Objective: To review the pharmacist’s role in preconception health.

Data sources: PubMed search using the terms preconception, immunizations, epilepsy, diabetes, depression, tobacco, asthma, hypertension, anticoagulation, pharmacist, pregnancy, and current national guidelines.

Data synthesis: Preconception health has become recognized as an important public health focus to improve pregnancy outcomes. Pharmacists have a unique role as accessible health care providers to optimize preconception health by screening women for tobacco use, appropriate immunizations, and current medication use. Counseling patients on preconception risk factors and adequate folic acid supplementation as well as providing recommendations for safe and effective management of chronic conditions are also critical and within the scope of practice for pharmacists.

Conclusion: Pharmacists play an important role in medication screening, chronic disease state management, and preconception planning to aid women in preparing for healthy pregnancies.

Keywords: Preconception health, pharmacist, pregnancy.
Preactivity questions
Before participating in this activity, test your knowledge by answering the following questions. These questions will also be a part of the CPE assessment.

1. Which of the following is the approximate percentage of women who report using a prescription medication during the first trimester of pregnancy?
   a. 20%  
   b. 30%  
   c. 50%  
   d. 80%

2. Which of the following medications is best to avoid in pregnancy?
   a. Valproate  
   b. Regular insulin  
   c. NPH insulin  
   d. Inactivated influenza vaccine

3. Which of the following immunizations is recommended during pregnancy?
   a. Tdap  
   b. Varicella  
   c. MMR  
   d. HPV

Introduction
The United States has long had an infant mortality rate far in excess of comparable countries.1 In the last several decades, a new approach for preventing excessive rates of poor pregnancy outcomes in the United States has emerged.2 This new strategy, known as preconception health promotion, evolved with recognition that prenatal care starts too late to have an impact on many causes of fetal and neonatal morbidity and mortality, and, most strikingly, congenital anomalies. Embryogenesis begins within 3 days of the first missed menstrual period and is generally complete by 56 days after conception. Therefore, even women starting prenatal care early will not have a first prenatal visit before the critical period of organogenesis is under way or complete.

Focusing appropriate preconception health promotion education and intervention only on women and couples who are actively planning a pregnancy will not address preconception health status for a large percentage of pregnancies in any year: at least 50% of pregnancies in the United States are unintended, and the rate has begun to increase.3,4 Thus, all women capable of becoming pregnant should be provided critical information to advance their own health as well as the health of their children.

Many contributors to poor pregnancy outcomes are already present and irreversible at initiation of prenatal care.5,6 These factors include planning of the pregnancy (associated with timing of entry to prenatal care and exposure to harmful substances such as teratogenic drugs, alcohol, and tobacco), inadequate nutrition (folic acid and iron intake), poor chronic disease control, and risk factors for low birth weight and prematurity (abnormal placentation, short interpregnancy intervals, maternal pregravid weight, tobacco use, and others). Prenatal care, the traditional approach for advancing healthy pregnancy outcomes, starts too late to protect against early first-trimester birth defects and other poor pregnancy outcomes.

Preconception health promotion has become accepted as an important pathway for the primary prevention of many poor pregnancy outcomes. In 2006, CDC, in a public-private partnership, established the Preconception Health and Health Care Initiative.7 The initiative defined preconception care as a set of interventions that aim to identify and modify biomedical, behavioral, and social risks to a woman's health or pregnancy outcome through prevention and management.7 A framework for reaching women with information and interventions that will provide both health promotion and disease prevention for immediate and long-term health is three-pronged and echoes routine primary care: give protection (e.g., against communicable diseases including sexually transmitted infections, against unintended pregnancies), manage conditions (e.g., chronic and acute diseases), and avoid harmful exposures (e.g., alcohol, tobacco, recreational drugs). Impacting women's health through this framework will improve preconception health status for those women who intentionally or unintentionally become pregnant, because healthy women have healthier pregnancies and outcomes.5,8 The health care system routinely devotes attention to reducing the risks for cardiovascular disease and cancer, and similarly has the opportunity to reduce the risks for unintended pregnancies and support promotion of healthier outcomes.

Evidence-based clinical content for preconception health care was critically examined and put forth in 2008.4 Using an adaptation of the U.S. Preventive Services Task Force criteria for determining the quality of the evidence and assigning strength to specific recommendations, guidance was offered for the following topics: (1) routine health promotion for all women of reproductive age (including family planning and reproductive life planning; physical activity; weight status; nutrient intake and folate supplementation; immunizations; substance exposures and prevention; and identification and treatment of sexually transmitted diseases), (2) immunizations, (3) infectious diseases, (4) medical conditions, and (5) medications.

Pharmacists are in a promising position to incorporate a number of these evidence-based recommendations for promoting healthy pregnancy outcomes in their routine interactions with women of childbearing age who have coexisting health conditions. For example, among women aged 18 to 44 years old, 9% have been diagnosed with arthritis; 14% with asthma and other respiratory conditions; 5% with diabetes; 9% with hypercholesterolemia; and 11% with hypertension.9 Use of prescription drugs in the first trimester of pregnancy has increased by more than 60% in the last 30 years; approximately 50% of women in the United States reported taking at least one prescription drug in early pregnancy, and 7.5% took four or more prescription drugs.10 Women's exposure to drugs with the potential to negatively affect organogen-
Pharmacists should be aware of several areas of preconception health promotion, including immunizations, folic acid, medication screening, and periconception management of chronic diseases.

**Opportunities for pharmacist intervention in preconception health**

**Screening for immunization needs**

Preconception care should include screening for appropriate immunizations. With legislation allowing pharmacists to administer vaccines, pharmacists are key providers of immunizations. Vaccines play an important role in pregnancy and preconception health. For women considering pregnancy, an immunization screen should be conducted for prior receipt of measles, mumps, rubella (MMR), varicella, human papillomavirus (HPV), hepatitis A, and hepatitis B vaccines. Immunization with these vaccines prior to pregnancy is recommended because of the potentially harmful effects these infections may have on the developing fetus. Furthermore, some vaccines are contraindicated during pregnancy, highlighting the need to administer vaccinations before conception.

In particular, MMR, varicella, HPV, and hepatitis A vaccines should not be given during pregnancy. The MMR and varicella vaccines are live-attenuated agents and are not recommended in pregnant women because of concerns regarding how these vaccines might affect the fetus. Prenatal screening for varicella and MMR immunity is recommended. If evidence is lacking or immunization history is unknown, recommendations call for administration of two doses of the respective vaccine with the appropriate time spacing between each dose. Nonpregnant women receiving the MMR or varicella vaccine should be counseled to avoid pregnancy for at least 28 days after receiving the vaccine. There are no contraindications to household members of a pregnant woman receiving vaccines.

Limited data are available on use of the HPV and hepatitis A vaccines in pregnancy; therefore, these vaccines should be recommended prior to pregnancy. In women planning to conceive, prevention and early detection of cervical cancer are particularly important. Screening, detection, and treatment of any grade of cervical cancer prior to pregnancy are ideal when possible. Cervical cancer during pregnancy can be complex and in some cases results in preterm delivery of the infant. Because the HPV vaccine is an inactivated formulation, vaccination during pregnancy may be considered with caution in women at high risk for infection. Similarly, the hepatitis A vaccine is an inactivated formulation, and vaccination during pregnancy may be warranted in women at high risk for infection. Inadvertent use of MMR, varicella, HPV, or hepatitis A vaccine in pregnant women does not constitute a need for termination of the pregnancy.

The hepatitis B vaccine series may be administered to an unvaccinated woman during pregnancy if risk factors are identified. Prior to pregnancy, serologic testing for hepatitis B surface antigen (HBsAg) is recommended as part of preconception screening to prevent perinatal transmission of hepatitis B. Perinatal transmission of hepatitis B from an HBsAg-positive mother to her infant results in chronic infection in approximately 90% of infants; therefore, pregnant women also may be screened for HBsAg.

Vaccines recommended during pregnancy include the inactivated influenza vaccine (IIV) and the tetanus, diphtheria, and pertussis (Tdap) vaccine. One dose of trivalent or quadrivalent IIV is recommended for all pregnant women during the influenza season. The vaccine may be administered during any trimester. Contracting the influenza virus during pregnancy may carry some risks to the mother and infant. In the first trimester, contracting influenza has been implicated in a higher risk of schizophrenia in the infant. In the second and third trimesters, it increases the risk of influenza-related morbidity and mortality due to impairment of the mother’s breathing from the increased pressure of the fetus on the diaphragm and lungs. In addition, providing maternal vaccination may transfer maternal antibodies to the fetus and lower the risk of influenza in the neonate. While it is important to vaccinate pregnant women against the influenza virus, only the IIV formulation should be provided during pregnancy. The live intranasal vaccine formulation should be avoided during pregnancy.

Tdap is another vaccine specifically recommended for use during pregnancy. Regardless of previous vaccination, one dose of the Tdap vaccine is recommended for all women during each pregnancy, ideally between 27 and 36 weeks of gestation. However, the vaccine may be given any time during the pregnancy. The antibodies may take several weeks to develop. Therefore, providing the vaccine during the last trimester provides protection at the time of delivery, and maternal antibodies transferred to the fetus late in pregnancy may provide some protection to the infant postdelivery.

Other vaccines such as the pneumococcal, meningococcal, and travel vaccines are not routinely recommended during pregnancy. However, if a woman is at significant risk for a specific illness, consideration of the individual vaccine’s benefit versus risk profile is warranted.

**Encouraging folic acid supplementation**

Pharmacists can play an active role in recommending OTC supplements to women of childbearing age. Preconception supplementation with folic acid (vitamin B9) is critical for optimal birth outcomes and neural tube development. Folic acid is particularly important for healthy fetal development in the first few weeks after conception. A deficiency in folic acid could result in defects that involve abnormal closing of the neural tube early in the pregnancy. Spina bifida (a condition in which the spine fails to close properly) is a result-
Case study 1
A 30-year-old woman is planning to discontinue use of her combination oral contraceptive when she finishes her current pill pack. She does not have any chronic medical conditions. Her body mass index (BMI) is 24, and her blood pressure is 118/70 mm Hg. She is a nonsmoker (quit 2 years prior), and she drinks approximately four beers each weekend. During your assessment of her home and work environments, you find out that she is exposed to secondhand smoke from her husband and is a laboratory technician at a local hospital. She remembers her most recent immunization to be the hepatitis B series at age 24. She reports receiving all of her recommended childhood vaccines. She denies use of any chronic prescription medications, vitamins, or nutritional supplements. She occasionally uses ibuprofen for headaches and pseudoephedrine or acetaminophen for cold symptoms. What are the opportunities to improve this woman’s preconception health?

There are multiple recommendations that can improve this woman’s preconception health. Her weight and blood pressure are optimal and should be maintained prior to pregnancy. She should be encouraged to continue tobacco avoidance and to discuss tobacco cessation plans with her husband to limit her exposure to secondhand smoke. She should discontinue alcohol intake while attempting to conceive. She should investigate any safety issues related to infectious exposures at her workplace and make plans to reduce her risk. A formal evaluation of her immunization records should be performed to determine if she has received the recommended doses of varicella vaccine or has evidence of immunity. Her immunity to measles, mumps, and rubella should be assessed to allow administration of any necessary live vaccines prior to conception. An influenza vaccine should be given based on the seasonal recommendations. She should start taking a daily vitamin supplement containing 400 mcg of folic acid prior to discontinuing her contraceptive use. She should be made aware of the risks of her occasional OTC medications, such as ibuprofen and pseudoephedrine, with emphasis on the need to consider possible pregnancy prior to their use.

Screening for medication safety
Prescription and OTC medication use during pregnancy is common. Surveillance data from the 33-year Slone Epidemiology Center Birth Defects Study indicate approximately 90% of women take at least one medication during pregnancy. In a 2005 study, 65% of women reported use of acetaminophen during pregnancy, while 18% and 15% used ibuprofen and pseudoephedrine, respectively. Evaluations of prescribing patterns for women of childbearing age indicate that the use of teratogenic medications frequently occurs without appropriate counseling about fetal risk or contraceptive planning. In 2005, a study of ambulatory prescriptions for women of childbearing age reported that the most commonly prescribed potentially teratogenic medications were
Assessment of medication risks

Medication use during pregnancy can lead to complications in fetal development as well as the labor and delivery process. It is estimated that approximately 3% of infants in the United States are born with birth defects, with the cause unknown in most cases. Less than 10% of birth defects are estimated to occur from environmental or drug exposures. Teratogenic medications appear to act through six primary mechanisms:

- Disruption of folate metabolism (e.g., methotrexate, anti-epileptic medications) is associated with neural tube defects and orofacial, limb, and cardiac anomalies.
- Interference with neural crest cell development (e.g., retinoids) leads to cardiovascular, craniofacial, and gastrointestinal anomalies.
- Alteration of endocrine function (e.g., diethylstilbestrol, testosterone) increases the risk for reproductive disorders.
- Oxidative stress (e.g., thalidomide) causes skeletal, limb, and cardiovascular anomalies as well as cleft lip or cleft palate.
- Disruption of vascular function (e.g., misoprostol, aspirin, ergotamine, pseudoephedrine) causes hypoperfusion and hypoxia associated with limb anomalies, gasto- trochisis, and gastrointestinal disorders.
- Inhibition of enzyme and receptor function (e.g., angiotensin-converting enzyme [ACE], hydroxymethylglutaryl-coenzyme A [HMG-CoA] reductase, cyclooxygenase [COX], 5-hydroxytryptamine [5-HT], gamma-aminobutyric acid [GABA]) leads to a wide variety of anomalies.

Several factors are associated with medication risk. The gestational timing of exposure is a key determinant. Exposure immediately following conception may lead to spontaneous termination prior to the pregnancy being recognized. Exposure during the period of organogenesis (approximately 18 to 60 days postconception) is associated with structural abnormalities such as neural tube defects, cleft lip, or cleft palate. Exposure during the second and third trimester may involve functional disorders of organ systems, such as pulmonary or gastrointestinal function. Exposure in the late third trimester may lead to complications in the labor and delivery process, such as increased risk of bleeding or withdrawal symptoms in the neonate.

The extent of medication exposure is an additional consideration. Influences include the frequency of use, route of administration, dose, and metabolism. For example, a low dose of a medication delivered by the transdermal route will affect risk differently than a higher dose delivered orally. Similarly, impaired drug metabolism from liver or renal impairment or drug interactions will result in higher systemic exposure than the same medication undergoing normal clearance.

The assessment of medication risk is complicated by the general lack of safety data from controlled clinical trials in pregnant women. Fetal risk often must be determined from controlled studies in animal models, case reports, retrospective cohort studies, and pregnancy registries. Currently, the FDA system for drug labeling uses a series of five categories of pregnancy risk based on available data in controlled studies in animals and pregnant women (Table 1).

The risk categories provide insufficient information on the type and timing of risk to allow for individualized clinical decision making. In 2008, FDA proposed revisions that remove the existing categories and improve the information available for drugs used in pregnancy and lactation. The first component of the proposed pregnancy section includes a summary of fetal risk that addresses structural anomalies, mortality, or impairment of physiologic function or growth. Subsequent sections summarize clinical considerations for counseling, data on drug exposure early in pregnancy, dosage and monitoring guidance during pregnancy, issues specific to labor and delivery, human and animal data, and available pregnancy registries. The revisions remain in the formal rulemaking process at this time.

A comprehensive preconception review of medication exposures should account for use of nutritional supplements and herbal products. Unfortunately, the teratogenic risks of herbal supplements are not well identified. Data from the National Birth Defects Prevention Study found 5.7% of the 4,239 women studied used an herbal product within 3 months of pregnancy.
prior to pregnancy, and 9.4% reported use during pregnancy.\(^7\) First-trimester use of an herbal product was reported by 6.9%. The most common herbal products taken within 3 months prior to pregnancy included herbal teas, chamomile, echinacea, ginger, and ephedra. Although ginger has demonstrated efficacy for nausea and vomiting during pregnancy in some randomized, controlled studies, there is a general lack of data supporting the benefits of herbal products for pregnancy-related conditions.\(^46,47\) Safety concerns such as myocardial infarction and stroke associated with the use of blue and black cohosh during pregnancy highlight the importance of encouraging women to disclose the use of all supplements during their preconception evaluation.\(^49\)

**Preconception evaluation of chronic conditions**

Chronic conditions that are routinely managed with medications should be carefully evaluated in the preconception period. The goals of preconception evaluation are to optimize control of any medical conditions prior to pregnancy, determine the risks and benefits of continuing drug treatment through the pregnancy, and identify and transition to appropriate alternatives, if available. Pharmacists encounter women of childbearing age with a broad range of medical conditions; the following section addresses select examples of common chronic conditions requiring preconception evaluation (Table 2).

**Asthma. Implications in pregnancy:** Asthma is a chronic condition treated in approximately 4% to 8% of pregnancies. Although some women experience improvement in their asthma control during pregnancy, approximately 30% experience worsening symptoms.\(^50\) Women with severe asthma prior to pregnancy are more likely to encounter poor symptom control. Other reasons for exacerbations during pregnancy include pulmonary infection, gastroesophageal reflux disease, smoking, and discontinuation of preventive medications.\(^51\) Poorly controlled asthma is associated with adverse perinatal outcomes, including preterm birth, low birth weight, and preeclampsia.\(^50\) Reducing the frequency of asthma exacerbations during pregnancy significantly reduces the risk for preterm labor and delivery.\(^52\) These effects emphasize the importance of using medication and avoiding triggers for asthma to achieve optimal symptom control.

**Preconception recommendations and medication assessment:** Asthma control should be maximized prior to conception using the stepwise approach outlined in the National Asthma Education and Prevention Program guidelines.\(^53\) Selection of medication regimens that are supported for use throughout pregnancy can be guided by recommendations for asthma.

### Table 2. Summary of medications to assess during the preconception period

<table>
<thead>
<tr>
<th>Medical condition</th>
<th>Key medications to assess</th>
<th>Pregnancy considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asthma</strong></td>
<td>Short-acting beta-2-agonists</td>
<td>Albuterol is preferred short-acting beta-2-agonist</td>
</tr>
<tr>
<td></td>
<td>Long-term controller agents (inhaled corticosteroids, leukotriene modifiers, long-acting beta-2-agonists, theophylline)</td>
<td>Inhaled corticosteroids are preferred long-term controllers (especially budesonide)</td>
</tr>
<tr>
<td><strong>Clotting disorders</strong></td>
<td>Warfarin</td>
<td>Pregnancy Category X</td>
</tr>
<tr>
<td></td>
<td>Low-molecular-weight heparin preferred during pregnancy</td>
<td></td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>ACE inhibitors</td>
<td>Pregnancy Category D</td>
</tr>
<tr>
<td></td>
<td>ARBs</td>
<td>Methylodopa, labetalol, nifedipine preferred during pregnancy</td>
</tr>
<tr>
<td></td>
<td>Direct renin inhibitors</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>Oral antidiabetic agents</td>
<td>Optimize A1C to &lt;7% prior to conception</td>
</tr>
<tr>
<td></td>
<td>Antihypertensives</td>
<td>Switch oral medications to insulin if considering pregnancy or pregnant</td>
</tr>
<tr>
<td></td>
<td>Medications for hyperlipidemia: HMG-CoA reductase inhibitors (statins)</td>
<td>(See above hypertension section)</td>
</tr>
<tr>
<td><strong>Seizure disorders</strong></td>
<td>All AEDs</td>
<td>Pregnancy Category X</td>
</tr>
<tr>
<td></td>
<td>Optimize seizure-free period of at least 9 months for best pregnancy outcomes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Switch to AED monotherapy if pregnancy is desired, using an agent other than valproate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ensure adequate folic acid supplementation while taking AEDs</td>
<td></td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>SSRI (especially paroxetine)</td>
<td>Mild depression: consider psychotherapy and medication taper</td>
</tr>
<tr>
<td></td>
<td>TCA</td>
<td>Moderate to severe depression: consider psychotherapy and pharmacotherapy with agents other than paroxetine (Pregnancy Category D)</td>
</tr>
<tr>
<td></td>
<td>SNRI</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations used: A1C, glycated hemoglobin A1C; ACE, angiotensin-converting enzyme; AED, antiepileptic drug; ARB, angiotensin receptor blocker; HMG-CoA, hydroxymethylglutaryl-coenzyme A; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
management in pregnancy from the American Congress of Obstetricians and Gynecologists (ACOG). Albuterol is specified as the preferred short-acting beta-2-agonist in pregnancy, and budesonide is the preferred inhaled corticosteroid for controller therapy. Continuation of an alternate inhaled corticosteroid used prior to pregnancy is also supported. Long-acting beta-2-agonists are preferred add-on therapies over theophylline or leukotriene receptor antagonists. Patients should be educated about appropriate inhaler technique to maximize drug delivery to the site of action and minimize systemic absorption, as well as about the importance of continuing medication therapy to avoid adverse outcomes. In addition to medication recommendations, a plan should be established for peak flow and symptom monitoring. Patient education should also include strategies for trigger avoidance such as mold, animal dander, and secondhand tobacco smoke.

Pharmacists can address medication considerations for associated conditions, such as allergic rhinitis. Clinical practice guidelines from the Joint Task Force on Practice Parameters for Allergy and Immunology identify first- and second-generation antihistamines, intranasal cromolyn, montelukast, and intranasal corticosteroids as appropriate options for management of allergic rhinitis symptoms during pregnancy. Use of systemic decongestants should be avoided, especially during the first trimester. As with asthma, preconception counseling allows for selection of the safest medication options for symptom management.

Clotting disorders. Implications in pregnancy: Pregnancy is a hypercoagulable state characterized by increased clotting factors and decreased anticoagulant activity. Venous thromboembolism (VTE) occurs in approximately 1 in 1,600 births. Inherited thrombophilias, such as factor V Leiden mutation, prothrombin G20210A mutation, or antithrombin, protein C, or protein S deficiencies are associated with an increased risk for VTE during pregnancy. The decision to use anticoagulant therapy during pregnancy is based on the type of thrombophilia and the history of prior VTE.

Preconception recommendations and medication assessment: Prenatal screening for inherited thrombophilias is recommended by ACOG in women with a first-degree relative with a high-risk thrombophilia and in those with a personal history of provoked VTE. Women receiving chronic anticoagulant therapy prior to pregnancy, such as those with a history of VTE or at high risk due to mechanical heart valves or thrombophilias, face a unique dilemma related to the known teratogenicity of vitamin K antagonists such as warfarin. Warfarin increases the risk for miscarriage by up to 56% and is associated with cartilage and skeletal defects and central nervous system abnormalities. Bleeding complications during labor and delivery are also of concern. Highly effective contraception is desirable when chronic anticoagulation is necessary; however, choices are limited to non–estrogen-containing products, owing to prothrombotic concerns.

When pregnancy is desired, the approach to anticoagulation varies depending on the indication for the anticoagulant. In general, the American College of Chest Physicians recommends the use of low-molecular-weight heparin (LMWH) in pregnancy over vitamin K antagonists. LMWH is preferred to unfractionated heparin because of a lower risk for heparin-induced thrombocytopenia and osteoporosis. Data are too limited on the target-specific oral anticoagulants such as dabigatran, rivaroxaban, and apixaban to broadly recommend their use during pregnancy at this time.

The transition from warfarin to LMWH can involve several approaches. Early substitution for warfarin prior to conception provides a complete avoidance of fetal exposure. However, the preconception period is unknown, and extended use of LMWH prior to pregnancy contributes to higher costs and adverse effects such as injection-site reactions and osteoporosis. An alternate strategy is to continue warfarin while attempting to conceive and frequently test for pregnancy in order to transition to a LMWH as soon as pregnancy is identified (within the first few weeks of pregnancy). This approach relates to data identifying a higher risk for malformations with warfarin after the fourth or fifth week of gestation. In very rare cases of high thrombotic risk, warfarin use is continued into the third trimester under the guidance of a specialist, with a transition to an alternate anticoagulant at the time of delivery due to the risk for hemorrhage. In all cases, the transition plan must carefully weigh individual thrombotic risks with those of the anticoagulant and involve clear communication of all risks with the patient.

Hypertension. Implications in pregnancy: Five percent of pregnant women have chronic hypertension, defined by ACOG as hypertension (systolic blood pressure \( \geq \) 140 mm Hg or diastolic blood pressure \( \geq \) 90 mm Hg) existing before pregnancy or before 20 weeks of gestation. Many adverse outcomes are associated with chronic hypertension during pregnancy, including higher rates of cesarean delivery, gestational diabetes, and postpartum hemorrhage. Additionally, preeclampsia develops in approximately 13% to 40% of women with chronic hypertension, which can lead to target organ damage, fetal growth restriction, and perinatal mortality.

Preconception recommendations and medication assessment: The identification of hypertension during the preconception period provides an opportunity to optimize blood pressure control and modify associated risk factors for preeclampsia such as diabetes, obesity, renal disease, and secondary hypertension caused by pheochromocytoma and renovascular disease. In addition to lifestyle modifications, blood pressure control prior to pregnancy often requires chronic medication use. Current clinical practice guidelines for adults with hypertension recommend ACE inhibitors, angiotensin receptor blockers (ARBs), and calcium channel blockers as preferred first-line agents. ARBs and ACE inhibitors are associated with multiple malformations with second- or third-trimester exposure, including neurologic, renal, and cardiac anomalies that have been termed the fetal renin-angiotensin system.
blockade syndrome. Emerging evidence has identified risk for malformations with first-trimester exposure as well. To avoid these risks, ACOG recommends against the use of ACE inhibitors, ARBs, renin inhibitors, and mineralocorticoid receptor antagonists in women of reproductive age unless there is a compelling need, such as proteinuria.

Of interest, blood pressure often decreases during the first trimester and may allow for discontinuation of antihypertensive medications during that time. In balancing the maternal cardiac risks with fetal perfusion, pharmacotherapy is generally not recommended for treatment of chronic hypertension in pregnancy for those with systolic blood pressure <160 mm Hg or diastolic blood pressure <105 mm Hg if there is no evidence of target organ damage or preeclampsia. If drug therapy is deemed necessary for blood pressure control, labetalol, nifedipine, or methyldopa are recommended above all other oral antihypertensive medications because of the potential teratogenic effects of lipid-lowering agents such as HMG-CoA reductase inhibitors (statins) and antihypertensive agents such as ACE inhibitors and ARBs is warranted; diabetic women who take antihypertensive medications should also be counseled on appropriate birth control methods (see hypertension section of Table 2). Because retinopathy may worsen during pregnancy, women should be counseled about the potential development or progression of diabetic retinopathy and recommended to have a comprehensive eye exam. The eye exam should take place during the first trimester, with close monitoring throughout pregnancy and 1 year postpartum. Women should also be screened for diabetic nephropathy before pregnancy by having serum creatinine and albuminuria assessed.

Seizure disorders. Implications in pregnancy: In 2008, approximately 500,000 women in the United States with epilepsy were of reproductive age. Epilepsy is characterized as a condition in which a person suffers from recurrent, unprovoked seizures and generally requires the long-term use of antiepileptic drugs (AEDs) for maintenance of seizure remission. Unfortunately, some of the most effective AEDs are also potential teratogens. In addition, many of the available hormonal contraceptive products may have decreased efficacy when used with an AED. Therefore, women of childbearing age need to be counseled about the possible effects of these medications on the fetus should pregnancy occur.

If epilepsy is not treated, seizures may result. Dangers of seizures during pregnancy can include decreased oxygen to the fetus, trauma or harm to the fetus due to maternal falls, and an increased risk of premature labor and premature rupture of membranes. Monitoring of AED levels during pregnancy is imperative to ensure adequate control of seizures. Changes in pregnancy such as decreased albumin and induction of hepatic enzymes due to increased sex steroid hormones may increase clearance of several AEDs, resulting in subtherapeutic drug levels and increasing the risk for seizures. Reports suggest that approximately one-fifth to one-third of women with epilepsy will have an increase in seizures while pregnant, one-quarter will experience a decrease, and more than one-half will experience no change in seizure frequency.

Because many AEDs are hepatic enzyme inducers, they also enhance the metabolism of vitamin K, increasing the risk for vitamin K deficiency in the fetus. This may increase the risk of intracranial bleeding in the newborn upon delivery. Although somewhat controversial, maternal use of 10 mg
of oral vitamin K daily during the last month of pregnancy has been suggested to decrease bleeding risk.66 Regardless, 1 mg intramuscular vitamin K should be administered to the newborn immediately after birth.

**Preconception recommendations and medication assessment:** A majority of women with epilepsy will have a normal pregnancy.65 Studies indicate that women who are seizure free for at least 9 months prior to pregnancy are likely to remain so throughout their pregnancy.65 With the appropriate management and proper medications used during the preconception and pregnancy period, most women can have a healthy pregnancy. If a woman is planning to conceive, it is preferable to streamline her medications to one agent if possible. Data show that the risk for major congenital malformations increases up to two- to threefold with AED polytherapy versus monotherapy.66 In particular, agents such as carbamazepine and valproate may decrease folic acid levels and should be avoided if possible. ACOG recommends that women taking AEDs such as valproate or carbamazepine and planning to become pregnant should take daily folic acid supplements for 1 to 3 months before trying to conceive.69 There is debate whether the 400 mcg daily dose of folic acid is sufficient for those taking AEDs or if a 4,000 mcg daily dose should be recommended for women taking AEDs.65,66

Women with a history of a seizure disorder should be evaluated and counseled about the need for AEDs. In women who have been seizure-free for 2 years or more, a tapered withdrawal of medications may be appropriate. If possible, these women should be free of AEDs for at least 6 months before trying to conceive.70 Many women may have a fear of using medication while pregnant, which may affect seizure control. Patient counseling should address adherence to a properly selected agent. Patients should also be educated on the risks and benefits of medication use.

Several of the AEDs may affect a growing fetus. Even though folic acid supplementation is recommended prior to pregnancy for women on AEDs (particularly valproate and carbamazepine), neural tube defects are known to occur despite its use. Major congenital malformations may include cleft palate, cleft lip, and cardiovascular and urinary tract anomalies. In addition to teratogenic risks, some AEDs may have an effect on neurodevelopment of the child after birth. Valproate has shown high risk for teratogenicity and negative neurodevelopment outcomes such as lower verbal IQ scores for those children exposed in utero.66 Other AEDs have more favorable neurodevelopmental outcomes, with the exception of phenobarbital and primidone.68 The teratogenic effects of valproate also appear to be dose dependent, with a higher incidence of birth defects in those taking doses higher than 1,100 mg.66 Therefore, valproate should be substituted with another AED prior to conception, if possible. Carbamazepine, topiramate, oxcarbazepine, phenytoin, lamotrigine, phenobarbital, and primidone have been shown to increase the risk of major congenital malformations. Of these, lamotrigine has the lowest risk of teratogenicity but still has a risk of malformations that is higher than the general population, with cleft lip or cleft palate being reported.66,71 There are minimal data on the risks with newer AEDs; thus, their risks are unknown.

Women who use AEDs during pregnancy should receive the lowest effective dose for the lowest effective plasma level for preventing seizures.66 A plasma-free drug level should be monitored regularly at every trimester during pregnancy because of pharmacokinetic changes such as increased plasma volume, decreased albumin, and effects of nausea and vomiting. If possible, use of multiple AEDs is not recommended during pregnancy.66,71 If a woman unexpectedly becomes pregnant, switching AEDs is not recommended because the switch may precipitate seizures and expose the fetus to a greater number of potential teratogens.66,71 Therefore, adequate counseling regarding pregnancy planning and appropriate birth control methods (including potential interactions with hormonal contraceptives) should be discussed with patients receiving AED therapy.

**Depression.** Implications in pregnancy: Depression affects women twice as often as men and is characterized by symptoms such as depressed or irritable mood, anhedonia, feelings of excessive guilt or worthlessness, change in appetite, lethargy, change in sleep, psychomotor agitation or retardation, or suicidal ideation.72 Untreated depression in a pregnant woman can lead to low birth weight, premature birth, fetal growth restriction, and developmental delays in the infant.72,73 Decreased self-care can lead to decreased pre-
nental care, substance abuse, and poor nutrition, which can have negative effects on the infant. Additionally, newborns of mothers with untreated depression during pregnancy have been reported to cry more and be more difficult to console. One study demonstrated that maternal depression during pregnancy can affect the brain development of offspring, making these children more prone to depression later in life. Thus, adequate treatment of depression is crucial during pregnancy.

Preconception recommendations and medication assessment:
The American Psychiatric Association and ACOG developed a joint report on the treatment of depression in pregnant women. Common assessments of depression include the Beck Depression Inventory and, more commonly in pregnant women, the Edinburgh Postnatal Depression Scale. Pharmacists may play a role in assessing depression and counseling about antidepressant use. Several factors for treatment selection must be considered, including the patient’s history of depression, severity of depression (e.g., suicidal ideation), and psychotic features. For most women with mild depression considering pregnancy, the first-line treatment is psychotherapy such as cognitive behavioral therapy or interpersonal therapy.

In women who have been taking an antidepressant prior to pregnancy, the recommendation for treatment length is 6 to 12 months for a major depressive episode. For women who have been symptom-free for 6 months or who are considered to have mild depression, a medication taper may be considered prior to attempting to conceive. If medication is discontinued, a slow taper of 25% reduction in dose every 1 to 2 weeks is recommended, with close supervision for relapse.

For depression unresponsive to psychotherapy or for more moderate to severe depression, pharmacotherapy in addition to psychotherapy is recommended. Proper selection of a treatment agent is critical to the health of the mother and developing fetus. Selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and other antidepressants (non-SSRI and non-TCA) are generally considered the main therapies for depression in nonpregnant patients. SSRIs (with the exception of paroxetine, serotonin-norepinephrine reuptake inhibitors [SNRIs], and bupropion) are generally considered first-line options if treatment is required in pregnancy; available safety data in pregnancy indicate that lower risks are associated with their use. Concerns with antidepressant use in pregnancy include teratogenicity and neonatal abstinence syndrome (NAS) in the newborn, particularly with SSRIs.

Of note, there is conflicting information on the safety of SSRIs in pregnancy. Most data suggest low risks in early pregnancy, with the designation of most agents as Pregnancy Category C. Paroxetine, however, is classified as Pregnancy Category D because of associations with anencephaly, craniosynostosis, and omphalocele. While there is an increase in these malformations associated with paroxetine, the risk overall remains low. Other studies found small risks of various malformations with sertraline, citalopram, and fluoxetine. Overall, reports of these various malformations associated with SSRIs have been conflicting, with some small studies reporting cardiac defects (particularly with paroxetine), and other studies finding no associations with other SSRIs. An increased risk of respiratory distress leading to persistent pulmonary hypertension has also been reported in infants whose mothers used SSRIs, particularly in the later trimesters. Longer use of SSRIs during pregnancy may increase the risk of respiratory complications in the infant. Neonatal abstinence syndrome is also a concern for infants born to mothers who used SSRIs in the last trimester. Symptoms of NAS include weak cry, poor muscle tone, jitteriness, mild respiratory distress, and transient shortness of breath, which may lead to admission to the neonatal intensive care unit.

Furthermore, conflicting data have been reported in studies of TCAs used in pregnancy. Most studies have not shown a risk between TCA use in pregnancy and structural malformations. However, perinatal complications such as jitteriness, irritability, and convulsions in the infant have been reported with maternal use of TCAs during pregnancy. It is also important to consider potential maternal adverse effects of TCA agents, such as cardiac toxicity and complications from overdose.

Other antidepressants used in pregnancy, such as bupro-

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<th>Table 3. Preconception resources for pharmacists</th>
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<tr>
<td><strong>Organization</strong></td>
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<td>Before, Between, and Beyond Pregnancy</td>
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<td>CDC: Preconception health and health care</td>
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<td>March of Dimes</td>
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<td>Organization of Teratology Information Specialists: MotherToBaby</td>
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<td>Reproductive Toxicology Center: REPROTOX⁴</td>
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<td>Rx for Change: Clinician-Assisted Tobacco Cessation</td>
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<td>Teratogen Information System⁴</td>
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⁴Subscription required for access.
pion, venlafaxine, mirtazapine, nefazodone, trazodone, and duloxetine, have not been shown to significantly increase the risk of congenital malformations in infants.73 Bupropion has more data than others on risk in pregnancy, with one study showing some increased risk of spontaneous abortion but no increased risk of malformations.73 Use of mirtazapine early in pregnancy has been associated with spontaneous abortion, while use late in pregnancy has been associated with an increased risk of preterm delivery.74 The limited data available for these antidepressants suggest that they do not have congenital malformation risks associated with use during pregnancy; however, the data available are not enough to completely rule out any risk. The pharmacist, provider, and patient should consider the risks of medication use in pregnancy versus the risks of untreated maternal depression on an individual basis.

Summary
Pharmacists are ideally positioned to provide preconception care for women of childbearing age. Prevention and management interventions aim to identify, assess, and modify pharmacological, behavioral, and social risks to a woman’s health or pregnancy outcome. Opportunities for pharmacist intervention in preconception health include screening for immunization needs, encouraging folic acid supplementation, screening for tobacco use, screening for medication safety, and assessing risks. Optimizing control of chronic medical conditions prior to pregnancy is ideal, and the feasibility of transitioning to medications with lower risk for fetal malformation should be assessed. Table 3 lists additional Web-based resources to help pharmacists become further involved in preconception health promotion and education. Pharmacist participation in screening, educating, and facilitating health care during the preconception period serves to optimize pregnancy outcomes.

References


CPE Assessment

Instructions: This exam must be taken online; please see “CPE information” for further instructions. The online system will present these questions in random order to help reinforce the learning opportunity. There is only one correct answer to each question.

1. Which of the following is the approximate percentage of women who report using a prescription medication during the first trimester of pregnancy?
   a. 20%
   b. 30%
   c. 50%
   d. 80%

2. After a missed menstrual period, embryogenesis begins in how many days?
   a. 1 day
   b. 3 days
   c. 10 days
   d. 30 days

3. Which of the following immunizations is recommended during pregnancy?
   a. Tdap
   b. Varicella
   c. MMR
   d. HPV

4. Which of the following vaccines may be provided during pregnancy?
   a. Live-attenuated influenza
   b. Inactivated influenza
   c. MMR
   d. Varicella

5. Which of the following is the daily recommended dose of folic acid for a nonpregnant woman of reproductive age?
   a. 400 mcg
   b. 600 mcg
   c. 800 mcg
   d. 1000 mcg

6. Folic acid supplementation during pregnancy can help to prevent which of the following?
   a. Macrosomia
   b. Retinopathy
   c. Neural tube defects
   d. Cardiac defects

7. Which of the following A1C values is the ideal goal for a woman with diabetes who is planning to become pregnant?
   a. <5%
   b. <7%
   c. <10%
   d. <12%

8. Which of the following medications is best to avoid in pregnancy?
   a. Valproate
   b. Regular insulin
   c. NPH insulin
   d. Inactivated influenza vaccine

9. Which of the following medications, if taken during pregnancy, has been associated with persistent pulmonary hypertension in the newborn?
   a. Bupropion
   b. Amitriptyline
   c. Paroxetine
   d. Mirtazapine

10. Use of SSRIs late in the third trimester increases the risk for which of the following conditions for the newborn?
    a. Neonatal abstinence syndrome
    b. Macrosomia
    c. Anencephaly
    d. Hyperglycemia

11. Which of the following methods of tobacco cessation during pregnancy is recommended as first-line therapy by the 2008 U.S. Department of Health and Human Services clinical practice guidelines for the treatment of tobacco dependence?
    a. Nicotine patches
    b. Nicotine lozenges
    c. Varenicline
    d. Psychosocial intervention

CPE information

To obtain 2.0 contact hours (0.2 CEUs) of CPE credit for this activity, you must complete the online Assessment and Evaluation. A Statement of Credit will be awarded for a passing grade of 70% or better on the Assessment. You will have two opportunities to successfully complete the CPE Assessment. Pharmacists who successfully complete this activity before June 1, 2017, can receive CPE credit. Credit will be awarded upon achieving a passing grade of 70% or better. Please visit CPE monitor for your transcript at www.nabp.net/programs/cpe-monitor-cpe-monitor-service.

CPE instructions:
1. Log in or create an account at pharmacist.com and select LEARN from the top of the page; select Continuing Education, then Home Study CPE to access the Library.
2. Enter the title of this article or the ACPE number to search for the article and click on the title of the article to start the home study.
3. To receive CPE credit, select Enroll Now or Add to Cart from the left navigation and successfully complete the Assessment (with randomized questions), Learning Evaluation, and Activity Evaluation.

Live step-by-step assistance is available Monday through Friday from 8:30 am to 5:00 pm ET at APhA Member Services at 800-237-APhA (2742) or by e-mailing education@aphanet.com.
12. Cleft lip/palate is most associated with a teratogenic exposure during which of the following time periods?
   a. First trimester of pregnancy
   b. Second trimester of pregnancy
   c. Third trimester of pregnancy
   d. Breastfeeding

13. Which of the following describes the FDA pregnancy category for a medication where no studies have been conducted with animals or women?
   a. Category A
   b. Category B
   c. Category C
   d. Category D

14. Which of the following best describes the mechanism of teratogenicity of isotretinoin?
   a. Disruption of folate metabolism
   b. Interference with neural crest cell development
   c. Alteration of endocrine function
   d. Disruption of vascular function

15. Which of the following agents is the preferred medication for asthma control during pregnancy?
   a. Theophylline
   b. Leukotriene modifier
   c. Systemic corticosteroid
   d. Inhaled corticosteroid

16. Which of the following medications for allergic rhinitis should be avoided during the first trimester of pregnancy?
   a. Oral antihistamine
   b. Intranasal corticosteroid
   c. Oral decongestant
   d. Intranasal cromolyn

17. According to the American College of Chest Physicians, which of the following anticoagulants is preferred for use during pregnancy?
   a. Warfarin
   b. Rivaroxaban
   c. Low molecular weight heparin
   d. Unfractionated heparin

18. Which of the following contraceptives is most appropriate for a patient who has factor V Leiden mutation and takes warfarin for a history of deep vein thrombosis?
   a. Progestin-only intrauterine system
   b. Combination estrogen–progestin oral contraceptive
   c. Combination estrogen–progestin intravaginal ring
   d. Combination estrogen–progestin transdermal patch

19. Which of the following antihypertensive agents is recommended for treatment of chronic hypertension during pregnancy?
   a. Methyldopa
   b. Enalapril
   c. Losartan
   d. Hydrochlorothiazide

20. KL is a 28-year-old woman with chronic hypertension who is at 20 weeks of gestation. An antihypertensive agent should be recommended for KL if her blood pressure is:
   a. 130/82 mm Hg
   b. 144/90 mm Hg
   c. 156/100 mm Hg
   d. 162/104 mm Hg