The clinical content of preconception care: immunizations as part of preconception care

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Many vaccine-preventable diseases have serious consequences for the pregnant mother, the fetus, and the neonate. This article reviews the rationale and impact of including vaccinations as part of preconception care and provides recommendations for clinical care. Vaccinations that are recommended highly in preconception care include the hepatitis B and the measles, mumps, and rubella vaccines. The role of human papillomavirus, varicella, diphtheria, tetanus, and pertussis vaccinations as part of preconception care is also discussed.

Key words: immunization, preconception care, vaccine

Many vaccine-preventable diseases may have serious consequences for both the mother and fetus during pregnancy, which makes the immunization status of women of reproductive age an important focal point for preconception care. Prevention of congenital rubella syndrome is a prototype for preconception care because it is needed before conception and is very effective in preventing a congenital disease that has significant morbidity and mortality rates. Some immunizations act by preventing congenital infection, others by preventing perinatal transmission. Some vaccines are recommended in the preconception period because they cannot be administered during pregnancy; others have maternal benefits because they avoid treatment that might have adverse consequences for the pregnancy. This article reviews the evidence for immunizations as part of a comprehensive preconception healthcare program.

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Human papillomavirus (HPV)

Burden of suffering. HPV is 1 of the most common forms of sexually transmitted infections; it appears as flat or papillary warts on the cervix, vagina, and vulva. Its prevalence in women ranges from 16-84% in study populations.[1] Several viral types have been determined as the etiologic factor that leads to cervical dysplasia and cervical cancer. There is evidence that links maternal HPV infections to juvenile-onset recurrent respiratory papillomatosis or laryngeal papillomatosis, which is an extremely rare disease that is associated with low mortality but high morbidity rates.[2] Research has documented a higher rate of exposure to HPV with vaginal delivery than cesarean section,[3] but no difference in infection rates. The risk of neonatal papillomatosis is very low, so there is no indication for a cesarean section delivery.

How detectable is the condition? Genital warts are detected by visual examination and the occasional need for biopsy to confirm the diagnosis. HPV infection is generally detected by cytologic screening, which aims to detect abnormalities in the epithelium of the cervix. Screening for high-risk types of HPV through nucleic acid tests is usually done in conjunction with cytologic screening when certain findings (atypical squamous cells) are found on cytologic examination. Direct screening for high-risk HPV is also used in the follow-up of patients with cytologic abnormalities and as a primary screening method in women ≥ 30 years.

How effective are the current treatments? Treatment of abnormal cytologic findings is highly effective in the prevention of cervical cancer.[1]

Impact of preconception care. The diagnostic evaluation of cervical cytologic

abnormalities is less complicated outside of pregnancy because certain diagnostic tests may be contraindicated during pregnancy (eg, endocervical curettage). Treatment of abnormalities that are caused by HPV is more straightforward before pregnancy; more treatment options are available before pregnancy. Because the primary screening method for HPV is cervical cytologic screening in conjunction with DNA detection, women should undergo this screening at regular intervals, which is recommended by various groups. Primary prevention for HPV has become available recently through an HPV vaccine for selected HPV types. This vaccine has the potential of reducing the incidence of HPV-related genital disease, which includes cervical, penile, vulvar, vaginal, and anal cancer and precancerous lesions.[4] The quadrivalent vaccine, by decreasing the incidence of genital warts, has the potential to reduce laryngeal papillomatosis among the children of those vaccinated.[4] Another potential benefit of the vaccine is avoidance of loop electrosurgical excision procedure and cone biopsy, which can impact cervical performance during pregnancy.[5]

Recommendations by other groups. The Advisory Committee on Immunization Practices (ACIP) currently recommends the HPV vaccine for women and girls aged 9-26 years who have not yet completed the series, with the recommendation to begin vaccination in girls who are 11-12 years old.[6] The US Preventive Services Task Force (USPSTF), American Cancer Society (ACS), and American College of Obstetricians and Gynecologists (ACOG) all recommend cytologic screening beginning at age 21 years or 3 years after the onset of sexual activity (whichever comes first).[7-9] The groups vary on the screening interval, with the USPSTF stating that most of the benefit of screening occurs with screening every 3 years; ACS recommends annual screening with conventional methods, every 2 years with liquid-based cytology; although ACOG recommends annual screening until age 30, then every 2 to 3 years if there are no previous abnormalities.[7-9]

Recommendation. Women should be screened routinely for HPV-associated abnormalities of the cervix with cytologic (Papanicolaou) screening. Recommended subgroups (ie, women and girls 9-26 years of age) should receive the HPV vaccination series for the purpose of decreasing the incidence of cervical abnormalities and cancer. By avoiding the need for procedures on the cervix because of abnormalities that are caused by HPV, the vaccine could help decrease the proportion of pregnancies that end in preterm birth that is related to cervical incompetence during pregnancy. *Strength of recommendation*: B; *quality of evidence:* II-2.

Hepatitis B

Burden of suffering. Hepatitis B is predominantly a sexually transmitted disease in the United States.[10] Causes of hepatitis B transmission include blood transfusions and transmission through semen, infected wounds or needles, and vaginal secretions. Persons at high risk for hepatitis B include men who have sex with men, intravenous drug users, and those with multiple sex partners. Almost 25% of sexual contacts of a seropositive partner will become infected. The risks of neonatal transmission range from 10% if the woman has an acute hepatitis B infection during the first trimester to 90% during the third trimester.[11] If a woman is infected chronically (demonstrated by hepatitis B surface antigen [HBsAg] seropositivity), the risk of perinatal transmission is 10-20%. If she is chronically infected and seropositive for both HBsAg and hepatitis B e antigen, the risk of transmission to a fetus is approximately 90%. Chronic infection occurs in $>$ 90% of infected infants. Chronic infection poses a risk of cirrhosis and hepatocellular carcinoma.

How detectable is the condition? Hepatitis B is detectable through clinically available serum antibody and antigen panels.

How effective are the current treatments? Vaccination is the primary method of hepatitis B prevention. Studies have not shown a decreased risk in long-term outcomes when the general population is screened, but high-risk women who were not vaccinated previously should be tested. Vertical transmission of hepatitis B is prevented by the administration of immunoprophylaxis at birth to infants with seropositive mothers. However, infants who are exposed to acute infection in utero have additional risks that include low birthweight[12] and prematurity.[13] The infants of women who are chronic carriers should receive the hepatitis B immune globulin within 12 hours of delivery and hepatitis B vaccination at birth, 1, and 6 months. This vaccination series conveys a high protective efficacy (95%) against perinatal transmission. Breastfeeding is not contraindicated for infants who have been immunized.

Impact of preconception care. There are no studies specifically of a preconception immunization program, but it makes sense to initiate this immunization before pregnancy for those who have not received it previously, rather than wait until pregnancy.

Recommendations by other groups. The USPSTF Force recommends screening pregnant women for HBsAg at the first prenatal visit (an "A" recommendation). They recommend against screening the general population for hepatitis B. In 1997, the ACIP recommended vaccination of all children ages 0-18 years. Their most recent recommendations for adults include offering vaccination to those who request the vaccine and those who are at high risk (household contacts or sex-partners of HBsAg-positive persons, sexually active persons not in a long-term monogamous relationship, men who have sex with men, those with HIV or a recent sexually transmitted infection, patients who are being treated with hemodialysis or with renal disease that may require hemodialysis, healthcare workers and public safety personnel, patients who receive certain blood products, staff and clients at institutions for the developmentally disabled, inmates of long-term correctional facilities, and persons who travel to high-risk areas).[14]

Recommendation. All high-risk women (household and sexual contacts of hepatitis B virus carriers, injection drug users,

women with sexually transmitted diseases or other high-risk behaviors that include multiple sex partners, international travelers, prisoners, and workers in healthcare, public safety, and institutions) who have not been vaccinated previously should receive hepatitis B vaccine before pregnancy; women who are chronic carriers should be instructed on ways to prevent transmission to close contacts and how to prevent vertical transmission to their babies. *Strength of recommendation:* A; *quality of evidence:* III.

Varicella

Burden of suffering. Chickenpox (varicella) is a highly contagious disease. In children, varicella is usually mild but can be severe in adults and fatal in neonates and immunocompromised persons. Infants of women with active disease during the first trimester or early second trimester are at risk for limb atrophy, scarring of the skin of the extremities, central nervous system abnormalities, and eye problems. The risk of congenital varicella from perinatal transmission during the first and second trimesters ranges from 0.4-2.0%, with a greater risk in the second trimester. Additionally, the maternal risk for severe infection, which includes varicella pneumonia, is high.[15]

How detectable is the condition? Varicella is diagnosed most commonly on the basis of its clinical presentation.

How effective are the current treatments? A 2-dose vaccination regimen has 98% efficacy against varicella infection.[16]

Impact of preconception treatment. The availability of varicella vaccine, the rare occurrence of a congenital varicella syndrome, and the severity of neonatal disease in infants of women who contract varicella late during pregnancy suggest a benefit for preconception immunization of those women who do not have a history of chickenpox.[15] A 2-dose varicella vaccine schedule is now approved for use in women of childbearing age without a history of chickenpox.[17] Because the vaccine contains live virus it should not be given to pregnant women, and women who have been vaccinated should be advised to avoid becoming pregnant for 1 month.[18,19] Breastfeeding is not contraindicated in women just vaccinated.[16]

Recommendations by other groups. The Centers for Disease Control and Prevention (CDC) ACIP recommends that all healthy children should receive their first dose of varicella vaccine routinely at 12-15 months of age and a second dose by 4-6 years of age. For those children, adolescents, and adults who received only a single dose (an earlier recommendation of ACIP), ACIP currently recommends a second catch-up vaccination to improve individual protection. The CDC ACIP recommends that all women be assessed prenatally for evidence of varicella immunity (by either a history of previous vaccination, previous varicella infection that is verified by a healthcare provider, or laboratory evidence of immunity). Those women who are not immune should be offered the vaccine (2 doses). The guideline includes specific recommendations that, if this is discovered during pregnancy, the series be initiated immediately after delivery (or termination of pregnancy) with a second vaccination in the series at the 6-week postpartum visit.[16] Because the effects of the varicella vaccine on the fetus are unknown, pregnant women should not be vaccinated. Because the varicella vaccine is a live vaccine, nonpregnant women who are vaccinated should avoid becoming pregnant for 1 month after each injection.

Recommendation. Because the varicella vaccine is contraindicated during pregnancy, screening for varicella immunity (by either a history of previous vaccination, previous varicella infection that is verified by a healthcare provider, or laboratory evidence of immunity) should be done as part of a preconception visit. All nonpregnant women of childbearing age who do not have evidence of varicella immunity should be vaccinated against varicella. *Strength of recommendation:* B; *quality of evidence:* III.

Measles, mumps, and rubella (MMR)

Burden of suffering. Measles (rubeola) is characterized by a rash and can be complicated by otitis media, pneumonia, and diarrhea; less frequent outcomes are encephalitis with long-term disability (1 in 1000 cases) and death (1-2 in 1000 cases). Measles during pregnancy has been associated with spontaneous abortion, prematurity, and low birthweight. Measles has been confirmed not to be a cause of birth defects.[20] Classic mumps causes parotitis often preceded by headache, myalgia, malaise, and anorexia. This classic presentation occurs in approximately one-third of cases; the rest are either asymptomatic (one-fifth) or cause a nonspecific respiratory illness. Serious complications such as meningitis are more likely in adults who experience the condition. There has been some association of mumps with first trimester abortion, but a specific congenital syndrome has not been described.[20] Rubella infection during pregnancy, particularly during the first 16 weeks, can result in spontaneous abortion, stillbirth, or a baby with congenital rubella syndrome. The incidence of rubella has declined by $>$ 99% since 1969, the year the rubella vaccine was licensed.[21] However, serologic surveys of various populations, which includes migrant populations in particular, found that 10-20% of women of childbearing age lack serologic evidence of immunity to rubella.

How detectable is the condition? MMR are identified by standard clinical activities.

How effective are the current treatments? The MMR vaccine has been determined to be very efficacious for all 3 viral illnesses.[20]

Impact of preconception care. Congenital rubella syndrome can be prevented by preconception screening and vaccination. Women who are not immune to rubella at a preconception visit should be vaccinated. A history of rubella during childhood is frequently inaccurate. Even with such a history, women who have not been tested previously, who have not received 2 doses of the MMR vaccine, and who are not pregnant should receive the vaccine without any testing. Women who receive the vaccination should be advised to avoid pregnancy for 3

months. Should conception occur soon after vaccination, the woman can be reassured that she is not at appreciable risk regarding the vaccination. Several large series have identified no cases of vaccination-related congenital defect.[20,22]

Recommendations by other groups. The CDC ACIP recommends that children receive a 2-dose primary series of MMR vaccination during childhood (the first at 12-15 months and the second at 4-6 years).[16] The CDC ACIP recommends that women of childbearing age who do not have acceptable evidence of rubella immunity or vaccination receive the MMR vaccine before pregnancy.[20]

Recommendation. All women of reproductive age should be screened for rubella immunity. MMR vaccination, which will provide protection against measles, mumps, and rubella, should be offered to those who have not been vaccinated or who are nonimmune and who are not pregnant. Because it is a live vaccine, women should be counseled not to become pregnant for 3 months after receiving the MMR vaccination. *Strength of recommendation:* A; *quality of evidence:* II-3.

Influenza

Burden of suffering. Epidemic influenza during fall and winter outbreaks is common and causes an annual average of 200,000 hospitalizations and 36,000 deaths. Morbidity and death is more likely in children who are < 2 years old, adults who are ≥ 65 years old, and those with medical conditions that put them at risk for complications.[23] For women with influenza during pregnancy, there is an increase in morbidity in the second and third trimesters and a possible increased abortion rate. Influenza causes increased morbidity in pregnancy that results in both serious medical complications and hospitalization.[24]

How detectable is the condition? Influenza is identified easily in standard clinical care.

How effective are the current treatments? Vaccination is approximately 70-90% effective in preventing influenza against viruses that are targeted in the preparation.[24] Vaccination of pregnant women against influenza is recommended to reduce the risk of complications and to provide passive protection to the neonate.[25-28] Inactivated influenza vaccines are generally well-tolerated, with reactions seen in $< 5\%$ of cases. Common side-effects consist of low-grade fever and mild systemic symptoms. The vaccine is prepared from viruses grown in eggs; therefore, a small amount of egg protein is present in these vaccines. Women with a history of anaphylaxis to eggs should not be vaccinated. An increased risk of Guillain-Barré syndrome is associated with the influenza vaccine, but this risk appears to be rare and significantly smaller than the overall risk that is posed by naturally occurring influenza infection. There have been no reported adverse outcomes from influenza vaccination in pregnancy. A study of influenza immunization in > 2000 pregnant women did not find adverse fetal effects that were associated with the vaccine.[24] However, the potential for adverse effects in pregnancy from influenza vaccination has been reported. Thimerosal, a mercury-based preservative that is present in most inactivated formulations of the vaccine, has been implicated in human neurodevelopment disorders, which includes autism.[29] CDC studies have not confirmed these findings.[23] Two forms of "preservative-free" vaccine are available. Fluzone (Sanofi-Pasteur, Swiftwater, PA) is manufactured without thimerosal, and Fluarix (GlaxoSmithKline, Philadelphia, PA) has the thimerosal removed at the end of the manufacturing process.[30] Serious morbidity that results from influenza infection in early pregnancy must be balanced with the rare potential for adverse effects of vaccination. Parenteral inactivated virus vaccine should be administered intramuscularly to all women who will be pregnant during influenza season from October to mid November and continues as late as May, when peak influenza activity may occur. The intranasal vaccine (LAIV, FluMist; MedImmune, Gaithersburg, MD) is a live, attenuated influenza vaccine and should not be used in pregnant women.[31]

Impact of preconception care. There are no specific data on influenza vaccination in a preconception population. Generalizations and recommendations for vaccination in the preconception period must be made on the basis of risks for women who may become pregnant or are in early gestation. Fetal exposure to influenza during the first trimester has been implicated in a nested case-control study potentially to increase the risk of schizophrenia. The biologic mechanism is not defined; however, investigators noted that it may be worth considering routine vaccination of nonpregnant women several weeks before pregnancy, given the possibility that the antibody response to influenza, rather than direct infection, may be responsible for the observed increase in risk of schizophrenia.[32]

Recommendations by other groups. The CDC currently recommends influenza vaccine in all pregnant women, regardless of gestational age during influenza season.[33]

Recommendation. Influenza vaccination is recommended for women who will be pregnant during influenza season and for any woman with increased risk for influenza-related complications, such as cardiopulmonary disease or metabolic disorders, before influenza season begins. *Strength of recommendation*: C; *quality of evidence:* III.

Diphtheria, tetanus, and pertussis (Tdap)

Burden of suffering. Pertussis, or "whooping cough," is a respiratory condition that causes long-term cough. Estimates in the United States from prospective studies suggest that from 300,000-600,000 cases of symptomatic pertussis occur each year. Complications in adults include rib fracture, pneumonia, and cough syncope. Infants who are < 12 months old are susceptible for pertussis-related death. The number of cases has dropped since the introduction of the vaccine in the United States in the 1940s until 1976; since then there has been a steady increase, especially in adolescents and adults.[34] Tetanus is a condition that is caused by the inoculation of *Clostridium tetani* spores, which are found throughout the environment, through a break in the skin. This leads to

the development of a neurotoxin in oxygen-poor wounds. Symptoms include lockjaw (trismus) followed by rigidity of skeletal muscle, including those involved in respiratory function. Five hundred fifty-four cases were reported in the time period from 1990-2001 in the United States. Neonatal infection with infection of the umbilical stump at birth is rare in the United States (3 cases in 14 years); however, it has worldwide significance, being implicated in 250,000 deaths worldwide in 1997.[35] Diphtheria causes a respiratory illness that is distinct for the development of a grayish membrane over the pharynx, palate, and nasal mucosa that can obstruct the airway. Diphtheria is rare, with only 7 cases reported in 6 years in the United States.[36]

How detectable is the condition? Pertussis may be difficult to diagnose, given its wide ranging symptoms and large differential diagnosis with other respiratory conditions. Given the rarity of tetanus and diphtheria in the postvaccine era, both may be difficult to diagnose in a timely manner.

How effective are the current treatments? One risk group of concern for pertussis is young infants (< 12 months), so household contacts of infants should be targeted for vaccination. There is no evidence that the tetanus and diphtheria toxoids (Td) vaccine is teratogenic when used extensively; the data are more limited for Tdap. Neither vaccine is believed to be contraindicated in pregnancy when given in the recommended second or third trimester.[37] The Tdap vaccine is believed to prevent some of the morbidity in adults, which includes pregnant women, given the burden of disease in this age group.

Impact of preconception care. Because passive immunity is protective against neonatal tetanus, immunization before pregnancy would be of benefit. Administration of tetanus toxoid during pregnancy is well supported and also might be preventive, especially in developing countries. Immunization before pregnancy with Tdap may protect the newborn infant with passive immunity,[38] although it is unknown whether this passive immunity might result in hindrance of the development of an immune response when infants are vaccinated.[37]

Recommendations by other groups. The CDC ACIP recommends that children receive a 4-dose primary series of Tdap to be completed by 4-6 years of age. The CDC recommends a single dose of Tdap to prevent pertussis in all adults; this may be given if a patient has not received a Td booster in the past 10 years and may be as early as 2 years after a Td immunization. To protect against pertussis in infants < 12 months, close contacts of infants should receive the Tdap vaccine. For this reason the CDC recommends Tdap for any woman who might become pregnant or for women immediately after delivery who have not been vaccinated previously.[37]

Recommendation. Women of reproductive age should be up-to-date for tetanus toxoid, because passive immunity is probably protective against neonatal tetanus. The Tdap vaccine is recommended for women who might become pregnant or immediately after delivery to avoid complications of pertussis in the newborn infant. *Strength of recommendation:* B; *quality of evidence:* III.

Comment

Adherence to the recommended immunization schedule for children (for Tdap, hepatitis B virus, HPV, MMR, and varicella vaccines); administration of catch-up, booster, and risk-appropriate immunizations to adolescents and women of reproductive age (for Tdap, hepatitis B virus, HPV, influenza, and varicella vaccines); the screening of women of reproductive age for immunity to specific infections (varicella, rubella), and provision of immunization before pregnancy for those women who are found to be nonimmune are important components of a comprehensive preconception care program. Hepatitis B and MMR vaccines are highly recommended as part of any preconception care program because there is convincing evidence that there is benefit to giving these immunizations before pregnancy and that they are highly effective at preventing maternal disease and vertical transmission (hepatitis B) and in preventing congenital rubella syndrome (MMR). Those immunizations that are recommended, but with less convincing evidence that they should be part of preconception care, are the HPV vaccine (because it may avoid treatments that can affect obstetric outcomes adversely), varicella vaccine, and Tdap vaccine, because it might prevent the severe effects of neonatal infection. Each of the immunizations are lacking strong evidence to support that intervention in the preconception period prevents the consequences that affect the pregnancy, the fetus, and newborn infant. Influenza vaccination has a "C" recommendation because vaccination to avoid the consequences of influenza infection can be administered safely either in the preconception period or in pregnancy during the flu season. ■

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