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Vaccination in Pregnancy

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Pregnant women and newborns are vulnerable to several pathogens and are at high risk of exposure to various infectious diseases. Part of this increased susceptibility in pregnant women is due to pregnancy-related hormones that interact with the immune response. Maternal vaccination is an effective strategy for protecting the mothers as well as their infants and newborns against vaccine-preventable infections acquired at birth via transplacental transfer of maternal antibodies. At present, vaccines routinely recommended for pregnant women are the influenza and Tdap vaccines. A single dose of influenza vaccine is recommended for all pregnant women during the influenza season, which should be repeated during each pregnancy and the Tdap vaccine is recommended during every pregnancy, between 27 and 36 weeks of gestation. In addition, since pertussis infection in newborns or infants is often caused by family members and caregivers who come in direct contact with the baby, obstetrician-gynecologists should encourage the administration of the Tdap vaccine to these individuals at least 2 weeks before coming into contact with the newborn. In addition to influenza and Tdap vaccines, some vaccines such as hepatitis A and B vaccines can be used to protect from infectious diseases through vaccination in high-risk conditions or practices, such as travel to endemic areas, exposure, and during outbreaks. Maternal immunization is an important public health strategy to protect pregnant women and their babies. Healthcare providers should confidently promote vaccination during pregnancy as they are regularly trained to advise women on the latest immunization information.

Key Words: Vaccines, Pregnancy, Whooping cough, Influenza, Immunization

Introduction

Vaccination has effectively prevented the occurrence of various infectious diseases that have been a serious threat to the health of infants, children, or adults, resulting in a sharp decrease in mortality. Nevertheless, infectious diseases are still a major cause of morbidity and mortality. Vaccination for pregnant women is essential because certain changes in the immune system make pregnant women, fetuses, and newborns particularly vulnerable to infectious diseases, including those that are vaccination-preventable and associated with severe morbidity and mortality. It can also provide infants with passive immunity against vaccine-preventable infections acquired after birth. In this paper, the types of vaccines currently in use and vaccines recommended for use during pregnancy are summarized according to recent research results and guidelines.

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Maternal immune system in pregnancy

In the early stages of pregnancy, when embryos are implanted and the placenta is formed, extensive tissue remodeling occurs in the mother, while in the second and third trimester of pregnancy, fetal growth is rapid, and anti-inflammatory reactions occur mainly to allow the mother and fetus to coexist well.[1] Immunity is the body's ability to distinguish between itself and foreign materials and to resist harmful microorganisms. Since most pathogens are recognized by the immune system as foreign substances, immunity plays a role in protecting the body from infectious diseases. Because the fetus is perceived as a foreign body in pregnant women, semi-allogeneic fetal immune tolerance by the maternal immune system is required for a successful pregnancy. Immune adaptations during pregnancy may help explain changes in the severity and susceptibility to infectious diseases, even in immunocompetent pregnant women.[2]

The balance between T-helper 1 (Th1) and T-helper 2 (Th2) immune responses is essential for fetal growth and pregnancy maintenance. The Th2 immune response required for fetal and placental development maintains a dominant environment, while the predominance of the Th1 immune response hinders fetal and placental developments through their respective cytokines.[3] Hormonal changes in pregnant women play a critical role in determining the differentiation of T lymphocytes and cytokine secretion patterns. In general, estradiol is associated with modulation of T-cell mediated immune responses during pregnancy. The effect of estradiol on immunity can vary depending on the concentration.[4] Progesterone inhibits the maternal immune response while contributing to Th1/Th2 balance.[5] The placenta is an immune-modulatory organ that can protect against infection by passing maternal immunoglobulin (Ig) G antibodies to the fetus and regulating the maternal immune response. In general, maternal tolerance is mediated by the restriction and regulation of leukocytes that penetrate the placenta. For leukocytes with access to the placenta, intracellular communication of decidual stromal cells, trophoblasts, and immune cells can promote phenotypic and functional changes occurring in leukocytes.[6]

Immunity to microorganisms can usually be determined by the presence of disease-specific antibodies. Immunity is largely divided into active and passive immunity, depending on how it is acquired. Active immunity is naturally acquired through accidental exposure to a pathogen that causes antibody production by the immune system. Passive immunity is acquired through the transfer of antibodies or activated T-cells derived from an immune host with short-lived protection lasting from several weeks up to 3 or 4 months, requiring booster doses. The most common form of passive immunity is the transplacental passive antibody that the infant receives from the mother.

Goals of vaccination in pregnancy

Antibodies are transmitted through the placenta in the last 3 months of pregnancy, and as a result, full-term infants have antibody titers similar to those of their mothers.[7] With these antibodies, infectious diseases can be prevented up to the first year of life.[8] In the case of pregnant women, it is most desirable to complete vaccinations before pregnancy, especially for rubella or hepatitis B, which can cause congenital infections in the fetus. However, pregnant women may need vaccination because they are generally considered at high risk when exposed to pathogens, such as influenza, due to their greater severity and higher frequency of complications. In addition, since newborns do not yet have sufficient immunity to defend themselves against infectious agents such as viruses, bacteria, and fungi, they suffer more seriously for a longer period of time than adults, especially if they are born prematurely, which is known to increase the risk. Therefore, vaccination during pregnancy is important for the health of the mother, and for passive immunity to protect the baby up to 6 months after birth, as high-strength IgG antibodies formed in the mother pass through the placenta and are delivered to the fetus. Table 1 summarizes the recommended maternal vaccinations during pregnancy. In addition to influenza and Tdap vaccines, the table lists vaccines that can protect from infectious diseases through vaccination in high-risk conditions or practices, such as travel to endemic areas, exposure, and during outbreaks.

Table 1. Recommendations of Maternal Vaccination during Pregnancy

Vaccine	Vaccines recommended routinely	Vaccine recommended in special circumstance[a]	Vaccines contraindicated
Inactivated influenza	√		
Tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap)	√		
Pneumococcal vaccine		√	
Meningococcal vaccine		√	
Hepatitis A		√	
Hepatitis B		√	
Measles-mumps-rubella			√
Varicella			√
Zoster			√

[a]Travel to endemic areas, exposure, and during outbreaks.

Type of vaccine

Vaccines are largely divided into live attenuated vaccines and inactivated vaccines according to manufacturing methods. Live attenuated vaccines are prepared by weakening pathogens of wild bacterial or viruses. They can grow and replicate in the human body to acquire immunity without causing illness. Although live pathogens exist in live attenuated vaccines, they are attenuated to the extent that they cannot cause infection. However, even in an attenuated state, live vaccines are prohibited in patients with weakened immunity because the growth of pathogens can lead to serious infections. Therefore, in the case of pregnant women, live vaccines are contraindicated because there is a theoretical possibility that it can be transmitted to the fetus and cause congenital diseases such as rubella or chickenpox. However, if the necessary vaccine is a live vaccine, it is essential not to become pregnant for at least four weeks after vaccination and check whether pregnancy has occurred considering the last menstrual date before immunization.

An inactivated vaccine, also called a killed vaccine, is inactivated by heat or chemicals after culturing a pathogen. They are prepared from the whole or part of inactivated bacteria or viruses. Vaccines made from partial fractions of pathogens are called fractional vaccines, which are made on a protein-based or polysaccharide-based. The protein-based vaccine includes a toxoid vaccine containing inactivated bacterial toxin and a subunit vaccine containing a viral subvirion as the main component. Most polysaccharide-based vaccines consist of polysaccharides present in the bacterial capsule. A protein conjugate polysaccharide vaccine contains a polysaccharide that is chemically bound to a protein and becomes a more effective vaccine by binding to the protein.

In the case of a fractional vaccine, only the components to be included in the vaccine by treating the pathogen are purified. Inactivated vaccines cannot replicate in the body because they are not alive. The inactivated vaccine is administered by injection, and the antigen contained in the vaccine cannot cause infection even if administered to an immunocompromised person. The antigen of the inactivated vaccine is less affected by circulating antibodies than the antigen of the live vaccine. Almost all inactivated vaccines require several doses. Unlike live vaccines, immune responses induced by inactivated vaccines are mostly humoral immune responses, and cell-mediated immune responses are rarely generated. The antibody titer to the antigen of the inactivated vaccine decreases over time. Therefore, in the case of some inactivated vaccines, regular booster vaccine is required to increase the antibody titer.

The polysaccharide vaccine is a T-cell-independent vaccine that can stimulate B cells without helper T cells. T-cell-independent antigens, including polysaccharide vaccines, do not form antibodies well when administered to infants under 2 years of age, whose immune system is immature. Most inactivated protein vaccines increase the antibody titer more than the previous inoculation; however, this effect does not appear in the polysaccharide antigen. Antibodies produced by polysaccharide vaccines are also less functional than those produced by protein antigens, because most of the antibodies produced by polysaccharide vaccines are IgM antibodies

with almost no IgG antibodies. In the late 1980s, a technology for chemically conjugating proteins to polysaccharides was developed to compensate for these drawbacks. Through this protein binding, it is possible to convert a T-cell-independent immune response to a T-cell-dependent response, so that the immunogenicity can be increased even when an infant is vaccinated, and it is possible to induce a synergistic effect of the antibody titer following multiple inoculations.

A recombinant vaccine is one that is manufactured using an antigen produced by genetic engineering technology. The hepatitis B, human papillomavirus (HPV), and influenza vaccines are all produced by inserting a part of each virus' gene into the gene of a virus or yeast cell. This modified yeast cell or virus produces purified hepatitis B virus (HBV) surface antigen, HPV capsid protein, or influenza hemagglutinin, respectively, while proliferating. It is recommended for the mother and for the health of the fetus to vaccinate prior to pregnancy, according to the adult vaccination recommendations.

Influenza

Every year, about 20% of pregnant women show symptoms of upper respiratory tract infection, and approximately 10% of them have influenza.[7] When pregnant women get influenza, the symptoms are more severe than those of the general population; therefore, the hospitalization rate, cardiopulmonary complications, respiratory failure, and mortality all increase. In fact, when the 2009 H1N1 influenza epidemic occurred worldwide, the influenza-related mortality rate was significantly higher in pregnant women compared to the entire patient group (1% vs. 5%).[9] In addition, the frequency of obstetric complications such as miscarriage, stillbirth, low birth weight, premature birth, and neonatal death increases according to the severity of the infection.[10] Therefore, an inactivated influenza vaccine should be obtained by pregnant women during an influenza epidemic. Vaccination in pregnant women has been shown to minimize the risk of flu-related acute respiratory infections by up to 50%, and reduces the risk of hospital admissions with the flu by an average of 40%.[11] In addition, the passive immunity effect is excellent not only in mothers but also in newborns. Maternal influenza vaccination has been shown to reduce the risk of influenza infection or influenza-related hospitalizations in infants during the first 6 months of age by 48% and 72%, respectively.[12] In countries that have recommendations for maternal influenza vaccination, a single dose is recommended for all pregnant women during the influenza season, which should be repeated during each pregnancy.

Tetanus, diphtheria, pertussis

Pertussis is a highly contagious respiratory illness caused by the bacterium Bordetella pertussis, also known as 'whooping cough'. The initial symptoms are similar to those of a mild upper respiratory tract infection, but after 1 to 2 weeks and as the disease progresses, the traditional symptoms of pertussis appear with violent and rapid hacking cough followed by a high-pitched intake of breath that sounds like a "whoop." Pertussis is more serious and life-threatening in infants than in adults, and adults can act as a reservoir for infections in very young infants. In 2012, the incidence of pertussis increased rapidly in the United States and Europe, with higher mortality rates in infants under 12 months of age compared to other age groups, especially those under 3 months of age, who account for 75% of the total deaths.[13,14] According to current guidelines, the vaccination schedule for newborns and children with tetanus, diphtheria, and pertussis is recommended to be three times at 2, 4, and 6 months of age with additional inoculations at ages 15-18 months, 4 to 6 years, and 11 to 12 years. However, in the case of pertussis, it is said that the role of passive immunity by the maternal antibody delivered to the fetus through the placenta before birth until 6 months of age is crucial because in infants, the first vaccine series is administered at 2 months after birth and the preventive effect from the formation of antibodies is shown only after 2-3 or more vaccinations. According to the 2013 Advisory Committee on Immunization Practices (ACIP), the US Centers for Disease Control and Prevention recommends that pregnant women receive a single dose of Tdap vaccine during each pregnancy regardless of prior history of receiving the Tdap vaccination or consecutive

pregnancies within 12 months. The opinion is that it is good to vaccinate between 27 and 36 weeks of gestation to maximize the transfer of passive antibodies and maternal immune reaction.[15] In Korea, pertussis patients increased more than six times in 2009. The number of patients surged to 230 in 2012 and 980 in 2018, showing a typical trend of pertussis in developed countries where the epidemic repeats every 2 to 3 years.[16] Therefore, the Korea Centers for Disease Control and Prevention (KCDC) expanded the scope of recommendations for the adult Tdap vaccine in 2018 in preparation for the pertussis epidemic,[17] and the Korean Society of Infectious Diseases (KSID) also updated the Tdap vaccine guidelines in 2019.

The KCDC17 and the KSID[18] recommend that women who have not been vaccinated with the Tdap vaccine should receive one dose immediately after childbirth or before pregnancy. Regarding vaccination during pregnancy, Tdap vaccination is recommended at 27 to 36 weeks of pregnancy to prevent pertussis in newborns. In addition, since pertussis infection in newborns or infants is often caused by family members and caregivers who come in direct contact with the baby, obstetrician-gynecologists should encourage the administration of the Tdap vaccine of the individual in charge of primary care. Family members, such as partners, grandparents, and infant caregivers who do not have a history of Tdap vaccination should be encouraged to be vaccinated at least two weeks before coming into contact with the newborn. If not vaccinated during pregnancy, the Tdap vaccine should be administered immediately postpartum to women who have not received a prior dose of Tdap.[19] In addition, the Tdap vaccine can be administered at any time during pregnancy under certain circumstances, such as wound management and a pertussis outbreak. If a pregnant woman was vaccinated before 27 weeks of gestation, it does not need to be repeated at 27 to 36 weeks of pregnancy. However, it seems that more research is needed in the future to determine the effectiveness of vaccination during pregnancy, the appropriate timing of vaccination, and the safety of repeated vaccination in pregnant women.

Hepatitis A

Hepatitis A is transmitted via the fecal-oral route by ingesting food or water contaminated with the hepatitis A virus. In the past, patients with asymptomatic hepatitis A in childhood acquired immunity naturally. However, as the environment and sanitation conditions in Korea have improved, the incidence of hepatitis A is increasing rapidly in adults in their 20s and 30s who have never been exposed to the hepatitis A virus.[20] In the United States, the ACIP recommends hepatitis A vaccination for adults at high risk of hepatitis A exposure because of international travel, behaviors, medical conditions, or exposure during an outbreak. The hepatitis A vaccine is an inactive vaccine that is not expected to cause any abnormalities in the mother or fetus. Therefore, the ACIP recommends vaccination for pregnant women at risk for catching hepatitis A or for having severe disease from hepatitis A infection who have not previously been vaccinated, as in ordinary adults.[21]

Hepatitis B

HBV is transmitted through percutaneous or mucosal exposure to blood or body fluids infected with the hepatitis virus. Neonatal infection mainly occurs during childbirth, but it is known that intrauterine fetal infection is possible if the mother develops acute hepatitis B in the second half of pregnancy.[22] If hepatitis B becomes chronic, it is highly likely to progress to liver cirrhosis and liver cancer. The chronicity rate varies greatly depending on the time of infection. The majority of adults infected with HBV will clear the virus and only 2% to 8% will develop chronic hepatitis B. However, chronic HBV infection occurs in 80% to 90% of infants infected perinatally and 30% to 50% of children infected before 6 years of age.[23] To prevent perinatal infection in newborns, if a pregnant woman is positive for the hepatitis B surface antigen, hepatitis B vaccine and hepatitis B immunoglobulin should be administered within 12 hours of birth. The hepatitis B vaccine is effective in preventing infection because high titer antibody formation occurs in more than 90% of the inoculated with three doses of a recombinant

vaccine. It is desirable to vaccinate even during pregnancy if the pregnant woman has not been vaccinated before and therefore, does not have antibodies, or if her spouse is in a high-risk group such as if they are HBV carriers. Although data on the safety of the hepatitis B vaccine are still limited, there are no maternal and fetal side effects associated with vaccination.

Conclusion

Vaccination during pregnancy provides fetal and neonatal benefits through the passive transfer of protective antibodies across the placenta. There is no evidence of fetal side effects from inactivated virus, bacterial vaccine, or toxoid vaccination in pregnant women, and data growth has demonstrated the safety of its use. Therefore, all pregnant women should be vaccinated against influenza during the influenza season and receive Tdap each time they become pregnant. As stated in this article, additional vaccines are indicated during pregnancy in women under certain conditions. Maternal vaccination can improve maternal and child health by reducing maternal and infant morbidity and mortality associated with diseases caused by pathogens associated with perinatal and early life.

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Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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