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Why Should We Advocate Maternal Immunization?

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Abstract

Maternal vaccination provides a method for protecting the pregnant woman, fetus, and neonate during a period when there is increased susceptibility to infectious diseases. A dynamic state of immune tolerance during pregnancy and the need to develop adaptive memory to a new foreign antigen-rich environment lead to windows of vulnerability to infection for the mother and neonate, respectively. Passive transfer of humoral immunity through the placenta and breast milk from the mother can bridge the gap in immunity for the neonate. Studies on boosting this natural process of antibody transfer have led to the recommendation for administering inactivated influenza, diphtheria, tetanus toxoid, and acellular pertussis vaccines during pregnancy. Several new maternal vaccine candidates are on the horizon.

Keywords

Maternally-acquired immunity; immunization; vaccines; newborn; neonate; pregnancy

RATIONALE BEHIND IMMUNIZING PREGNANT WOMEN

Vaccination is one of the greatest public health achievements. The concept of transferring immunity against infection from mother to newborn has been described as far back as the late 19th century (1). Certain infections disproportionately affect pregnant women. Pregnant women are either more susceptible or have more severe outcomes from infections with influenza, *Listeria*, malaria, varicella, hepatitis E, and herpes. Pregnant women are at higher risk for more severe influenza infection, with higher rates of hospitalization and mortality compared to the general population, and poor fetal outcomes (2). *Listeria* has a predilection for the placenta and causes meningoenzephalitis as well as miscarriages and stillbirths (3, 4). Malaria similarly has the potential to invade the placenta, is more severe in women in their first pregnancy, and causes anemia, preterm birth, and low birthweight (5, 6). Varicella zoster virus infection in the mother during pregnancy is associated with pneumonia, particularly in the third trimester, as well as risk of congenital varicella in the neonate (7). In studies from South Asia, hepatitis E may cause higher rates of fulminant hepatitis in pregnant women and is associated with increased mortality (8). Primary herpes simplex virus infection in pregnancy is associated with dissemination and fulminant hepatitis (9).

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CONFLICTS OF INTEREST

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Neonates also have increased susceptibility to infections and death, particularly in the developing world. Annually, 41% of all under-five child deaths are among neonates, and 12% of neonatal causes of death are due to infection, including sepsis/pneumonia, tetanus, and diarrhea (10). Therefore, vaccination of the mother has the potential to protect the mother, the developing fetus, and the neonate from infections during a period of vulnerability.

IMMUNOLOGY OF MATERNAL VACCINATION

THE IMMUNE SYSTEM DURING PREGNANCY

The classic theory of the immune system during pregnancy consists of an anti-inflammatory or Th2-type state that allows for fetal development, whereas a sudden shift towards a pro-inflammatory Th1-type immune response could lead to pregnancy complications, such as abortion and preterm birth (11).

In recent years, it has been established that pregnancy is a much more complex interplay of both pro- and anti-inflammatory cytokines between the fetus and the mother. Recent studies have shown that a pro-inflammatory Th1-type tissue environment can be found in early healthy pregnancies and shifts to an anti-inflammatory state by the third trimester (12, 13). Natural killer (NK) cells, macrophages, dendritic cells, and an expanding T regulatory cell population have all been detected at the maternal-fetal interface and are theorized to play a beneficial role in successful fetal implantation, rather than increasing the risk of miscarriage (14, 15). Cytokines, such as interleukin (IL-10), colony stimulating factor (CSF-1), and transforming growth factor- β are essential for trophoblast invasion during the implantation process and are expressed by endometrial immune cells (16). These conflicting findings may be explained by considering pregnancy as a developmental process with different immunological stages rather than as a single homogeneous event. Rises in progesterone and estradiol lead to shifts in immunity as pregnancy progresses, with dampening of cell-mediated immunity, Th1 activity, and NK cell and B cell counts, and with increases in phagocytic activity, α -defensin levels, and monocyte, dendritic-cell, and polymorphonuclear-cell counts (17).

PLACENTAL ANTIBODY TRANSFER

Placental transfer of IgG, preferentially IgG1, from mother to fetus generally begins in the second trimester and peaks during the third trimester so that infant antibody concentrations often exceed those of the mother by the time of birth (18). These then rapidly decay over the course of the first several months of life, leaving a window of vulnerability for infectious diseases before infants are able to effectively generate their own antibodies (19, 20). The concept of maternal vaccination is to boost antibody titers during pregnancy so that higher titers persist for a longer time in the infant, thereby closing this window of vulnerability (Figure 1). Routine maternal immunizations that are recommended in the US include influenza and tetanus, diphtheria, and pertussis, and, globally, maternal tetanus toxoid administration has virtually eliminated neonatal tetanus (21).

Antibody transfer across the placenta occurs via the neonatal Fc gamma receptor (FcRn), specifically for IgG. Maternal IgG is endocytosed at the syncytiotrophoblast. Antibody binding to the neonatal Fc gamma receptor within the endosome is pH-dependent, occurring only in an acidic environment. This is then transferred across to the fetal circulation, where at a physiologic pH, IgG dissociates from FcRn.

Many factors impact antibody transfer, including timing during pregnancy, IgG subclass, and chronic infections such as malaria and HIV (22). There is very little antibody in the fetal circulation at the beginning of the second trimester, 50% by the end of the 2nd trimester, and greater than 100% by term birth in infants (23). The vast majority of transplacental antibody transfer occurs for IgG1, followed by IgG2 and then IgG3 and 4 (24). Protein-based vaccines, such as tetanus, tend to induce predominantly IgG1, whereas polysaccharide vaccines, such as pneumococcus, tend to induce IgG2 (25). HIV exposure *in utero* also decreases vaccine-specific antibody titers for Haemophilus influenzae type B, pertussis, pneumococcus, and tetanus in HIV-exposed uninfected (HEU) infants at birth. These infants were still able to mount a robust antibody response to routine childhood vaccinations after birth, possibly due to having less interference from maternal antibody (26).

In other studies, HEU infants also had lower antibody titers at birth after maternal vaccination against pandemic H1N1 influenza as well as season influenza (27). Malaria infection in the placenta may also impair antibody transfer, with a correlation between higher levels of placental parasitemia and lower umbilical cord tetanus-specific IgG (28). Alternatively, more recent studies suggest that maternal hypergammaglobulinemia rather than placental malaria interferes with antibody transport, possibly through saturation of placental FcRn.

BREAST MILK ANTIBODY TRANSFER

Breast milk antibody from maternal immunization may also play a role in protection of infants, particularly after transplacental antibody transfer has decayed in the first few months of life. Breastfeeding is important in protecting against mucosal pathogens, and this is particularly important in developing countries. Most pathogens use the mucosa as portals of entry and epidemiological data show an association between breastfeeding and protection against diarrhea and pneumonia (29, 30). The polymeric Ig receptor (pIgR) is responsible for transporting polymers of secretory (s) IgA and IgM into breast milk, particularly colostrum (31). Therefore, sIgA represents the major immunoglobulin in breast milk, followed by sIgM and then IgG. In humans, ingested breast milk antibodies do not enter the neonatal circulation, but secretory IgA can prevent microbial colonization and invasion by coating mucosal surfaces. Secretory IgA in colostrum can prevent HIV transcytosis across epithelium by direct neutralization (32). Breast milk IgG can also provide protection against HIV infection through antibody-dependent cytotoxicity (33). A correlation between breast milk IgG against respiratory syncytial virus with protection against acute respiratory infection has also recently been reported (34).

CURRENT VACCINATION RECOMMENDATIONS AND GUIDELINES

Inactivated influenza, tetanus toxoid, diphtheria, and acellular pertussis vaccines are now widely recommended during pregnancy due to strong evidence supporting their safety and efficacy. Live attenuated vaccines are contraindicated during pregnancy given the potential for infecting the fetus (35). Table 1 summarizes the current recommendations adapted from the ACIP on maternal vaccination (36).

INFLUENZA

The Advisory Committee on Immunization Practices (ACIP) currently recommends that all pregnant women receive inactivated influenza vaccine at any time during the influenza season. The World Health Organization (WHO) also recommends that pregnant women are the highest priority group for influenza vaccination in case of a shortage (37). The rationale behind these guidelines is that pregnant women are disproportionately at increased risk for hospitalization and death (38). During the influenza pandemic of 1918, mortality in pregnant women with pneumonia was greater than 50% as compared to 33% overall at a public hospital in Chicago (39). In the 2009 pandemic in the United States, up to 7% of all deaths were among pregnant women, although pregnant women represent only about 1% of the U.S. population (2).

During the 2009 H1N1 pandemic, infection during pregnancy also was associated with increased risk of adverse fetal outcomes, including miscarriage, preterm birth, and stillbirths (2).

Multiple large studies have demonstrated the safety of influenza vaccination during pregnancy. No unusual patterns of adverse pregnancy or fetal outcomes have been found in post-licensure reporting national registries, including the Vaccine Adverse Event Reporting System (VAERS) or in the Vaccine Safety Datalink (VSD) (40–42). However, one case-control study of women with and without miscarriage reported that H1N1 influenza vaccination from 2010–2011, but not in 2011–2012, was associated with increased risk of miscarriage (42). In a post-hoc analysis, influenza vaccination in the previous season was associated with increased risk for spontaneous abortion. This effect was not seen among women not vaccinated in the previous season. These results have yet to be reproduced, so caution is needed in interpreting these data in light of the many other studies showing influenza safety in pregnant women and also increased risk of adverse effects of influenza on mother and the fetus.

No randomized trials of influenza vaccine in pregnancy have been performed in the United States or Europe. The first study to examine maternal influenza immunization in a randomized clinical trial was performed in Bangladesh, with a comparison arm of pneumococcal vaccination (43). In this study, the efficacy in reducing lab-confirmed influenza in infants was 63%. An effect on reducing the risk of being born small for gestational age was also found in post-hoc analysis, suggesting that the prevention of febrile respiratory illness during pregnancy could have an effect on reducing growth restriction *in utero*. Since then, three other studies in Nepal, Mali, and South Africa have reproduced these results and found that influenza vaccination during pregnancy was efficacious at preventing

disease in mothers and infants (44). Importantly, in Nepal, women were randomized to second or third trimester vaccination to evaluate whether timing of vaccination during pregnancy would affect efficacy. No difference in efficacy was observed by trimester of vaccination (45).

TETANUS, DIPHTHERIA, AND PERTUSSIS

In the United States, the ACIP recommends tetanus, diphtheria, and acellular pertussis immunization with each pregnancy between 27 and 36 weeks, irrespective of receipt of prior doses of Tdap with earlier pregnancies (46). Vaccination is particularly important with the resurgence of pertussis in the US and UK, possibly due to lower vaccine uptake in certain populations, genetic selection of antigenic escape mutants, and less durable protection with the acellular formulation (47, 48). Approximately one-third of infants get pertussis from their mother, and the highest mortality from pertussis occurs under 6 months of age (49, 50). Cocooning by vaccinating all close contacts can be logistically challenging, difficult to implement, and also may be too late to prevent disease in neonates. The age of first vaccination is 2 months, leaving a window of vulnerability between birth and 2 months. In an observational study of different age groups in the UK, the incidence of pertussis was highest in adolescents and infants < 3 months and peaked in 2012. The British government recommended universal Tdap vaccination during pregnancy in October 2012, and a decline in incidence was observed thereafter (51).

Multiple studies, including the VSD have demonstrated the safety of Tdap vaccination during pregnancy (52–54). One retrospective study in California found a small but statistically significant increase in chorioamnionitis but this finding has not been reproduced in other studies since then (52, 54). A large retrospective cohort study conducted by Kaiser Permanente Northern California from 2006–2015 showed an efficacy of 91.4% for maternal Tdap vaccination during pregnancy in preventing infection of the infant during the first 2 months of life and 69% during the entire first year of life (55). In the US, vaccination against pertussis is currently recommended in the third trimester to protect young infants from pertussis. However, a recent study comparing cord blood antibody titers in infants who were born to mothers vaccinated in the second versus third trimester showed, surprisingly, that earlier Tdap vaccination was associated with higher cord blood pertussis antibody titers at the time of birth (55). This finding could potentially widen the opportunity for immunization during pregnancy.

VACCINE COVERAGE AND BARRIERS TO VACCINATION

Pertussis vaccine coverage in pregnancy is low for both influenza and Tdap in the US and UK (56). In the US between 2016–2017, pregnant women who received a recommendation for and an offer of vaccination from a doctor or other medical professional were more likely to be vaccinated compared with women who received only a recommendation but no offer or received no recommendation. Self-reported vaccination coverage among these women was 63.4%, 37.5%, and 12.8%, respectively (57). 89% of women reported that they would get immunized with pertussis vaccine during pregnancy if their physician recommended it (58). Barriers to vaccination include concerns regarding safety, doubt about efficacy, lack of

perception of risk with natural infection, and lack of knowledge about burden of disease. Interventions to facilitate uptake include national recommendations, disseminating safety information, and training health care providers to recommend, offer, and provide vaccinations during pregnancy.

ON THE HORIZON

Several new maternal vaccines are in various phases of clinical trials. One nanoparticle vaccine candidate against respiratory syncytial virus (RSV), an important cause of bronchiolitis in infants, has reached an on-going phase III trial in pregnant women (59). Several vaccine candidates against Group B Streptococcus, an important cause of neonatal sepsis, have reached phase II trials (60). A vaccine against Zika virus which can cause microcephaly at birth has been studied in animal models of pregnancy and in women of child-bearing age but has yet to enter clinical trials in pregnant women (61, 62).

CONCLUSIONS

Pregnant women and neonates are at risk for severe complications from infectious diseases. Routine vaccination in pregnancy protects the mother, the fetus, as well as the infant by boosting transplacental and breast milk antibody. Factors such as preterm birth, HIV, and malaria can impact antibody transfer across the placenta. Influenza and TDaP vaccinations in pregnancy are safe, efficacious, and recommended. New maternal vaccines are on the horizon. Provider recommendation and offering increases vaccine uptake.

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— Maternal antibody in the fetus/infant
 — Antibody in the mother

Figure 1.

Model of the kinetics of maternal antibody transfer through the placenta from the mother to fetus prior to birth and the subsequent decay over time after birth. The panel on the right shows the effect of maternal vaccination on boosting both antibody levels in the mother and fetus such that higher levels are present at birth. As a result, antibody levels above the threshold of protection persist for a longer time, shortening the window of vulnerability to severe infection in the earliest period of life.

Table 1.

Current guidelines for maternal vaccination

Vaccine	Recommendation	Pregnancy Category
Inactivated influenza	Routine: any time during pregnancy in influenza season	B
TDaP	Routine: third trimester, and potentially second	B
HAV	If indicated for another reason	C
HBV	If indicated for another reason	C
Meningococcus	If indicated for another reason	B, C
Inactivated polio	If indicated for another reason	Not known
Rabies	If indicated for another reason	C
Inactivated typhoid	If indicated for another reason	C
HPV	Not recommended because of limited information	B
Pneumococcus	No recommendation because of limited information	C or data are insufficient
Japanese encephalitis	If high risk of exposure	B
Acellular anthrax	If high risk of exposure	D
Any live attenuated *	Avoid if possible	C, D, or contraindicated

Table adapted from the Advisory Committee on Immunization Practices (36).

Category B - no evidence of risk in studies; C - risk cannot be ruled out; D - evidence for fetal risk

Bolded vaccines are routinely recommended

Abbreviations: TDaP for tetanus, diphtheria, and acellular pertussis; HAV for hepatitis A virus; HBV for hepatitis B virus; HPV for human papillomavirus.

* Yellow fever and small pox can be considered if benefits outweigh risks