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Review Article

Immunization during pregnancy: To do or not to do?

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ABSTRACT

Immunization is the most cost-effective primary prevention strategy for control and elimination of infectious diseases. Immunization during pregnancy deserves special focus due to added benefit to the newborn. However, theoretical risk to the fetus, mainly due to live vaccines of organisms that are known teratogens, dictates that women are immunized against these infections either before or in-between pregnancies. This article summarizes the contemporary guidelines regarding immunization during periods around pregnancy.

Keywords: Immunization, Pregnancy, Vaccine

INTRODUCTION

Vaccine-preventable diseases are infectious diseases, for which a safe and effective vaccine is available to prevent the disease. Globally, control of vaccine-preventable diseases through immunization has prevented premature mortality and mitigated morbidity in the most cost-effective manner.

PREGNANCY AND VACCINE-PREVENTABLE DISEASES

Vaccine-preventable diseases are responsible for significant maternal, fetal, and early childhood morbidity and mortality. Pregnant women are at elevated risk for influenza-related morbidity and mortality as well as adverse pregnancy outcomes. Rubella and varicella infections during pregnancy can lead to congenital anomalies. Vertical transmission of hepatitis B virus (HBV) is associated with higher risk of chronicity of the infection and its sequelae in the newborn. For prevention of these infections, i.e., those which have potential to adversely influence the pregnancy outcomes, women should be immunized before pregnancy. However, there is another group of diseases, immunization against them during pregnancy is beneficial to the newborn because the transfer of immunoglobulin G antibodies from the mother protects the newborn during initial period of life.[1] The newborn is benefitted in two situations; first, to protect neonate against infection before active immunization to neonate becomes effective, for example, tetanus and pertussis, and second for infections, for which a vaccine is not yet licensed for early use, for example, influenza.

DOES PREGNANCY ALTER IMMUNE RESPONSE?

Immunologically, pregnancy is a state when the woman tolerates a semi-allogeneic fetus. During the course of pregnancy, changing levels of sex hormones induce variable immune responses. Increase in estradiol levels stimulates Type 2 helper T-cells and depresses activity of Type 1

helper T-cells. Similarly, increasing progesterone levels are associated with a reduction in immune responses. Other components of immune system such as phagocytic activity, population of neutrophils, monocytes, and dendritic cells are maintained or may even increase after the first trimester.[2] The compromise in cell-mediated immunity explains suboptimal responses to infections, for example, influenza that require optimal cell-mediated immunity. This may also be one of the reasons for lower immunogenic response to vaccinations against hepatitis B, pertussis, and yellow fever (YF) during pregnancy as compared to non-pregnant state.[2]

CLASSIFICATION OF VACCINES

Vaccines are classified as live-attenuated, inactivated or killed, toxoid, subunit, or conjugate vaccines. Live vaccines contain living organisms that have been attenuated to lose their pathogenicity, while maintaining immunogenicity. Technically, clinical infection can occur following live vaccination, although it is not only rare but also milder than the natural infection. However, live-attenuated vaccines are contraindicated during pregnancy due to the potential risk of vaccine caused infection resulting in congenital defects, for example, rubella and varicella. Inactivated or killed vaccine cannot result in infection as the disease agent has been exposed to inactivate physical or chemical environment. Toxoids are vaccines against non-invasive bacteria producing disease by exotoxins, for example, tetanus and diphtheria. Inactivated vaccines and toxoid maintain their ability to generate an immune response, though less robust than by live vaccines. Antibody levels achieved by inactivated vaccines or toxoids wane overtime, necessitating multiple dosing, booster doses or both, to ensure sustained immunity. Subunit vaccines contain fragments of the pathogens that provoke a protective immune response. A cellular pertussis, hepatitis B vaccine, and human papillomavirus (HPV) vaccines are subunit vaccines. Conjugate vaccines are created by chemically combining portion of the bacterial coat with a carrier protein. This mitigates the limitation of the bacterial antigen alone to generate an adequate immune response.

IMMUNIZATION DURING PREGNANCY

Hepatitis A

Hepatitis A virus (HAV), an RNA picornavirus, causes fever, nausea, abdominal pain, and jaundice due to acute, self-limiting liver infection. HAV is transmitted through the fecal–oral route after close contact with infected individuals or contaminated food or drinks. Hepatitis A vaccine contains inactivated HAV, hence, it unlikely to cause infection or harm to mother, fetus, or infant. Pregnant women should receive HAV vaccine when the risk of infection outweighs the theoretical risk of administration of the vaccine.[3]

Hepatitis B

HBV infection can be acute self-limiting or achieve a chronic carrier state associated with long-term complications including cirrhosis, liver cancer, liver failure, and death. HBV during pregnancy, both acute episode and chronic carrier state, carries a significant risk of vertical transmission. Perinatally acquired HBV infection is associated with a very high risk of developing chronic disease for the offspring. The current HBV vaccine is a recombinant DNA formulation based on the hepatitis B surface antigen (HBsAg) envelope protein. All pregnant women should be screened for HBsAg status. At-risk neonates (mother being HBsAg positive) should be treated with HB immunoglobulin prophylaxis and receive the first HBV vaccine dose within 12 h. This protocol is an effective strategy against peripartum transmission, the most common period for transmission of virus from mothers positive for HBsAg positive.

Women who develop acute infection during antenatal period can also transmit infection, *in utero*, the risk being the highest in late pregnancy. Therefore, HBV vaccination is indicated for unprotected pregnant women during antenatal period. Three-dose HBV vaccine schedule should be initiated for unimmunized pregnant women. This is more relevant for those at high risk of acquiring infection, namely, those with multiple sexual partners, present or past evidence of sexually transmitted diseases, history of an HBV-positive sexual partner or household contact, or intravenous drug use. Although 0, 1, and 6 months schedule in ideal, 0, 1, and 2 schedule is recommended if woman reports late in pregnancy.[3]

Pneumococcal disease

Streptococcus pneumoniae (pneumococcus) is a Gram-positive bacterium associated with significant morbidity and mortality related to pneumonia, bacteremia, meningitis, and otitis media. There are currently insufficient data to support routine administration of pneumococcal conjugate vaccine 13 or pneumococcal polysaccharide vaccine 23 (PPSV23) during pregnancy. A systematic review of the use of PPSV23 in pregnancy showed no increase in unfavorable pregnancy outcomes. CDC recommends PPSV23 during pregnancy for women who have a medical risk factor(s), for example, chronic heart disease, chronic liver disease, congenital or acquired immune deficiencies, sickle cell disease, functional or anatomic asplenia, etc.[3]

Japanese encephalitis (JE)

JE is caused by mosquito-borne RNA *Flavivirus* which is the most common vaccine-preventable disease cause of encephalitis in India. Unfortunately, there is lack of adequate studies of the vaccine during pregnancy. It is recommended that JE vaccination should be considered for pregnant women

when the theoretical risk of immunization is outweighed by the risk of infection.[3]

Measles, mumps, and rubella (MMR)

MMR vaccines should not be administered to women known to be pregnant or attempting to become pregnant. Due to the theoretical risk to the fetus, when the mother receives a live virus vaccine, women should be counseled to avoid becoming pregnant for 28 days after receipt of MMR vaccine. If the vaccine is inadvertently administered to a pregnant woman or a pregnancy occurs within 28 days of vaccination, she should be counseled about the theoretical risk to the fetus. Routine pregnancy testing of women of childbearing age before administering a live virus vaccine is not recommended. MMR vaccination during pregnancy should not be considered a reason to terminate pregnancy. All pregnant women who are susceptible to rubella should be vaccinated immediately postpartum, thus reducing or eliminating risk to the fetus in subsequent pregnancies.[3]

YF

YF vaccine, a live vaccine is not recommended for pregnant women, unless the women are traveling to a high-risk area. Although no specific data are available, a woman should wait at least 4 weeks after receiving YF vaccine before conceiving.[3] The Government of India advisory for passengers arriving or returning to India from YF countries does not exclude pregnant women from the necessity of vaccination.

Meningococcal vaccines

Randomized controlled trials have not been conducted to evaluate the use of meningococcal vaccines during pregnancy. Vaccination should be deferred in pregnant women unless the woman is at increased risk, and the benefits of vaccination are considered to outweigh the potential risks.[3]

Oral polio vaccine (OPV)

Although a number of large studies have demonstrated the safety of OPV for infants born to vaccinated women and no evidence of increased rates of adverse pregnancy outcomes, there remains a small risk of adverse effects of OPV administration during pregnancy. Immunization of pregnant women at high risk of endemic or epidemic exposure is recommended by the Strategic Advisory Group of Experts on Immunization (WHO).[3]

Inactivated poliovirus vaccine (IPV)

Although no adverse effects of IPV have been documented among pregnant women or fetuses, routine vaccination of pregnant women should be avoided because the safety of IPV in pregnancy has not been well established. However, if a pregnant woman is at increased risk for infection and requires immediate protection against polio, IPV can be administered in accordance with the recommended schedules for adults.[4]

Varicella

Varicella-zoster virus, a member of the herpes virus family, causes chicken pox. Infection during pregnancy is associated with neonatal infection, and congenital varicella syndrome characterized by skin scarring, limb hypoplasia, low birth weight, and numerous other anomalies. Congenital varicella syndrome occurs in 1–2% of cases of maternal varicella infection, with the highest risk of occurrence if maternal infection occurs during 12–20 weeks of gestation. Varicella vaccine is contraindicated in pregnancy due to its live-attenuated formulation. Non-pregnant women who are vaccinated should avoid becoming pregnant for 1 month after vaccination. If a pregnant woman is inadvertently vaccinated or becomes pregnant within 4 weeks after varicella vaccination, she should be counseled regarding risk to the fetus. Analogous to rubella vaccination in early pregnancy, no cases of congenital varicella syndrome have yet been reported after inadvertent varicella vaccination during pregnancy. Hence, varicella vaccination during pregnancy is not an indication for termination of pregnancy.[4]

Herpes zoster

Zoster vaccine should not be administered to pregnant women. In addition, Zostavax is licensed for the age groups more than 50 years that exclude women of childbearing ages. Like the varicella vaccine, the decision to terminate a pregnancy should not be based on whether the zoster vaccine was administered during pregnancy.[5]

HPV

HPV vaccines are not recommended for use in pregnant women. If a woman is found to be pregnant after initiating the vaccination series, the remainder of doses should be delayed until completion of pregnancy. Pregnancy testing is not needed before vaccination. If a vaccine dose has been administered during pregnancy, no intervention is needed.[5]

Anthrax

In general, the risk of exposure to *Bacillus anthracis* in pregnancy is low; hence, routine vaccination of pregnant women is not indicated. However, if a pregnant woman gets exposed to aerosolized *B. anthracis* spores and is at high risk for infection, pregnancy is not a contraindication to post-exposure prophylaxis with three doses of anthrax vaccine.[6]

Bacille Calmette–Guerin (BCG)

BCG vaccination should not be given during pregnancy. Even though no harmful effects of BCG vaccination on the fetus have been observed, evidence regarding its safety is insufficient.[6]

Influenza

Influenza, an RNA virus with A and B serotypes, is responsible for both endemic and pandemic flu. Both types are responsible for endemic flu while type A, due to antigenic drift, is responsible for pandemics. Pregnant women infected with flu have increased rates of hospitalization, cardiopulmonary complications, and death when compared to the general population. Multiple complications including spontaneous abortion, stillbirth, neonatal death, preterm birth, and low birth weight have been reported among influenza-infected women. Immunization is the best strategy for flu prevention. It is recommended that all pregnant women receive inactivated influenza vaccine during flu season. Live-attenuated vaccine is contraindicated in pregnancy, though inadvertent administration during the first trimester has not been associated with adverse outcomes.[7]

Dengue

CYD-TDV is a tetravalent, live-attenuated dengue vaccine developed by Sanofi Pasteur. The safety of the vaccine is disputed and has not been evaluated in pregnancy. Moreover, the vaccine contains live virus and hence is contraindicated during pregnancy.[8]

Tetanus

Tetanus toxoid during pregnancy is a part of National Immunization Schedule of India, and its safety and effectiveness in prevention of maternal and neonatal tetanus are well recognized.[9]

Diphtheria and pertussis

The Indian Academy of Pediatrics recommends immunization of pregnant women with a single dose of Tdap (adult tetanus, diphtheria, and pertussis) during the third trimester. Tdap should be repeated in every pregnancy. These recommendations are mainly to prevent pertussis during neonatal and early infancy, i.e., period before effective protection of infant by active immunity evoked by DPT/pentavalent vaccine.[10]

Typhoid fever is a serious disease caused by the bacterium *Salmonella* Typhi. There are two vaccines against *S.* Typhi currently available which are a live-attenuated oral vaccine and a polysaccharide vaccine. There are no data supporting the efficacy and safety of either vaccine in pregnancy. Pregnant women are advised to take precautions to avoid exposure to infection by ensuring "sanitation barrier." When the risk of exposure is high, typhoid vaccine is indicated. The inactivated Vi polysaccharide vaccine should be preferred in pregnancy due to theoretical risk of fetal infection from live vaccine.[11]

Cholera

Cholera is a serious dehydrating diarrhea disease which causes serious complications including fetal loss. Moro and Sukumaran reviewed the various studies on safety of oral killed cholera vaccines during pregnancy and concluded that "although good sanitation measures are ideal, cholera vaccines approved by the WHO can be safely used during pregnancy."[12]

Rabies

Due to the potentially fatal consequence of rabies exposure, pregnancy is not a contraindication to post-exposure prophylaxis. Studies have indicated no increased incidence of abortion, premature births, or fetal abnormalities associated with rabies vaccination. If the risk of exposure to rabies is substantial, pre-exposure prophylaxis is recommended during pregnancy.[13]

PASSIVE IMMUNIZATION DURING PREGNANCY

No known risk exists for the fetus from passive immunization of pregnant women with immune globulin preparations.[14]

BREASTFEEDING AND VACCINATION

Neither inactivated nor live virus vaccines administered to a lactating mother affect the safety of breastfeeding for women or their infants. Although live vaccine viruses can replicate in mothers, most viruses are not excreted in breast milk except rubella which also loses its capacity to infect the infant.[14]

PREGNANCY SCREENING

Routine pregnancy testing beyond the history of women of childbearing age before administering a live virus vaccine is not recommended.

ANTENATAL SCREENING

Pregnant women should be screened for immunity to rubella and varicella, in addition to test for the presence of HBsAg during pregnancy. Women susceptible to rubella and varicella should receive vaccination immediately after delivery. The actions to be carried out if found to be HBV non-immune or infected have been discussed above.[14]

CONCLUSION

Pregnancy is a physiological state but has considerable morbidity and mortality including due to infectious diseases. The risk of vaccine-preventable infections can be significantly reduced by immunization. Antenatal period also provides us the opportunity to protect the newborn against neonatal and early infancy infections. Thus, immunization during pregnancy is a vital tool in primary prevention of diseases, both in the mother and in newborn. National Immunization Schedule has clear guidelines regarding immunization of pregnant women against tetanus. However, rising awareness and purchasing power of Indian populace dictate that comprehensive guidelines on indications and contraindication of all available vaccines during pregnancy in Indian context are discussed by public health experts, obstetricians, and pediatricians to provide inputs for national consensus and development of national policy on the subject.

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Conflicts of interest

There are no conflicts of interest.

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