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Vaccine-preventable disease in women of reproductive age

FACULTY

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DISCLOSURES

Lee P. Shulman, MD, reports that he is on the speakers bureaus of Barr Laboratories/Duramed, Bayer HealthCare Pharmaceuticals, GlaxoSmithKline, Organon, Ortho, Roche, and Wyeth. Dr Shulman is also on the advisory boards of Barr Laboratories/Duramed, Bayer HealthCare Pharmaceuticals, Organon, and Ortho, and is an investigator for Barr Laboratories/Duramed and Wyeth.

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A guide to navigating the special concerns of women of reproductive age in efforts to immunize adults

Introduction

The need for greater efforts to immunize the adult population to prevent diseases, limit outbreaks, and protect the health of the community at large is underscored by the following facts^{1,2}:

- By age 50, 80% of unvaccinated women will be infected with human papillomavirus (HPV), which causes cervical and other cancers, genital warts, and other diseases. Nearly 10,000 new cases and 4000 deaths from cervical cancer are reported annually.
- Almost one-third of reported pertussis (whooping cough) cases are now in adults.
- Rubella (German measles) that occurs during pregnancy can result in severe birth defects, miscarriage, and stillbirths.
- Adolescents and adults are more likely than children to develop severe complications when infected with varicella (chickenpox).

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) provides guidance to clinicians regarding effective control of vaccine-preventable diseases, including guidelines for special populations such as the elderly, immunocompromised, and women who are pregnant or breastfeeding. Formulation of recommendations for vaccination of pregnant and breastfeeding women is especially challenging because of the limited availability of scientific evidence needed to guide decisions.³

The US Food and Drug Administration (FDA) requires that each product be classified under one of 5 pregnancy categories (A, B, C, D, or X), based on risk of reproductive and developmental adverse effects or, in some instances, on the basis of risk weighed against potential benefit. Category A designation indicates that adequate, well-controlled studies in women fail to demonstrate a risk to the fetus in the first trimester with no evidence of a risk in later trimesters, and that the possibility of fetal harm appears remote. In category D, there is positive evidence of human fetal risk based on experience or studies in humans, but potential benefits may warrant use of the drug.

In category X, the risks involved in use of the drug in pregnant women clearly outweigh potential benefits. To promote use of a consistent process and uniform technology, ACIP is currently developing guiding principles for drafting recommendations for vaccination of breastfeeding and pregnant women.³

Among the vaccines commonly used in adult women are those that protect against influenza; tetanus, diphtheria, and pertussis (Tdap); rubella; varicella; herpes zoster; and HPV.

Influenza

Although there is no evidence that pregnant women are more susceptible to influenza than women who are not pregnant, they are at increased risk for severe sequelae of the disease.⁴ The increased risk for severe influenza-related illness has been postulated to be the result of the mechanical, hormonal, and immunologic alterations that occur during pregnancy.

Changes in respiratory and cardiovascular systems, especially during the second and third trimesters, include increased heart rate, stroke volume, and oxygen consumption, as well as decreased lung volume. The modulated immune response during pregnancy—a shift away from cell-mediated immunity—is believed to reduce the capacity to resist infection. These changes render pregnant women more susceptible and more severely affected by certain viral pathogens, potentially leading to a higher rate of morbidity and mortality. As might be expected, fetal growth and development are also affected by these changes.

Although women's healthcare providers are generally well informed regarding the increased risk during pregnancy and the importance of immunization against seasonal influenza, few actually administer the vaccine. Rather, most elect to refer patients, requiring an additional visit to a provider and increasing the likelihood that the patient will eschew vaccination altogether. This may be one reason why the vaccination rate for pregnant women is among the lowest among adults recommended by ACIP for immunization against seasonal influenza.⁵ Other reasons include the influence of a well-publicized ongoing campaign of misinformation questioning the safety of vaccines, as well as issues relating to practice, such as cost, insurance, and storage.

As with seasonal influenza, pregnant women are at increased risk of morbidity and mortality from the H1N1 pandemic. About 6% of confirmed H1N1 2009 influenza deaths in the United States have been in pregnant women, although only 1% of the general population is pregnant at any given time.⁶ ACIP designated pregnant women as one of the initial target groups to receive the H1N1 vaccine as soon as it became available.

The CDC and the American Society for Reproductive Medicine have issued a joint statement calling on fertility clinics to encourage patients planning pregnancy to be vaccinated for both seasonal influenza and H1N1.

Vaccination has been shown to prevent febrile respiratory illness in pregnant women and to protect newborn infants up

to 6 months of age, at which time they may be vaccinated.⁷

ACIP recommends that any of the available trivalent inactivated influenza vaccines be administered to pregnant women for prevention of seasonal influenza. (Live attenuated vaccine, administered as a nasal spray, should NOT be given to a pregnant woman.)⁸

Antiviral treatment is recommended for pregnant women with suspected or confirmed influenza, regardless of trimester, and should not be delayed because of a negative rapid influenza diagnostic test, inability to test, or while awaiting test results.

CASE 1

A 30-year-old G2P1 at 15 weeks reports that her mother was recently diagnosed with seasonal influenza and is in the hospital being treated for pneumonia. She is also concerned about her 2-year-old son. She reports never having had a "flu shot," and was told by a neighbor to get the "nasal spray" flu vaccine. How do you counsel this woman?

Counsel her that, despite the advice of her well-meaning neighbor, the "nasal spray" vaccine is not meant to be administered to pregnant women. Tell her she should be vaccinated as quickly as possible with the trivalent inactivated vaccine to protect her and her baby from seasonal influenza. Strongly suggest that when she is vaccinated against seasonal influenza, she is also vaccinated against H1N1.

Pertussis

Pertussis is one disease that is not well controlled in the United States. Incidence of pertussis has been gradually increasing since the early 1980s and, in recent years, adolescents and adults (19 years and older) have accounted for an increasing proportion of cases. In 2004 and 2005, approximately 60% of reported cases were among persons 11 years of age and older.

Parents and others at risk of acquiring and transmitting pertussis to infants should be vaccinated with Tdap as soon as possible. Although ACIP guidelines suggest a 2-year interval from the previous tetanus toxoid-containing vaccine because of the possibility of painful local reactions, such reactions are extremely rare and these concerns may be outweighed by the need to prevent pertussis in the newborn.

The CDC recommends the preferential use of Td vaccine in pregnancy rather than Tdap.⁸ However, Tdap is not contraindicated in pregnancy and may be used if warranted, eg, when other infants are present in the household and it is important to protect the mother and other children from developing pertussis. However, if a pregnant woman is traveling to a diphtheria-endemic country and a tetanus toxoid is needed for tetanus prevention, Td would be indicated.

For adults aged 19 through 64 years who have not received a dose of Tdap previously, ACIP recommends a one-time dose of Tdap, to be followed by a Td booster every 10 years.⁹ If a woman is pregnant and received the last Td vaccination 10 or more years previously, Td should be administered

during the second or third trimester. If the woman received the last Td vaccination less than 10 years previously, Tdap should be administered in the immediate postpartum period. Tdap is recommended for postpartum women if they have not previously received Tdap. An interval of 2 years is suggested between vaccinations, although shorter intervals may be used. Td may be deferred during pregnancy and Tdap substituted in the immediate postpartum period, or Tdap may be administered to a pregnant woman instead of Td after an informed discussion with the woman.

CASE 2

A 33-year-old G3P2 at 11 weeks is informed that one of her children has pertussis. She is asymptomatic at this time. What is an appropriate course of action?

Although ACIP does not as a rule recommend use of the Tdap vaccine in pregnancy, this situation calls for an informed discussion between the mother and her obstetrician or an infectious disease specialist. Tdap is an activated vaccine and is not contraindicated in pregnancy. In this case, there could be great benefit to receiving the vaccine to prevent pertussis. In addition, all siblings of the pertussis-infected child should receive a booster vaccination with Tdap, even if they have received a booster within the last 12 months. When there is a community outbreak of pertussis or an infant in the household, ACIP allows for shorter intervals.

Rubella

Rubella is a viral disease included in the MMR (measles, mumps, rubella) vaccine. The main public health objective of vaccination against rubella is prevention of congenital rubella syndrome (CRS), which can occur when the pregnant mother is infected with the rubella virus. The severity of damage to the fetus in CRS depends on the gestational age at which infection occurs. CRS infection may affect all organ systems and classically causes deafness, visual impairment, and cardiac diseases. It can also lead to preterm delivery and fetal death.¹⁰ Up to 85% of infants will be affected if the mother is infected during the first trimester.

Although the MMR vaccine is highly effective in preventing initial infection, it is a live vaccine and thus contraindicated during pregnancy and in women who plan to become pregnant within the next few months.⁸ Because of the urgency of preventing CRS, ACIP recommends screening of all women of childbearing age.⁹ The criteria used to determine a person's immunity to rubella can consist of laboratory evidence or age-appropriate vaccination. Women who do not have evidence of immunity should receive MMR upon completion or termination of pregnancy and before discharge from the healthcare facility.

Despite the fact that some live vaccines interfere with antibody-containing blood products, women who are taking anti-Rho(D) globulin can and should receive MMR vaccine in the postpartum period, both to avoid missing an

opportunity to vaccinate and to prevent future risks. Finally, while administration of MMR is not recommended during pregnancy because of a biological potential for teratogenicity with a live attenuated vaccine, there has been no evidence of teratogenicity when it has been given inadvertently in early stages of pregnancy over decades of clinical use.

Varicella

While varicella is often thought of as a benign disease, the fatality rate increases in the population most likely to become pregnant—women aged 30 years and older.¹¹ Women's healthcare providers should keep this in mind when screening for history of varicella immunity. An additional concern is that a number of diseases, including congenital varicella syndrome (CVS), can result from maternal infection during pregnancy. The risk is small (<2%) but runs highest during the first 20 weeks of pregnancy.¹² CVS is characterized by low birth weight, atrophy of limbs and other extremities, skin scarring, and eye and neurologic abnormalities.

Neonatal varicella occurs when the infant is infected in the perinatal period. Rash onset can occur during a period ranging from 5 days prior to delivery to 48 hours after delivery. This is significant because it indicates that the mother was susceptible up to the point of delivery and did not have antibodies to the varicella zoster virus and was thus unable to transfer antibodies to protect the neonate. Fatality rates of infants with neonatal varicella are estimated to reach as high as 30%.¹³

The varicella vaccine is another live vaccine that should not be administered during pregnancy. ACIP recommends that pregnant women be assessed for evidence of varicella immunity.⁸ Women who do not have evidence of immunity should have the first dose of varicella vaccination upon completion or termination of pregnancy and before discharge from the healthcare facility. The second dose should be administered 4 to 8 weeks after the first dose.

For women who are exposed to varicella during pregnancy, ACIP recommends administration of VariZIG[™], a purified human immune globulin preparation, which providers may obtain from the manufacturer by calling 800-843-7477.

Human papillomavirus

HPV is the most common sexually transmitted disease in the United States.⁹ Each year more than 6 million Americans acquire a new genital HPV infection, nearly 76% of which occur in individuals aged 15 to 25 years.¹⁴ Several studies have suggested that another peak occurs approximately between the ages of 30 and 40 years.¹⁵ About 20 million male and female Americans are currently infected.⁸

Estimates are that 80% of sexually active women will have had at least one HPV infection by age 50. Because most HPV infections are asymptomatic, most infected persons are unaware that they are infected and possibly transmitting the virus.¹⁶

More than 100 types of HPV infect humans, 40 of which affect the lower genital tract.⁸ Infection with multiple types

is common. The first genital HPV infection is often acquired soon after sexual debut.

HPV types 16 and 18 are responsible for 70% of all cervical cancers, whereas HPV types 6 and 11 are responsible for 90% of genital warts, which are benign but highly contagious.¹⁶ Approximately 90% of anal cancers; 40% of cancers of the vulva, vagina, and penis; and 10% to 20% of oropharyngeal cancers are also associated with HPV.⁸ Infants born vaginally to mothers infected with HPV types 6 and 11 may, in rare instances, develop recurrent respiratory papillomatosis, a potentially devastating disease that can have significant morbidity and mortality due to airway compromise or malignant transformation.¹⁶

The healthcare cost burden of HPV infection is considerable, with the direct medical cost of treating genital warts even greater than that of treating cervical cancer.¹⁷ Upwards of one million new cases of genital warts are reported each year, leading to over 300,000 office visits.

Two vaccines are currently available for protection against HPV, a quadrivalent vaccine (Gardasil[®]; Merck)¹⁸ and a bivalent vaccine (Cervarix[®]; GlaxoSmithKline).¹⁹ The quadrivalent vaccine, licensed by the FDA in 2006, protects against HPV types 6, 11, 16, and 18. The bivalent vaccine, licensed in the United States in 2009, protects against HPV types 16 and 18.

The quadrivalent vaccine is indicated in girls and women aged 9 through 26 years for prevention of cervical, vulvar, and vaginal cancer, and genital warts; cervical intraepithelial neoplasia (CIN) grade 2 and grade 3 and cervical adenocarcinoma in situ (AIS); CIN grade 1; vulvar intraepithelial neoplasia grade 2 and grade 3; vaginal intraepithelial neoplasia grade 2 and grade 3; and in boys and men aged 9 through 26 years for prevention of genital warts. The bivalent vaccine is approved for use in females aged 10 through 25 years for prevention of cervical cancer, CIN grade 2 or worse, AIS, and CIN grade 1.

Both vaccines are administered by a series of 3 intramuscular injections over a 6-month period. Because the bivalent vaccine was licensed only recently, ACIP recommendations are

available only for the quadrivalent vaccine. The vaccine is recommended universally for females without contraindications between ages 11 and 26 years, even if they have been exposed to some of the HPV types included in the vaccine.⁸ (The recommendation to target 11- and 12-year-olds is based on the hope that providers will administer the HPV vaccine simultaneously with other scheduled adolescent vaccines.)

Catch-up vaccination is recommended for females aged 13 to 26 years even if they are sexually active. Vaccination may be given in special circumstances (eg, equivocal or abnormal Pap test, positive HPV DNA test, genital warts, immunosuppression, breastfeeding).

Most adverse reactions to the quadrivalent HPV vaccine are similar to those seen with all vaccines (redness, soreness, or itching at the injection site) and usually resolve within 48 hours. However, an increase in the number of reports of syncope has been detected by the Vaccine Adverse Event Reporting System (VAERS), mostly among females aged 11 to 18 years, and some serious injuries have been reported.²⁰ Thus, providers should strongly consider observing patients for 15 minutes after they are vaccinated.

Both the quadrivalent and bivalent HPV vaccines are classified as category B with regard to pregnancy; however, neither is licensed for use during pregnancy because of the lack of robust clinical data in pregnant women. Thus, ACIP recommends that the vaccine be delayed until the pregnancy is completed. A registry has been established by the manufacturer of the quadrivalent vaccine for women found to be pregnant after initiating the vaccine series. In such instances the provider should call 800-986-8999. Nevertheless, pregnancy is not a cause for concern, and the series may be resumed when the pregnancy is completed, regardless of how much time passes.

A provider whose patient has worries about the vaccine would be correct in saying that the CDC considers the quadrivalent HPV vaccine to be as safe as, or safer than, any other vaccine. n

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