 50% reduction in blood loss. The levonorgestrel-releasing intrauterine devices (IUD) can also be very effective for reducing menstrual flow, with a 79% to 97% reduction in blood loss. Progesterone-only containing products, such as the oral pill or depot medroxyprogesterone acetate injection, can be reserved for women in whom COC or IUD use would not be appropriate. NSAID use during menses can also be effective. NSAIDs have been associated with a 20% to 50% reduction in blood loss in up to 75% of treated women. Tranexamic acid is another option and is FDA-approved for primary treatment of heavy uterine bleeding. It is associated with a 26% to 60% reduction in blood loss.

Dysmenorrhea²⁶

Dysmenorrhea is one of the most common gynecologic complaints with prevalence rates up to 90%. Most of the time dysmenorrhea is associated with normal menstrual cycles (known as primary dysmenorrhea), but in about 10% of cases, it could be due to an underlying anatomic issue (known as secondary dysmenorrhea). Primary dysmenorrhea is caused by the release of prostaglandins and leukotrienes by the endometrium. This leads to vasoconstriction and contraction of the uterine wall lining which causes pain. Secondary dysmenorrhea can be caused by conditions such as endometriosis, adenomyosis, or fibroids.

Dysmenorrhea can often be treated with nonpharmacologic approaches, such as topical heat therapy and exercise. NSAIDs that are available over the counter can also be effective. If a woman wants to prevent pregnancy, hormonal contraceptives can help improve dysmenorrhea. Hormonal contraceptives, such as COCs and progestin-only products, decrease symptoms of dysmenorrhea by inhibiting endometrial tissue proliferation and preventing ovulation. This reduces the release of prostaglandins from the endometrial tissue and ultimately decreases pelvic pain. The levonorgestrel-releasing IUDs have also been able to improve dysmenorrhea.

After you describe to Candice that she might be experiencing occasional amenorrhea due to her intense marathon training, she tells you that she's actually thankful to have missed periods because when she does have periods she has extreme mood issues the week before. These mood problems sometimes lead her to stay home from school and work. She wonders if there's anything she can do to both help improve the predictability of her bleeding and help out with the mood symptoms. What mood disorder could Candice be experiencing? What can be done to help treat the period irregularity and the mood disturbances experienced when she does have periods?

PMS and PMDD²⁶

PMS symptoms are common, with up to 75% of menstruating women experiencing them. PMDD is less common with only 3% to 8% of women being diagnosed. While hormone fluctuations are thought to be a likely contributing cause, it isn't entirely clear what causes PMS or PMDD.

The goal of treatment is to help improve quality of life by decreasing symptoms. Nonpharmacologic therapy may be helpful for women with PMS. Lifestyle changes that could be implemented are exercise and decreasing the intake of caffeine, refined sugar, and sodium. Vitamin B6 (50 to

100 mg daily) and calcium supplements (1,200 mg daily) may also help reduce PMS symptoms.^{30,39} SSRIs are a first-line treatment for PMDD, with data available to support the use of citalopram, escitalopram, fluoxetine, paroxetine, or sertraline.⁴⁰ It isn't clear if SSRIs should only be given during the luteal phase when symptoms are most likely to begin, or if they should be dosed continuously. Both approaches have been found to be effective, though it isn't clear which is better. SNRIs can also be used, with venlafaxine having the most data. Hormonal contraceptives that suppress ovulation are likely to have the biggest impact on symptoms of both PMS and PMDD. COCs have been studied the most and some products even have an approved indication for PMDD (Yaz, Gianvi, etc [ethinyl estradiol 20 mcg and drospirenone 3 mg for 24 days]). GnRH agonists, which completely suppress ovulation, may be used in patients that have failed on preferred therapy with antidepressants and COCs. GnRH agonists will be discussed in more detail as a treatment option for endometriosis.

Review this chart for a summary of the causes and treatment options for common menstruation-related disorders:²⁶

Causes and Pharmacologic Treatment of Menstruation-Related Disorders		
Disorder	Causes	Examples of Pharmacologic Treatment Options
Amenorrhea	<ul style="list-style-type: none"> • Congenital uterine abnormalities • Eating disorder • Intense exercise • Hypothyroidism • Medications that increase prolactin levels (antipsychotics, verapamil, etc) • PCOS • Premature ovarian failure • Other genetic abnormalities 	<ul style="list-style-type: none"> • Depends on the cause, but treatment may include: <ul style="list-style-type: none"> ◦ Bromocriptine (hyperprolactinemia) ◦ Ethinyl estradiol patch (to prevent bone loss in patients with premature ovarian failure) ◦ COCs ◦ Oral medroxyprogesterone acetate ◦ Norethindrone ◦ Micronized progesterone
Anovulatory Abnormal Uterine Bleeding	<ul style="list-style-type: none"> • Exercise • Hypothyroidism • Medications that increase prolactin levels (antipsychotics, verapamil, etc) • PCOS • Physical or emotional stress • Premature ovarian failure • Weight loss 	<ul style="list-style-type: none"> • Depends on the cause, but treatment may include: <ul style="list-style-type: none"> ◦ COCs ◦ Progestin-only therapies ◦ Levonorgestrel-releasing IUDs ◦ If ovulation is desired, it can be induced with letrozole (preferred for PCOS) or clomiphene citrate
Dysmenorrhea	<ul style="list-style-type: none"> • Adenomyosis • Endometriosis • Fibroids • Normal prostaglandin production by the endometrium during the menstrual cycle 	<ul style="list-style-type: none"> • COCs • Depot medroxyprogesterone acetate injections • Levonorgestrel-releasing IUDs • NSAIDs
Heavy Uterine Bleeding	<ul style="list-style-type: none"> • Adenomyosis • Cirrhosis • Coagulation disorders (von Willebrand's disease, idiopathic thrombocytopenic purpura, etc) • Endometrial polyps • Fibroids • Gynecologic cancers • Hypothyroidism • PCOS 	<ul style="list-style-type: none"> • COCs • Levonorgestrel-releasing IUDs • Medroxyprogesterone acetate - both the oral pills and depot injections • NSAIDs • Tranexamic acid
PMS	<ul style="list-style-type: none"> • Not completely clear, but partly due to cyclic hormonal changes 	<ul style="list-style-type: none"> • Lifestyle changes • NSAIDs • Symptoms are improved when ovulation is suppressed. Drugs that suppress ovulation include: <ul style="list-style-type: none"> ◦ COCs ◦ Depot medroxyprogesterone acetate injections
PMDD	<ul style="list-style-type: none"> • Not completely clear, but partly due to cyclic hormonal changes 	<ul style="list-style-type: none"> • Based on the severity of the mood disorders patients may benefit from: <ul style="list-style-type: none"> ◦ SSRIs ◦ SNRIs • COCs <ul style="list-style-type: none"> ◦ Symptoms are improved when

- Symptoms are improved when ovulation is suppressed
 - Extended- or continuous- cycle regimens are thought to be most helpful
 - Extended-cycle drospirenone-containing regimens have labeled indications for PMDD
- GnRH agonists such as leuprolide (last-line due to cost and need for IM injection)

Endometriosis

Naomi is a 25-year-old patient who is filling a new prescription for a combined hormonal contraceptive designed to be taken as active pills for 21 days followed by inactive iron-containing pills for 7 days. She tells you that she was just diagnosed with endometriosis and that her doctor told her that this medication should help with the pain she has been experiencing. She wonders what other options are available if this doesn't work. What would you tell Naomi? How can her therapy be maximized? What other drugs can help?

Endometriosis is estimated to affect about 5% to 10% of women in the general population.^{41,42} This prevalence increases to 38% in women with infertility and up to 87% in women with chronic pelvic pain.^{41,43} Endometriosis is characterized by the growth of endometrial tissue outside of the uterus, in areas where endometrial tissue does not usually grow. The most common areas of endometrial tissue growth seen with endometriosis are the ovaries, the area of the pelvis where the ovaries lay, the ligaments that hold the uterus in place, and the portion of the peritoneal cavity between the posterior wall of the uterus and the rectum.⁴² It is unclear what causes endometriosis, but retrograde menstruation (menstrual blood flowing back into the body instead of out) is a widely accepted contributing factor. It's thought that retrograde delivery of menstrual material through the fallopian tubes into the pelvic cavity leads to endometrial tissue cell invasion and proliferation. However, retrograde menstruation alone is not the only cause. In fact, retrograde menstruation is thought to occur in up to 90% of menstruating women. So while retrograde menstruation may be an initial mechanism for how endometrial tissue makes its way into areas outside of the endometrium, there are additional genetic and immunologic factors at play. Other contributing mechanisms include increased exposure to menstrual debris via heavy menstrual flow, defective immune surveillance, or apoptosis failure.^{42,44} There are most likely several genetic mutations involved with the development of endometriosis.⁴⁰

Endometriosis is considered to be a chronic inflammatory disease with characteristics similar to that of malignancies. Like a solid organ tumor, endometriosis exhibits cellular proliferation, tissue invasion, and angiogenesis (blood vessel growth).⁴⁰ As previously mentioned, endometriosis can cause secondary dysmenorrhea. This pain is due to increased concentrations of inflammatory chemicals such as prostaglandins. There may also be an overexpression of nerve growth factors leading to more nerve fibers in the endometrial tissue.⁴⁰ Endometriosis is also associated with infertility, but the cause of this is less defined. In more advanced disease, inflammation and ovarian lesions may physically block the fallopian tubes and make the endometrium a hostile environment for implantation.⁴⁰ Inflammatory chemicals can also damage sperm. Hormonal imbalances caused by the disease can contribute to infertility as well.⁴⁰

Goals of therapy are to improve fertility and/or reduce pain. There are no pharmacologic interventions to help improve fertility.⁴⁰ This can only be achieved through surgery to remove endometrial lesions. Surgery can also be used to help reduce pain, but often pharmacologic options are tried first since surgery can lead to scarring and tissue adhesions.⁴⁰

First-line treatment for pain associated with endometriosis includes [hormonal contraceptives](#), both combined and progestin-only, and NSAIDs. Continuous dosing with combined hormonal contraceptives (i.e., skipping the hormone-free interval) may help improve efficacy. Hormonal contraceptives are able to improve symptoms by suppressing proliferation of endometrial cells.⁴²

Other second-line treatments available include the levonorgestrel-releasing IUDs, GnRH agonists, and GnRH antagonists.⁴⁰ Locally administered levonorgestrel via an IUD causes atrophy of the endometrium, which can help relieve pain.⁴²

GnRH agonists work by binding to GnRH receptors on the pituitary.⁴² They act as negative feedback to cause the pituitary gland to decrease the production of LH and FSH which disrupts the normal menstrual cycle.⁴² By directly blocking GnRH receptors, GnRH antagonists also suppress LH and FSH secretion. With both GnRH agonists and antagonists, the production of estrogen, which is normally responsible for endometrial tissue growth, is reduced. GnRH agonists and antagonists are not preferred because they cannot be used long-term, are expensive, and cause bone mineral density loss.⁴⁰ "Add-back" therapy can be used with GnRH agonists to protect against bone mineral density loss and extend its use beyond six months. Add-back regimens used along with GnRH agonists include progestins alone or estrogen and progestin combination therapy.^{40,41} Examples of GnRH agonists include goserelin (*Zoladex*), leuprolide (*Lupron Depot*), and nafarelin (*Synarel*). Elagolix (*Orilissa*) is a GnRH antagonist that is FDA-approved to treat endometriosis-associated pain.

Patients on elagolix must use non-hormonal contraception during treatment and for one week after stopping treatment.⁴⁵ Estrogen-containing contraceptives may decrease the effectiveness of elagolix and the effects of progestin-only contraception on elagolix are not known. Contraception is important during elagolix use because it is contraindicated during pregnancy.

In the past, danazol was the primary pharmacologic treatment used for endometriosis.⁴² Its popularity has decreased with the introduction of agents that have more favorable side effect profiles.⁴² However, danazol has been shown to be effective and is an additional option. Danazol is an orally available synthetic steroid that is antiestrogenic and weakly androgenic.⁴² The low estrogen environment that is induced by danazol leads to atrophy of endometrial tissue and improvement in symptoms.⁴² However, danazol is teratogenic and has a high rate of androgenic side effects including hair growth, acne, and mood changes.^{40,42}

For more information on drug treatment for endometriosis, including drug pricing and other therapeutic options not discussed here, check out our [chart: Drug Treatment for Endometriosis](#)



The Bottom Line

Pharmacists expanding their role in the care of their patients through education, providing [screening tests](#), delivering [medication therapy management services](#), ordering medications via [collaborative drug therapy management agreements](#), and more. Pharmacist involvement in services related to women's health are increasing as states start to expand the pharmacist's scope of practice to include assessing patients for the appropriateness of hormonal contraceptives and prescribing these medications.

In order to begin to provide these services, pharmacists must understand the steps that women should take to make sure they are getting appropriate preventive healthcare services. Understanding the well-woman visit and what takes place during this annual appointment can help pharmacists educate and encourage women to schedule them. Knowing how to counsel patients on appropriate preconception healthcare and guiding them to develop talking points or questions to ask during their well-woman visit is also important. Being familiar with common reproductive health concerns women face can help pharmacists select or recommend the most appropriate hormonal contraceptive or other appropriate treatment option.

Quiz Questions



Question #1

At what age does ACOG recommend starting clinical breast exams for patients?

- a. 13
- b. 25
- c. 39
- d. 55

Question #2

What can you tell a 30-year-old patient about cervical cancer screenings?

- a. A pelvic exam is not required as part of cervical cancer screening.
- b. The HPV test involves the visual inspection of abnormal cells.
- c. You only need to get the screening every three years with an HPV co-test.
- d. There's a new exam that uses a blood sample instead of a cervical sample.

Question #3

What is most likely to be potentially toxic to the reproductive system?

- a. Colored pencils
- b. Coffee
- c. Dry-cleaned clothes
- d. Tap water

Question #4

What preconception healthcare advice would you give to a 27-year-old female patient who isn't interested in getting pregnant anytime soon?

- a. Exposure to cigarette smoke is only a problem once you start trying to get pregnant.
- b. Being overweight can cause problems with menstruation, so it's better to be underweight.
- c. Before starting the birth control pill, you'll need a pelvic exam and blood pressure reading.
- d. You should take at least 400 micrograms of folic acid each day.

Question #5

Which menstruation-related disorder may patients also refer to as "cramps"?

- a. PMS
- b. PMDD
- c. Menorrhagia
- d. Dysmenorrhea

Question #6

What is the most common cause of anovulation in women during their reproductive years?

- a. PMDD
- b. PCOS
- c. Hypothyroidism
- d. Hyperprolactinemia

Question #7

Which treatment is the best option to help stimulate ovulation in a patient with polycystic ovarian syndrome?

- a. Combined oral contraceptives
- b. Letrozole
- c. Medroxyprogesterone
- d. Metformin

Question #8

Which menstruation-related disorder can be treated with antidepressants?

- a. Anovulation
- b. Amenorrhea
- c. Dysmenorrhea
- d. PMDD

Question #9

Mya is a 25-year-old patient who has been diagnosed with endometriosis. She wants to learn more about how endometriosis impacts her fertility. What can you share with Mya about endometriosis and fertility?

- a. Elagolix is a medication that can be used to improve fertility.
- b. Goserelin is a medication that can be used to improve fertility.
- c. Infertility is likely caused by a decrease in the number of eggs.
- d. Infertility is likely caused by a physical blockage of the fallopian tubes.

Question #10

Which drug class is preferred for the first-line treatment of pain associated with endometriosis?

- a. NSAIDs
- b. GnRH agonists
- c. GnRH antagonists
- d. Aromatase inhibitors

Submit your answers 

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Women's Reproductive Health **(19-247)**

Needs: Women's health is of particular concern in many countries. As pharmacists start to obtain the authority to prescribe hormonal contraceptives in some states, understanding the diseases and conditions that affect a woman's physical and emotional well-being becomes even more important for pharmacists. Pharmacists need to understand healthcare issues females face in order to get more involved with helping women make decisions about their reproductive health.

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

Goals and Objectives: The goal of this activity is to help pharmacists in all settings develop a better knowledge base of the diseases and conditions that affect women so that they can help patients make the best decisions about their reproductive health.

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

1. Explain preventive health recommendations from the American College of Obstetricians and Gynecologists.
2. Discuss preconception health considerations.
3. Identify 3 menstruation-related disorders and their potential causes.
4. List treatment options for polycystic ovarian syndrome (PCOS).
5. Describe the role of oral contraceptives for the treatment of endometriosis.

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