

Vaccinations for Pregnant Women

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In the United States, eradication and reduction of vaccine-preventable diseases through immunization has directly increased life expectancy by reducing mortality. Although immunization is a public priority, vaccine coverage among adult Americans is inadequate. The Institute of Medicine, the Community Preventive Services Task Force, and other public health entities have called for the development of innovative programs to incorporate adult vaccination into routine clinical practice. Obstetrician–gynecologists are well suited to serve as vaccinators of women in general and more specifically pregnant women. Pregnant women are at risk for vaccine-preventable disease-related morbidity and mortality and adverse pregnancy outcomes, including congenital anomalies, spontaneous abortion, preterm birth, and low birth weight. In addition to providing direct maternal benefit, vaccination during pregnancy likely provides direct fetal and neonatal benefit through passive immunity (transplacental transfer of maternal vaccine-induced antibodies). This article reviews: 1) types of vaccines; 2) vaccines specifically recommended during pregnancy and postpartum; 3) vaccines recommended during pregnancy and postpartum based on risk factors and special circumstances; 4) vaccines currently under research and development for licensure for maternal–fetal immunization; and 5) barriers to maternal immunization and available patient and health care provider resources.

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Vaccine-preventable diseases are defined as those infectious diseases for which an effective preventive vaccine exists and may be prevented by vaccinating individuals per standard recommendations.¹ In the United States, eradication and reduction of vaccine-preventable diseases through immunization have directly increased life expectancy by reducing infectious-disease mortality.² For example, deaths from invasive pneumococcal disease, hepatitis A and B, and varicella have dramatically declined over the past

decade.³ Infectious diseases remain a major cause of adult morbidity and mortality, with well more than 50,000 adults dying each year from vaccine-preventable diseases and associated complications.³

National immunization recommendations currently target 17 vaccine-preventable diseases across the lifespan. However, adult coverage for most routinely recommended vaccines is suboptimal and well below Healthy People 2020 goals.⁴ In 2011, only 20% of adults were appropriately vaccinated against pneumococcus; 12.5% against tetanus, diphtheria, and pertussis or hepatitis A; 35% against hepatitis B; and 43% of women against human papillomavirus.⁵ Considerable increases in vaccination coverage are needed to significantly reduce or eradicate the incidence of vaccine-preventable diseases in adults. The Institute of Medicine, the Community Preventive Services Task Force, and other public health entities have called for the development of innovative programs and incorporation of adult vaccination into routine clinical practice.^{6,7} With approximately 32,000 obstetrics and gynecology offices in the United States, integration of adult immunizations into routine obstetric and gynecology practice is one approach that would reach the vast majority of women across the lifespan.

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Obstetrician–gynecologists (ob-gyns) provide more general medical care to women than either family practice or internal medicine providers and thus would have opportunities to incorporate vaccination into standard clinical care.⁸ Moreover, ob-gyns specifically care for pregnant women who, along with their fetuses, are particularly vulnerable to vaccine-preventable disease-related complications. Pregnant women are at extremely high risk for influenza-related morbidity and mortality including adverse pregnancy outcomes (fetal growth restriction, preterm birth, and fetal demise).^{9–13} Rubella and varicella infections during pregnancy can lead to complex congenital anomalies. Although congenital hepatitis B does not cause malformations, vertical transmission is associated with lifelong disease and long-term sequelae. Thus, immunization before conception would be ideal for the prevention of vaccine-preventable diseases associated with congenital disease. However, for vaccine-preventable diseases associated with adverse maternal, fetal, or neonatal health, immunization during pregnancy provides not only maternal benefit, but may have the added benefit of direct neonatal protection. Passive immunity—transplacental immune globulin G antibody transfer from vaccinated mother to fetus—provides infant protection for up to 6 months of life.^{14,15} Maternal immunization is particularly important when considering vaccine-preventable diseases from which we have no other options for protecting young infants, such as influenza and pertussis. Specifically, influenza vaccine is not licensed for use before 6 months of age, and adequate antipertussis antibodies are only achieved after two to three doses of diphtheria and tetanus toxoids and acellular pertussis vaccine by 6 months of age.¹⁶

Ob-gyns are well-positioned to screen and vaccinate pregnant women against vaccine-preventable diseases, having demonstrated their capability through the near eradication of congenital rubella in the United States through routine antenatal surveillance and postpartum vaccination. Furthermore, ob-gyns were heavily involved in the extensive administration of H1N1 vaccine to pregnant women during the 2009 pandemic and have continued their efforts to increase maternal influenza vaccination, exceeding 50% coverage for the first time in 2012–2013.¹⁷ Among the vaccines recommended by the Centers for Disease Control and Prevention (CDC) for adults, two are directly recommended for administration during pregnancy, four are recommended in pregnancy based on additional risk factors, and two are specifically recommended during the postpartum period.¹⁸ With nearly 4 million U.S. births each year,

ob-gyns have the potential to greatly affect the health and well-being of mothers and infants through maternal immunization and contribute to the public health campaign for adult vaccine coverage. This article describes: 1) types of vaccines; 2) vaccines specifically recommended during pregnancy and postpartum; 3) vaccines recommended during pregnancy and postpartum based on risk factors and under special circumstances; 4) vaccines currently under research and development for licensure for maternal–fetal immunization; and 5) barriers to maternal immunization and available resources.

TYPES OF VACCINES

Based on laboratory methods, vaccines are classified as live attenuated, inactivated or killed, toxoid, subunit, or conjugate vaccines (Table 1). Live attenuated vaccines may contain living organisms that have been weakened or altered so as not to cause infection.^{19,20} Disease-causing pathogens are manipulated in the laboratory through multiple rounds of tissue culture or animal embryos, mutagenesis, or targeted genetic alterations to specifically select very low virulent strains. Manipulated pathogens do not cause overt human disease but adequately stimulate an immune response so that healthy people mount an immune response nearly equivalent to what would follow natural exposure or infection. Although technically possible for clinical infection to occur after live attenuated vaccination, it is extremely uncommon, and any illness that occurs is typically much milder than natural infection and is classified as an adverse reaction. However, immunocompromised individuals are at risk for unregulated pathogen replication followed by severe-to-fatal infection and cannot receive live attenuated vaccines. Similarly, live attenuated vaccines are contraindicated during pregnancy as a result of the theoretical risk of perinatal infection resulting in congenital disease, eg, rubella or varicella.

Inactivated or killed vaccines are created by inactivating a pathogen using heat or chemicals like formalin or formaldehyde.^{19,20} Inactivating processes destroy the pathogen's ability to replicate, because it does not contain any living or infectious particles and thus cannot result in clinical infection. Certain bacteria cause disease by producing a toxin rather than by direct bacterial interaction, as seen in *Clostridium tetani*. Vaccines against such diseases, called toxoid vaccines, are similarly created by inactivating the toxins using heat or chemicals. Inactivated and toxoid vaccines maintain their ability to generate an immune response, albeit less robust than the response after live attenuated vaccines. Antibody levels wane over time,



Table 1. Current Vaccine Recommendations for Pregnant Women

Vaccine	Vaccine Type	Pregnancy Recommendation	General Adult Recommendation
Vaccines recommended for all pregnant women			
Influenza	Inactivated viral subunit or live attenuated viral recombinant	1 dose of inactivated vaccine administered during flu season, any gestational age	1 dose of inactivated or live attenuated vaccine administered annually during flu season
Tdap/Td	Tetanus and diphtheria— inactivated toxoids; acellular pertussis— inactivated subunit	1 dose Tdap after 20 wk, preferably approximately 28 wk, regardless of prior Tdap receipt	Substitute 1 lifetime dose of Tdap for Td booster; return to Td booster every 10 y or sooner if exposure occurs
Vaccines recommended for postpartum women (contraindicated during pregnancy)			
MMR	Live attenuated viral	1 dose immediately postpartum if rubella nonimmune or equivocal	1–2 doses, lifetime; additional 1 dose older than 55 y if risk factor present
Varicella	Live attenuated (viral)	1 dose immediately if varicella nonimmune	2 doses, lifetime
Vaccines recommended for pregnant women with risk factors or special circumstances			
Hepatitis A	Inactivated whole-cell viral	2 doses if risk of infection outweighs theoretical risk of vaccine	2 lifetime doses
Hepatitis B	Inactivated viral recombinant subunit	3 doses if previously unvaccinated or at high risk of exposure	3 lifetime doses
Pneumococcal	Inactivated bacterial polysaccharide	1 dose if risk factor present	1–2 doses if risk factor present; 1 dose for all individuals 65 y or older
Meningococcal	Inactivated bacterial polysaccharide	1 dose if risk factor present	Can be used for children younger than 2 y and adults older than 55 y and during epidemics
Yellow fever	Live attenuated viral	1 dose if travel to endemic regions and risk of infection outweighs theoretical risk of vaccine	1 dose for travel to endemic regions
Japanese encephalitis	Live attenuated viral	1 dose if travel to endemic regions and risk of infection outweighs theoretical risk of vaccine	1 dose for travel to endemic regions
Typhoid	Live attenuated bacterial recombinant	Not recommended owing to lack of data	For travel to endemic regions
Anthrax	Inactivated subunit	Postexposure prophylaxis for all pregnant women; preexposure prophylaxis is not recommended owing to lack of data	Preexposure prophylaxis if risk factor; postexposure prophylaxis for all adults
Rabies	Inactivated whole-cell viral	Postexposure prophylaxis; consider preexposure prophylaxis if risk of exposure is very high	Preexposure prophylaxis if risk factor; postexposure prophylaxis for all adults

Tdap, tetanus, diphtheria, acellular pertussis; Td, tetanus, diphtheria; MMR, measles, mumps, and rubella.

thus requiring multiple dosing, booster dosing, or both to maintain adequate protection.

Subunit vaccines contain fragments of the pathogens they protect against, which subsequently provoke

a protective immune response.^{19,20} One method for creating a subunit vaccine is by isolating a specific antigenic protein like with acellular pertussis vaccine. Alternatively, several subunit vaccines are created through



genetic engineering or recombination. For hepatitis B vaccine, as an example, a gene encoding for a pathogen-specific protein is inserted into another virus or cell culture. For human papillomavirus vaccine, expression of a single human papillomavirus protein results in production of virus-like particles. Virus-like particles contain no actual viral genetic material and thus cannot cause infection. After vaccination, the immune system recognizes the expressed proteins from recombinant vaccines and develops protective antibodies against the target pathogen. Conjugate vaccines are similar to recombinant vaccines except they are created by chemically combining pieces of the bacterial coat with a carrier protein. The bacterial components are unable to cause infection and require the carrier protein to stimulate an adequate immune response.

VACCINES RECOMMENDED FOR USE IN PREGNANCY AND POSTPARTUM

Influenza

Influenza (flu) is an RNA virus with A and B serotypes and is responsible for both endemic and pandemic flu (Table 1). Both types are responsible for endemic flu, whereas type A, as a result of antigenic drift of its surface proteins hemagglutinin and neuraminidase, is responsible for flu pandemics.²¹ In a single flu season, it is estimated that 20% of the U.S. population contracts the illness, with the number increasing to 50% during pandemics. Each year, 20% of pregnant women will develop upper respiratory-like illness with 10% having laboratory-confirmed flu.²²

Pregnant women infected with flu have increased rates of hospitalization, cardiopulmonary complications, and death when compared with the general population.¹² Complications are further increased during pandemics, as seen during the 2009 H1N1 outbreak when 5% of all related deaths occurred in pregnant women, yet they only encompass 1% of the total population.¹¹ Multiple complications including spontaneous abortion, stillbirth, neonatal death, preterm birth, and low birth weight have been reported among influenza-infected women and likely correlate with disease severity.¹³ During the 2009 pandemic, the preterm birth rate increased threefold among infected pregnant women admitted to the hospital.²³

Immunization is the best strategy for flu prevention as supported by the current CDC recommendation that all pregnant women receive inactivated influenza vaccine during flu season. Live attenuated vaccine is contraindicated in pregnancy, although inadvertent administration during the first trimester has not been associated with adverse outcomes.²⁴ Regarding inactivated influenza vaccine efficacy in pregnancy, a recent

randomized study of 340 pregnant women revealed a 36% reduction in influenza illness.¹⁴ A large population-based study from Norway revealed a 70% reduction in flu illness in immunized mothers, suggesting an even greater maternal benefit than previously thought.¹⁰ In addition to maternal benefits, inactivated influenza vaccine during pregnancy carries significant fetal and neonatal benefits. Maternal immunization has been associated with an increase in birth weight and a reduction in low birth weight, preterm birth, and fetal death.^{10,14} Furthermore, a recent randomized trial of third-trimester maternal inactivated influenza vaccine compared with pneumococcal vaccine led to a 29% reduction in respiratory illness and a 63% reduction in laboratory-confirmed flu among newborns up to 6 months of age in the maternal inactivated influenza vaccine group.¹⁴ These findings have been confirmed in multiple population-based studies with confirmed flu cases reduced 39–47% and hospitalizations reduced up to 90% in infants up to 6 months of age.^{25,26} It is unknown whether maternal immunization during the first or second trimester will provide similar infant benefit. Future studies are required to address gestational age timing of vaccination because timing of administration may differ for maternal, fetal, or neonatal benefit.

Occurring in more than 90% of infected individuals, the most common symptoms of flu are fever and cough with a sore throat, myalgia, and headache occurring less commonly in approximately 30–50% of patients. Pregnant women who present with fever above 100.0°F, exhibit either sore throat or cough, and have no other explanatory causes can be presumptively diagnosed with the flu, and treatment should be initiated. Rapid tests are available, but poor sensitivity limits usefulness in high-risk populations such as pregnant women.²⁷ Confirmatory tests such as culture or polymerase chain reaction are extremely sensitive for the diagnosis of the flu but the delay in result reporting and lack of widespread availability limit their utility. According to the CDC, treatment should not be delayed while waiting for a result.²⁸ However, confirmatory testing remains important for public health surveillance of serotype and identification of drug resistance patterns.

Treatment of flu during pregnancy consists of oral (oseltamivir) or inhaled (zanamivir) therapy. Oseltamivir is preferred in pregnancy as a result of its safety profile and convenience unless high levels of oseltamivir resistance are encountered; then health care providers should shift preference to inhaled zanamivir.²⁹ Treatment should be initiated as rapidly as possible, because delay in initiation (more than 2 days of symptom onset) has been associated with worsening



morbidity (ie, intensive care unit admission, mechanical intubation, and death).

Tetanus, Diphtheria, and Pertussis

Vaccination against diphtheria, tetanus, and pertussis is included in the standard U.S. childhood vaccination schedule with the diphtheria, tetanus, acellular pertussis series starting at 2 months of age. *C tetani* releases the tetanospasmin neurotoxin, which causes tetanus infection or prolonged muscular contraction. *Corynebacterium diphtheriae* causes an upper respiratory infection called diphtheria. Tetanus and diphtheria infections are nearly eradicated in the United States through routine decennial Td booster dosing across the lifespan and exposure-related administration. However, pertussis—a respiratory infection caused by *Bordetella pertussis*—has not followed a similar pattern. Since the 1980s, pertussis has been on the rise in the United States after many years of effective disease control and prevention. From less than 5,000 reported cases in the early 1980s, pertussis reached to an all-time high of 48,277 cases in 2012 and dropped to 24,231 cases in 2013.^{30,31} It is unclear if the resurgence is the result of mutations in the *B pertussis* bacteria, heightened awareness combined with improved diagnostic testing and increased reporting, or rapid waning of postacellular vaccination immunity.^{32,33} Although reported cases have increased in the general population, pertussis-related morbidity and mortality disproportionately affect infants younger than 12 months of age.³⁴ Young infants usually are infected after exposure to a close contact, with 47–60% of cases resulting from exposure from infected parents.¹⁶ Adults with pertussis are often unaware of their diagnosis, given that many adults are either asymptomatic or have symptoms of a common cold.

Innovative strategies are needed to prevent infant pertussis given that infants do not have adequate vaccine-induced protection against pertussis until at least 6 months of age, after two to three diphtheria, tetanus, acellular pertussis vaccine doses.¹⁶ One strategy is to “cocoon” infants or decrease their risk of pertussis exposure by immunizing their close contacts against pertussis. In 2005, the CDC recommended that unvaccinated postpartum women and other close contacts of newborns receive the diphtheria and reduced tetanus toxoids and acellular pertussis vaccine to decrease neonatal exposure to pertussis.³⁵ Despite some progress in diphtheria and reduced tetanus toxoids and acellular pertussis vaccine administration during the immediate postpartum period, diphtheria and reduced tetanus toxoids and acellular pertussis vaccine cocooning programs have not been

successfully implemented. For example, new fathers and other close contacts are not routinely receiving diphtheria and reduced tetanus toxoids and acellular pertussis vaccine.³⁶ Moreover, it is unlikely that postpartum maternal immunization as a sole strategy is adequate to prevent infant pertussis.³⁷ In October 2011, the CDC’s Advisory Committee on Immunization Practices considered current safety data, the potential for protection against infant pertussis from transplacentally transferred maternal antibodies, and a decision analysis suggesting vaccination during pregnancy is superior to postpartum administration. During this meeting, the CDC changed their “cocooning” recommendation to administration of diphtheria and reduced tetanus toxoids and acellular pertussis vaccine to unimmunized women during the late second or third trimester of pregnancy. Immediate postpartum diphtheria and reduced tetanus toxoids and acellular pertussis vaccine vaccination should be offered to unimmunized women who did not receive diphtheria and reduced tetanus toxoids and acellular pertussis vaccine during pregnancy.^{38,39} This was followed by a swift adoption of CDC recommendations by the American College of Obstetricians and Gynecologists (the College) in March 2012, demonstrating strong support by the College for interventions proven to benefit both mother and infant.

Very soon after ob-gyns began working to implement office processes to administer diphtheria and reduced tetanus toxoids and acellular pertussis vaccine to unimmunized pregnant women in their practices, the CDC’s Advisory Committee on Immunization Practices voted unanimously in October 2012 to recommend diphtheria and reduced tetanus toxoids and acellular pertussis vaccine vaccination to all pregnant women regardless of her history of diphtheria and reduced tetanus toxoids and acellular pertussis vaccine receipt.⁴⁰ Such aggressive action was taken as a result of the record-breaking numbers of pertussis cases and deaths, 48,277 and 20 in 2012, respectively.⁴¹ Although passive infant immunity has been documented after maternal immunization,⁴² limited, statistically nonsignificant data have been extrapolated to suggest that the optimal timing for diphtheria and reduced tetanus toxoids and acellular pertussis vaccine is in the third trimester and at least 2 weeks before delivery to allow for an adequate maternal antibody response. Although it is imperative that ob-gyns routinely administer diphtheria and reduced tetanus toxoids and acellular pertussis vaccine to all pregnant women to avoid potentially devastating infant pertussis, many questions regarding vaccine effectiveness, optimal timing of vaccine administration, infant



antibody correlates of protection, and safety of repeated close-interval dosing in multiparous women remain unanswered. Ongoing studies of diphtheria and reduced tetanus toxoids and acellular pertussis vaccine in pregnancy will provide some of these answers.^{43,44}

Measles–Mumps–Rubella

Routine childhood vaccination and young adult booster dosing have dramatically diminished the incidence of measles, mumps, and rubella in the United States. Measles is a paramyxovirus that presents routinely with rash, diarrhea, and otitis media along with bronchopneumonia or encephalitis in severe cases. Infection during pregnancy increases the risk of spontaneous abortion, preterm birth, and low birth weight.⁴⁵ Mumps is another paramyxovirus that presents with flu-like symptoms and bilateral parotitis and is associated with spontaneous abortion. Rubella is a togavirus that presents with more nonspecific symptoms including lymphadenopathy, arthralgias, fever, and rash. Infection during pregnancy, especially in the first trimester, can be devastating. In the last U.S. rubella epidemic in 1964–1965, approximately 12.5 million rubella infections resulted in 11,250 spontaneous or therapeutic abortions, 2,100 neonatal deaths, and 20,000 neonates born with congenital rubella syndrome.⁴⁶ Serious sequelae of congenital rubella syndrome include deafness, cataracts, cardiac defects, neurologic damage, and death.

Although rubella cases dramatically declined over the past 40 years, inclusion of measles–mumps–rubella in the universal vaccination program occurred in 2004, after which elimination of endemic rubella virus transmission was documented in the United States.⁴⁶ From 2004 to 2012, 79 cases of rubella infection and six cases of congenital rubella syndrome were documented with all sources being foreign import or unidentifiable. Three of the six congenital rubella syndrome cases occurred in 2012 among mothers who had been in Africa during early pregnancy. Thus, measles–mumps–rubella vaccination continues to be of high relevance to obstetric care given the increasing immigration and global mobility of the U.S. population.

After two childhood measles–mumps–rubella doses, college or graduate students should receive additional doses or have documented immunity against all three viruses.⁴⁷ Given that measles–mumps–rubella is a live attenuated vaccine and contraindicated in pregnancy, pregnancy status should be queried among all women of childbearing potential before vaccination with counseling to avoid conception for 4 weeks postvaccination. Although the risk of

fetal harm or vaccine-induced infection is theoretical, the potential severe consequence of infection during pregnancy outweighs the potential benefit of vaccination in the United States. The CDC Vaccine in Pregnancy Registry demonstrates no reported cases of congenital rubella syndrome after unintentional first-trimester vaccination.⁴⁸ Thus, inadvertent measles–mumps–rubella vaccination during pregnancy should not be considered grounds for pregnancy termination.⁴⁸ Preconception screening and measles–mumps–rubella administration are ideal for avoiding congenital rubella syndrome during the next future pregnancy rather than awaiting screening and postpartum administration. However, screening for rubella immunity should be included in the routine prenatal laboratory panel. All pregnant women who are susceptible to rubella should be vaccinated immediately postpartum, thus reducing or eliminating risk in subsequent pregnancies and neonatal exposure risk.⁴⁷ Breastfeeding is not a contraindication for postpartum vaccination because any attenuated rubella virus excreted in breast milk and transmitted to the neonate results in asymptomatic infection.⁴⁷

Varicella

Varicella zoster virus, a member of the herpes virus family, causes chicken pox. Illness usually presents as a pruritic rash for 4–7 days, during which time the infected individual is highly contagious.⁴⁹ Viral transmission occurs by direct contact with skin lesions or inhalation of aerosolized particles. Infection during pregnancy is associated with neonatal varicella or herpes zoster and congenital varicella syndrome, which is characterized by skin scarring, limb hypoplasia, low birth weight, and numerous other anomalies.⁵⁰ Congenital varicella syndrome occurs in 1–2% of cases of maternal varicella infection with the greatest risk of occurrence associated with maternal infection from 13 to 20 weeks of gestation.

Varicella vaccine, a live attenuated vaccine, was first introduced in 1995, at which time there were more than 4 million cases, more than 10,000 hospitalizations, and approximately 150 deaths per year in the United States.⁵¹ Ten years after national recommendations to administer a two-dose regimen as part of the routine childhood vaccination schedule, disease incidence has dropped by 90%, with hospitalizations and deaths down by 71% and 97%, respectively. In 2003–2004, there were eight reported deaths resulting from varicella, six of which occurred in children. Thus, vaccination is the most effective means of preventing varicella infection and congenital varicella syndrome. However, varicella vaccine is contraindicated



in pregnancy as a result of its live attenuated formulation. Analogous to rubella vaccination in early pregnancy, no cases of congenital varicella syndrome have been reported after inadvertent varicella vaccination during pregnancy based on the VARIVAX Pregnancy Registry co-sponsored by Merck and Company, Inc., and the CDC. Therefore, the CDC recommends that unintentional vaccination in pregnancy does not imply a need for pregnancy termination.^{49,52} Moreover, preconception varicella vaccine administration is ideal to avoid congenital varicella syndrome during the next future pregnancy. Varicella immunity should be established for all pregnant women during early pregnancy by self-reported history of infection, history of vaccination, or documented serologic immunity. All pregnant women who are susceptible to varicella zoster virus infection should be counseled about the risk of perinatal infection and instructed to immediately contact their health care provider in case of exposure. Documented exposure should be followed by prompt administration of varicella zoster immunoglobulin.⁵³ Antivirals such as acyclovir should be used for actual chicken pox infection with consideration of hospital observation for development of varicella-related complications such as respiratory disease.⁵³ Mothers who are or suspected to be varicella zoster virus-susceptible should receive two doses of vaccine postpartum—the first immediately postpartum and the second 4–8 weeks later.⁴⁹

VACCINES RECOMMENDED IN PREGNANCY AND POSTPARTUM BASED ON RISK FACTORS AND SPECIAL CIRCUMSTANCES

Hepatitis A

Hepatitis A virus, a RNA picornavirus, causes fever, nausea, abdominal pain, and jaundice as a result of acute, self-limiting liver infection (Table 1). Hepatitis A virus is transmitted through the fecal–oral route after close contact with infected individuals or contaminated food or drinks.⁵⁴ First licensed in 1996, widespread hepatitis A virus vaccination in the United States began in 1999. From 2007 to 2011, the number of hepatitis A virus cases dropped from 2,979 to 1,398.⁵⁵ Although hepatitis A virus vaccine is included in the CDC childhood vaccination schedule at 12–23 months of age, the CDC also recommends adult hepatitis A virus vaccination for individuals deemed high risk for hepatitis A virus exposure. Risk factors include travel to endemic areas, men having sex with men, exposure to individuals with hepatitis A virus infection or those receiving clotting factor concentrates as a result of clotting factor deficiencies, and exposure to biological specimens. Although there is

not sufficient data to deem hepatitis A virus vaccine safe for use during pregnancy, the current vaccine formulation is inactivated with no live virus components and thus extremely unlikely to cause infection or harm to the mother, fetus, or infant. Pregnant women should receive hepatitis A virus vaccine when the risk of infection outweighs the theoretical risk of administration of an inactivated vaccine.⁵⁴

Hepatitis B

Hepatitis B virus, a DNA virus, causes acute liver infection with inflammation, vomiting, and jaundice. Hepatitis B virus can be self-limiting or achieve a chronic carrier state associated with long-term consequences including cirrhosis, liver cancer, liver failure, and death. Hepatitis B virus is transmitted after close contact with infected blood and bodily fluids. The current hepatitis B virus vaccine is a recombinant DNA formulation based on the hepatitis B surface antigen envelope protein. A three-vaccine series is highly effective for disease prevention, providing an indefinite protective antibody response in greater than 90% of vaccinated individuals.⁵⁶ Hepatitis B virus infections decreased 64% over the past decade, dropping from 8,036 cases in 2000 down to 2,890 cases in 2011 as a result of vaccine prevention.⁵⁵

Hepatitis B virus during pregnancy, both the chronic carrier state as well as primary infection, is concerning for the risk of vertical transmission. Perinatally acquired hepatitis B virus infection is associated with the highest risk of developing chronic disease for the offspring. All pregnant women should be screened for hepatitis B surface antigen status as part of standard prenatal laboratory testing. At-risk neonates should be treated with hepatitis B immunoglobulin prophylaxis and receive the first hepatitis B virus vaccine dose within the first hours of life.⁵⁷ Such a regimen is an effective strategy against peripartum transmission, which is the most common scenario. However, in utero transmission can and does occur, most likely in mothers who develop primary, acute hepatitis B virus infection in late pregnancy.⁵⁸ Therefore, hepatitis B virus vaccination is the best preventive measure, including administration both preconception and during pregnancy. The three-dose hepatitis B virus vaccine series should be initiated for pregnant women who have not been vaccinated previously and are at high risk of acquiring infection, namely those with one or more sexual partner in the past 6 months, history of a hepatitis B virus-positive sexual partner or household contact, or intravenous drug use.⁵⁶ Safety data, although somewhat limited, have not demonstrated any association



with adverse maternal or fetal outcomes, consistent with the expected safety profile of a recombinant inactivated product that does not contain live virus.⁵⁹ In addition to vaccination and hepatitis B immunoglobulin, newly emerging data advocate for the use of antiviral therapy during the third trimester to prevent in utero transmission or prophylaxis failure.⁵⁸ However, given the uncertain risks of antivirals during pregnancy, treatment is being considered only for pregnant women with advanced disease. Treatment may consist of lamivudine, telbivudine, or tenofovir but should only be considered in conjunction with a hepatology specialist.

Pneumococcal Disease

Streptococcus pneumoniae (pneumococcus) is a Gram-positive bacterium associated with significant morbidity and mortality related to pneumonia, bacteremia, meningitis, and otitis media.⁶⁰ Approximately 900,000 U.S. individuals get pneumococcal pneumonia, resulting in 400,000 hospitalizations and a 5–7% mortality rate annually. There are 12,000 cases of bacteremia and 3,000 cases on meningitis, which carries a mortality rate of 10–15%. Significant reductions in pneumococcal disease and related deaths occurred after inclusion of the seven serotype pneumococcal conjugate vaccines in the U.S. childhood vaccination schedule in 2000 (200,000 cases and 13,000 deaths prevented up to 2007).³ Furthermore, the introduction of 13 serotype pneumococcal conjugate vaccine in 2010 resulted in an additional 20,000 cases and 2,000 deaths averted (Moore M. Update on effectiveness and impact of PCV13 use among U.S. children. Paper presented at Advisory Committee on Immunization Practice, October 23, 2013, Atlanta, Georgia.). From 2010 to 2012, there was an 88% reduction in childhood disease, which would be expected given that pneumococcal conjugate vaccine is used exclusively in children. However, there was also a 47% reduction in adult pneumococcal disease, likely as a result of a reduction in exposure. Furthermore, a broader 23-serotype polysaccharide vaccine is recommended for children and adults with chronic medical conditions and all adults at or older than 65 years of age to prevent invasive pneumococcal disease.⁶¹ Risk factors include chronic heart disease, chronic lung disease including asthma, preexisting diabetes, cigarette smoking, alcoholism, chronic liver disease, cerebrospinal fluid leaks, cochlear implants, congenital or acquired immunodeficiencies, diseases requiring immunosuppressant therapy, sickle cell disease and other hemoglobinopathies, and functional or anatomic asplenia.

Per the CDC, there are currently insufficient data to support routine administration of 13 serotype

pneumococcal conjugate vaccine or 23-serotype polysaccharide vaccine during pregnancy.¹⁸ A systematic review of six observational studies of 23-serotype polysaccharide vaccine in pregnancy demonstrated no increase in spontaneous abortion, teratogenicity, or preterm labor.⁵⁹ Furthermore, a randomized trial of 60 pregnant women receiving 23-serotype polysaccharide vaccine at 35 weeks of gestation demonstrated no safety concerns or adverse outcomes.⁶² Maternal 23-serotype polysaccharide vaccine administration results in protective maternal antibody titers for up to 12 months postpartum and significantly increases neonatal antibody titers at delivery. However, it is unknown if passive immunity results in disease protection for the infant. Per the CDC's adult immunization schedule, 23-serotype polysaccharide vaccine should be administered during pregnancy for women who have a medical risk factor(s), which likely affects a substantial number of women given the increasing incidence of obesity and related chronic conditions in the United States.¹⁸

Meningococcal Disease

Approximately 1,000 individuals in the United States will experience meningococcal disease (meningitis and sepsis) caused by an encapsulated bacterium called *Neisseria*.⁶³ Despite the use of antibiotics, the mortality rate is 10–15% with up to 20% of survivors experiencing significant sequelae including limb amputations, strokes, and neurocognitive abnormalities such as seizures, deafness, and severe cognitive impairment. There are two effective vaccines against meningococcal disease: tetravalent meningococcal conjugate vaccine and a tetravalent polysaccharide vaccine. In 2000, the CDC recommended tetravalent polysaccharide vaccine before college entry based on risk. Although effective, tetravalent polysaccharide vaccine does not confer long-lasting immunity as seen with tetravalent meningococcal conjugate vaccine. Therefore, in 2005, tetravalent meningococcal conjugate vaccine was included in the U.S. childhood vaccination schedule as a two-dose regimen for adolescents aged 11–18 years. However, there are many individuals who remain at high risk for the disease and thus should be vaccinated with tetravalent meningococcal conjugate vaccine based on risk factors, ie, individuals living in close contact such as in dormitories or military barracks, individuals with complement deficiencies and functional or anatomic asplenia, researchers with routine exposure to *Neisseria meningitidis* isolates, and individuals living in hyperendemic areas. Based on available efficacy and safety data, tetravalent meningococcal conjugate vaccine should be used



through 55 years of age, whereas tetravalent polysaccharide vaccine is used after 55 years of age and for anyone at risk of exposure during an active disease outbreak.

Both tetravalent meningococcal conjugate vaccine and tetravalent polysaccharide vaccine are inactivated products and thus should not be associated with adverse maternal or fetal outcomes. However, the limited data that are available on meningococcal vaccination during pregnancy is using tetravalent polysaccharide vaccine and not tetravalent meningococcal conjugate vaccine. A systematic review documented no association with maternal tetravalent polysaccharide vaccine and teratogenesis, spontaneous abortion, or preterm birth.⁵⁹ A study of third-trimester tetravalent polysaccharide vaccine vaccination demonstrated an appropriate maternal antibody response but selective transplacental antibody transfer with rapid waning of infant immunity by 3 months of age.⁶⁴ A recently completed trial of more than 4,000 pregnant Malian women receiving influenza vaccine or tetravalent polysaccharide vaccine will provide much needed efficacy and safety data on tetravalent polysaccharide vaccine in pregnancy.⁶⁵ Given the lack of available safety data on tetravalent meningococcal conjugate vaccine, tetravalent polysaccharide vaccine is recommended for use during pregnancy based on risk factors described previously.¹⁸

Travel Vaccinations

Absent any specific medical or pregnancy-related contraindications, healthy pregnant women are able to travel safely without significant restrictions. The CDC recommends several vaccines for individuals traveling to areas with endemic vaccine-preventable diseases.⁶⁶ Therefore, pregnant women planning international travel should be advised to search the CDC travel web site, which provides up-to-date country-specific immunization recommendations and aids in risk factor determination. Three travel-related vaccine-preventable diseases that are frequently encountered are yellow fever, Japanese encephalitis, and typhoid fever.

Yellow fever, a mosquito-borne disease caused by an RNA flavivirus, is largely an asymptomatic infection. However, common symptoms are sudden onset of fever and headache with less common symptoms of photophobia, arthralgias, myalgias, vomiting, and epigastric pain. Severe infection is associated with multi-system organ failure, hemorrhage, and death. Yellow fever is endemic to tropical areas in South America and sub-Saharan Africa. Thus, live attenuated yellow fever vaccine is recommended for individuals planning

travel to endemic areas and is often required before issuance of travel visas.⁶⁶ Despite the general theoretical contraindication to live attenuated vaccines during pregnancy, yellow fever vaccine is the exception. Although there are limited data on the efficacy and safety of yellow fever vaccine during pregnancy, one study that documented inadvertent vaccination of pregnant women during an outbreak demonstrated no association with teratogenesis, spontaneous abortion, or preterm birth.⁶⁷ Therefore, the CDC recommends yellow fever vaccine during pregnancy if a woman must travel and her risk of exposure and infection is high enough (based on location, season, and activities planned during travel) to outweigh any potential theoretical risks of vaccination.⁶⁸ Nonpregnant women of childbearing potential should be counseled to avoid conception for 4 weeks postvaccination.

Japanese encephalitis is another mosquito-borne RNA flavivirus that represents the most common vaccine-preventable disease cause of encephalitis in Asia.⁶⁶ Less than 1% of infected individuals will manifest clinical symptoms of disease with mild disease limited to fever or aseptic meningitis. However, serious illness presents with sudden onset of fever, headache, vomiting, and neurologic abnormalities including generalized weakness, movement disorders or acute paralysis, and seizures. Although the mortality rate is 20–30%, approximately 30–50% of survivors will have serious neurocognitive and psychiatric sequelae. An inactivated Japanese encephalitis vaccine was licensed for use in the United States in 2009 and recommended by the CDC for travelers who plan to spend 1 or more months in endemic areas or during disease outbreaks. Unfortunately, there are no adequate studies of the vaccine during pregnancy. As a result of the lack of adequate data, the CDC has not made a specific recommendation on the use of Japanese encephalitis vaccine during pregnancy.¹⁸ However, the CDC recommends that Japanese encephalitis vaccination should be considered for pregnant women planning longer-duration travel to endemic areas when the theoretical risk of immunization is outweighed by risk of infection.⁶⁹

Typhoid fever is a life-threatening disease caused by the bacterium *Salmonella typhi* and is responsible for approximately 5,700 U.S. cases each year.⁷⁰ Approximately 75% of cases are contracted during international travel because typhoid fever is quite common in the developing world and affects more than 21 million people annually. Infected individuals usually present with fever, fatigue, headache, and anorexia, whereas severe disease is associated with intestinal hemorrhage and death. There are two vaccines against *S typhi* currently



available in the United States, which are a live attenuated oral vaccine and a polysaccharide vaccine, both of which are acceptable for adults traveling to endemic areas. Unfortunately, there are no data supporting the efficacy and safety of either vaccine in pregnancy. The CDC has made no formal, specific recommendation on the use of typhoid vaccines during pregnancy.

Zoonotic Vaccine-Preventable Diseases

Bacillus anthracis, a spore-forming bacterium, causes the zoonotic infection anthrax. Clinical manifestation depends on the exposure route (infected animal-to-animal tissue contact or bacterial spore exposure) and presents as cutaneous, injection (contaminated needle use), gastrointestinal, or inhalation anthrax with the latter two forms having high morbidity and mortality.⁷¹ Because *B anthracis* spores can be aerosolized and remain viable for a long time, anthrax has been identified as a potentially serious and deadly biological weapon. The inactivated subunit anthrax vaccine adsorbed is available in the United States. Preexposure vaccination is recommended by the CDC for individuals at high risk of exposure, ie, military personnel, environmental investigators, emergency responders, and postal processing staff. However, preexposure anthrax vaccine adsorbed is not recommended during pregnancy given the low risk for exposure. Pregnancy is a Department of Defense exemption for preexposure prophylaxis with vaccination recommended postpartum. For postexposure prophylaxis, individuals should be vaccinated with anthrax vaccine adsorbed followed by 60 days of antimicrobial therapy.⁷¹ Although preexposure anthrax vaccine adsorbed is not routinely recommended, postexposure prophylaxis is recommended and should be administered to any pregnant woman with an anthrax exposure.

Contact with the saliva or central nervous system tissue of an individual or animal infected with rhabdovirus results in rabies infection. Rabies initially presents with flu-like symptoms followed by neurologic abnormalities and ultimately death if left untreated. Vaccination of household pets is the most effective method of human rabies prevention.⁷² There are two inactivated rabies vaccines available for human use in the United States and are recommended for individuals at high risk of exposure, ie, veterinarians, animal handlers, and travelers to endemic areas. Postexposure prophylaxis includes either rabies vaccine in conjunction with human rabies immunoglobulin, although human rabies immunoglobulin is not necessary in individuals who have been previously vaccinated. Limited studies have shown no association between

maternal rabies vaccination and spontaneous abortion, teratogenesis, or preterm birth.^{73,74} Thus, the CDC recommends that postexposure prophylaxis with vaccination and human rabies immunoglobulin should be administered to any pregnant woman after a moderate-risk or high-risk exposure to rabies. Preexposure prophylaxis in pregnancy can be considered if the risk of exposure is deemed high.

VACCINES CURRENTLY UNDER RESEARCH AND DEVELOPMENT FOR LICENSURE FOR MATERNAL-FETAL IMMUNIZATION

To date, vaccines in the United States are not specifically licensed or targeted for use during pregnancy. However, vaccines aimed at fetal-infant immunization are in varying stages of research and development for which the target population will be pregnant women. Two examples are group B streptococcus (GBS) and respiratory syncytial virus. Group B streptococcus is the leading cause of invasive infection during the first 90 days of life and is the predominant cause of neonatal sepsis and meningitis, even in the setting of intrapartum antibiotic prophylaxis.⁷⁵ From 1993 to 2008, intrapartum antibiotic prophylaxis reduced the incidence of early-onset neonatal GBS infection from 1.7 to 0.28 cases per 1,000 live births but had no effect on late-onset GBS disease in the United States.⁷⁶ Given the significant unmet need of late-onset disease (0.29–0.47 per 1,000 live births) and evidence of protection in the setting of passive immunity,^{75,77} a GBS vaccine could be a more effective and reliable way to prevent both early- and late-onset disease. Moreover, a regimen of screening plus intrapartum antibiotic prophylaxis is neither feasible nor affordable in the developing world where invasive GBS disease remains a significant contributor to neonatal mortality and adverse pregnancy outcomes. A promising trivalent conjugated GBS vaccine is currently in phase II and III trials in pregnant women aimed at providing passive immunity to young infants.⁷⁸

Respiratory syncytial virus is a RNA paramyxovirus named for how its surface F-proteins cause respiratory cell membranes to merge or form syncytia. In the United States, 60% of infants will be infected during their first respiratory syncytial virus season.⁷⁹ Naturally induced immunity wanes over time so that people can be repeatedly infected over the lifespan. Infection may be asymptomatic or similar to a cold but may cause severe disease in the elderly. Respiratory syncytial virus is the most common cause of bronchiolitis and pneumonia during the first year of life, often necessitating hospitalization and resulting in recurrent wheezing. Given that infection with this ubiquitous virus is unavoidable, a preventive



vaccine would be ideal. A formalin-inactivated vaccine was developed and studied in the 1960s but was not efficacious and was associated with enhanced disease among vaccinated children.⁸⁰ At present, the only preventive therapy available is palivizumab, an effective yet costly monoclonal antibody that is given as monthly injections during the respiratory syncytial virus season. Given the significant cost and need for repeated dosing, palivizumab is restricted for use in high-risk infants, namely preterm infants, those with bronchopulmonary dysplasia, or those born with congenital heart or airway defects. A recombinant respiratory syncytial virus vaccine is currently in phase II clinical and dose-ranging trials in nonpregnant women with plans for a phase I trial in pregnant women in the near future.⁸¹

BARRIERS TO VACCINATION IN PREGNANCY AND PATIENT-PROVIDER RESOURCES

Although national vaccination programs have led to significant declines in vaccine-preventable diseases in the United States, meeting the Healthy People 2020 objectives for adult vaccination remains a daunting task. Acceptance of vaccination during pregnancy is affected by questions of maternal-fetal safety. Qualitative research involving patients and health care providers suggests that common perceived barriers include fear of adverse pregnancy outcomes, fear of vaccine-transmitted infection, lack of awareness of national recommendations, lack of health care provider recommendation, inconvenience of vaccination, and concerns about insurance coverage.^{82,83} For progress to occur, it is imperative that ob-gyns play an active role in overcoming such barriers, as evidenced by pregnant women being five to 50 more likely to accept a vaccine if directly recommended by their health care provider.⁸⁴⁻⁸⁶ To aid ob-gyns and patients, the College publishes and maintains up-to-date Committee Opinions on specific vaccines and guidance on implementing vaccination processes into obstetrics-gynecologic practice. In 2011, the College launched the Immunization for Women web site, which provides up-to-date information on vaccine recommendations, safety, and hyperlinks to College Committee Opinions, educational materials, and frequently asked questions, further demonstrating the College's commitment to immunization of women across the lifespan.⁸⁷ Immunizationforwomen.org also provides hyperlinks to numerous highly informative, user-friendly resources such as the CDC, Immunization Action Coalition, and the National Vaccine Program Office.

Specifically regarding vaccine safety, there has been much controversy over possible associations

between vaccines and complicated, multietiological health outcomes such as autism spectrum disorders in children. Research to date involving more than 100,000 children that has been vetted by the Institute of Medicine, CDC, World Health Organization, American Academy of Pediatrics, and numerous other agencies has very convincingly shown that there is no such association between vaccines and autism.^{88,89} On the contrary, these studies have further supported the safety and effectiveness of vaccines in reducing infectious disease and improving overall health. Continued research on the overall health effects and safety of vaccines is warranted.

Furthermore, ob-gyns who are concerned about potential liability related to vaccination providers can be reassured by the protection provided through the National Childhood Vaccine Injury Act, which covers all vaccines that are included in the childhood vaccination schedule regardless of who actually receives the vaccine, including adults and pregnant women. To aid all health care providers in safely administering vaccines, the CDC maintains a Vaccine Information Statement for every vaccine licensed for administration in the United States. A Vaccine Information Statement informs health care providers and vaccinees about the benefits and risks of a specific vaccine and is required by the National Childhood Vaccine Injury Act to be given to all vaccinees (or their parent or legal representative) before vaccination. Ob-gyns and nurses should be familiar with the information contained in the Vaccine Information Statements for any vaccines administered in their office so that they can effectively screen and counsel their patients on any vaccine contraindications, risks, and benefits. Ob-gyns should be aware of additional tools in the event that an adverse event does occur in a pregnant woman, which are the Vaccine Adverse Event Reporting System and the Clinical Immunization Safety Assessment Project. Cosponsored by the CDC and the U.S. Food and Drug Administration, Vaccine Adverse Event Reporting System is a national postmarketing national vaccine safety and side effect surveillance program initiated after the National Childhood Vaccine Injury Act.⁹⁰ Anyone can submit a Vaccine Adverse Event Reporting System report, because it is considered a public health entity and does not require individual authorization per Health Insurance Portability and Accountability Act criteria. With more than 200,000 reports since its inception in 1990 (mostly mild side effects), Vaccine Adverse Event Reporting System has demonstrated its public health importance by identifying risks that are small yet higher than chance alone, thus guiding national



recommendations. Sponsored by the CDC's Immunization Safety Office, Clinical Immunization Safety Assessment provides a free-of-charge clinical evaluation service of an adverse event that is unexpected or not explainable by available data.⁹¹ After obtaining all pertinent medical records, reviewing medical literature and Vaccine Adverse Event Reporting System, vaccine safety experts from the CDC and the Clinical Immunization Safety Assessment academic medical centers review the clinical case in conjunction with the reporting provider. Advice garnered from Clinical Immunization Safety Assessment consultation is to be used in further decision-making regarding future vaccination rather than immediate patient care.

CONCLUSION

Vaccination during pregnancy is a vital preventive measure in routine obstetric care, serving to protect mother, fetus, and infant. Influenza and diphtheria and reduced tetanus toxoids and acellular pertussis vaccine vaccines are specifically recommended for all pregnant women, whereas others are recommended for postpartum administration (measles–mumps–rubella and varicella) or depending on risk factors (hepatitis A and B, pneumococcal and meningococcal vaccines). In theory, inactivated vaccines should be safe for use during pregnancy but specific studies or data on use during pregnancy were limited for most vaccines. Thus, it is essential that future studies on vaccines in pregnancy focus on immunogenicity and safety for mother and infant and the potential for not only maternal, but also direct fetal and infant benefit. In light of the perceived and actual barriers to increasing adult vaccine coverage and the health consequences of vaccine-preventable diseases for pregnant women and young infants, ob-gyns must take an active role in educating and administering vaccines to pregnant women.

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