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Review

Vaccines and pregnancy: Past, present, and future

Sonja A. Rasmussen [a,*], Amelia K. Watson [b], Erin D. Kennedy [c], Karen R. Broder [d], Denise J. Jamieson [e]

[a] Influenza Coordination Unit, Office of Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA
[b] University of Georgia, Athens, GA, USA
[c] Immunization Services Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA
[d] Immunization Safety Office, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, GA, USA
[e] Division of Reproductive Health, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA, USA

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SUMMARY

Vaccination during pregnancy with certain vaccines can prevent morbidity and mortality in pregnant women and their infants. However, previous recommendations often focused on the potential risks of vaccines to the fetus when used during pregnancy. In recent years, additional data have become available on the absence of increased risks for adverse events associated with vaccines when administered during pregnancy and on their benefits to mothers and infants. Currently two vaccines – (i) inactivated influenza, and (ii) tetanus toxoid, reduced diphtheria toxoid and acellular pertussis (Tdap) – are recommended for use by all pregnant women by the United States Advisory Committee on Immunization Practices. Here we review the history of vaccination during pregnancy, the current status of recommendations for vaccination during pregnancy in the USA, and the potential for future advances in this area, including key barriers that must be overcome to accommodate these advances.

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1. Introduction

Vaccinations have had a substantial impact on decreasing morbidity and mortality in the USA and the world, and because of this impact, vaccinations are considered one of the top ten public health achievements in the twentieth century [1]. Vaccination during pregnancy has the potential to protect not only the mother, who may be at increased risk of morbidity and mortality from infectious disease, but also her infant through maternal antibodies that are transferred across the placenta during the second half of pregnancy. In addition, mothers vaccinated during pregnancy are less likely to transmit an infection to their infant after birth. Because of their immature immune systems, young infants are often particularly vulnerable to infectious diseases, and their ability to mount an immune response to vaccinations is often inadequate [2]. Past discussions regarding the use of vaccines during pregnancy often focused on potential risks to the infant, rather than on their benefits. In recent years, data have accumulated on the benefits of certain vaccines to infants when given to their mothers during pregnancy and on the absence of increased risks for adverse events associated with administration of vaccines during pregnancy. Here we review the history of the use of vaccines during pregnancy, what is known about the risks and benefits of vaccines during pregnancy on the mother and her infant, and the increasing emphasis in recent years on the benefits of certain vaccines when given during pregnancy. We also discuss future advances in the area of vaccines and pregnancy with the potential to improve maternal and infant health.

2. Past

The concept that vaccination during pregnancy could protect a newborn infant is not a new one. As early as 1879, it was recognized that newborn infants born to mothers who received 'Jennerian vaccination' (smallpox vaccination) during pregnancy were protected from vaccinia virus early in life [3]. The protective effect of maternally transferred antibodies on offspring was shown in 1892 using a mouse model [4]. In humans, it was recognized early in the twentieth century that many infants were resistant to some common infectious diseases during the first few months of life, especially if the mother was known to have had the disease [5], and this

* Corresponding author. Address: 1600 Clifton Road, MS A-28, CDC, Atlanta, GA 30333, USA. Tel.: +1 404 639 2297.
E-mail address: skr9@cdc.gov (S.A. Rasmussen).

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protection was correlated with the presence of maternal antibodies that were passed transplacentally from mother to the fetus [6].

Vaccination with tetanus toxoid during pregnancy has been used for many years to protect infants born to women in developing countries from neonatal tetanus. Observational studies in the 1960s provided evidence that neonatal tetanus could be prevented with tetanus toxoid vaccination during pregnancy, and a double-blind controlled trial subsequently provided confirmation: the neonatal tetanus death rate was 7.8 deaths per 100 births among infants born to mothers in the control arm, compared to no deaths among infants born to mothers who received two or three injections with tetanus toxoid more than 6 weeks apart [7]. These results subsequently led to the World Health Organization's Maternal and Neonatal Tetanus Elimination Initiative, a program focused on tetanus toxoid vaccination of pregnant and childbearing age women and promotion of hygienic deliveries. This initiative has resulted in a 93% reduction in neonatal deaths due to tetanus [8].

Much of the previous guidance on vaccinations during pregnancy emphasized concerns that vaccine exposure could place the fetus or infant at risk or could be perceived as doing so; however, as additional data on benefits of vaccines during pregnancy and on the absence of increased risks for adverse events after maternal vaccination have accumulated, that emphasis has changed. The history of recommendations by the Advisory Committee on Immunization Practices (ACIP), a group of experts that develops recommendations on use of vaccines in the USA [9], related to influenza vaccination during pregnancy is illustrative. Inactivated influenza vaccination of pregnant women and other groups at increased risk for influenza-associated complications was first recommended by the Surgeon General in 1960 [10], but many subsequent recommendations were less supportive. In 1990, the ACIP noted that an increased risk of influenza-associated complications in pregnant women had not been documented, except during pandemics. Thus, only pregnant women with underlying conditions were recommended to receive influenza vaccination, and waiting to vaccinate until after the first trimester was 'a reasonable precaution to minimize any concern over the theoretical risk of teratogenicity' [11]. In 1995, based on case reports and other studies, the ACIP recommendation was extended to women without underlying conditions, but only during the third trimester of pregnancy [12]. In 1997, after a study had shown an increased risk of influenza-associated hospitalizations among pregnant women during interpandemic periods, especially during the second and third trimesters [13], ACIP recommended second and third trimester vaccination [14]. The 1997 recommendations noted that many experts considered influenza vaccination to be safe in all trimesters of pregnancy, but that delaying vaccination until after the first trimester would avoid 'coincidental association' of the vaccine with first trimester spontaneous abortions [14]. In 2004, ACIP extended influenza vaccination to all pregnant women regardless of pregnancy trimester [15]. This recommendation followed the severe 2003–2004 influenza season during which many cases of severe influenza among pregnant women were reported and missed opportunities for vaccination were identified [16,17].

3. Present

Current ACIP recommendations regarding vaccination during pregnancy (Table 1) are based on considerations of the benefits of vaccination during pregnancy to mother and infant and the potential risks. Because of concerns about possible harm to the fetus, pregnant women have been typically excluded from premarketing clinical trials of medications and vaccines; thus, most data become available through postmarketing observational studies [43]. In developing recommendations for pregnant women, ACIP considers whether the vaccine is inactivated or live: inactivated viral or bacterial vaccines or toxoids have been considered to be safe during pregnancy, whereas live vaccines are considered potentially to be of concern because of the theoretical risk of transmission of the live vaccine component to the fetus [18].

3.1. Vaccines recommended for all pregnant women by ACIP

ACIP currently recommends two inactivated vaccines for all pregnant women, inactivated influenza vaccine and the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine. For both vaccines, evidence suggests that vaccination during pregnancy provides protection to the infant in early life because of maternally transferred antibodies [44,45].

Pregnant women are at increased risk for complications associated with seasonal and pandemic influenza because of changes in their immune, respiratory, cardiovascular and other systems during pregnancy [2,46]. Infants aged <6 months are also at increased risk of influenza-associated complications [2] and are unable to receive influenza vaccine because they fail to mount an adequate immune response; thus, maternal vaccination also protects these vulnerable infants from influenza [47]. Finally, infants born to women who become severely ill with influenza during pregnancy are at increased risk of adverse birth outcomes, such as low birth weight, small for gestational age, and preterm birth [47]. Consistent with these findings, recent studies have suggested that infants born to women who received inactivated influenza vaccine during pregnancy have a lower risk of these adverse birth outcomes, compared with infants born to unvaccinated women or to women who received another vaccine [47].

Although influenza vaccination has been recommended for pregnant women regardless of trimester since 2004, an increased focus has recently been placed on the importance of influenza vaccination during pregnancy. The finding that pregnant women were at higher risk for influenza-associated complications during the 2009 H1N1 pandemic likely played a role in this change in focus [48,49]. Shortly before the pandemic, results from a randomized controlled trial in Bangladesh were published that demonstrated a 63% reduction in influenza illness in infants in the first 6 months of life following maternal influenza vaccination during pregnancy, compared with infants born to women who had received pneumococcal polysaccharide vaccine [44].

Observational studies conducted to assess potential risks to the mother or infant associated with inactivated influenza vaccination (including with 2009 H1N1 vaccine) during pregnancy have been reassuring: no safety concerns have been identified among mothers or their infants [50–53]. However, data from the first trimester are limited; thus, future research should concentrate on these early pregnancy exposures [51,52].

After the introduction of vaccination against pertussis, the number of pertussis cases in the USA reported to the US Centers for Disease Control and Prevention (CDC) dropped substantially to fewer than 10 000 by 1965. However, gradual increases in the numbers of cases occurred in the 1980s, and in 2012, 48 277 cases were reported, the highest number since 1955 [54]. The highest incidence is reported in infants aged <1 year; among the 20 reported deaths in 2012, 16 were in infants aged <1 year and 15 were in infants aged <3 months [54].

Following licensure of Tdap vaccine by the US Food and Drug Administration (FDA) in 2005, ACIP recommended that women receive Tdap before pregnancy; for women not vaccinated before pregnancy, a dose of Tdap in the immediate postpartum period was recommended. ACIP also recommended vaccination of persons who have or who anticipate having close contact with an infant aged <12 months (a strategy called 'cocooning') as an approach to