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Review article

Influenza vaccination during pregnancy and its usefulness to mothers and their young infants

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ABSTRACT

The current approach to protecting pregnant women from influenza infection and serious influenza-related complications is vaccination. It is, therefore, critical to evaluate the vaccine's safety, immunogenicity, and protection efficacy during pregnancy. However, because it is affected by previous influenza vaccination or infection, the efficacy of the seasonal trivalent inactivated influenza vaccine is difficult to evaluate in pregnant women. The A/H1N1pdm pandemic in 2009 provided us with the opportunity to evaluate the immunogenicity of the influenza vaccine unaffected by previous vaccinations or infections. Vaccination with inactivated influenza virus during pregnancy elicited neutralizing antibody titers that were sufficient and comparable to those of naturally infected individuals. Furthermore, post-pandemic surveys provided a wealth of definitive information on vaccine efficacy and safety. In addition, transplacental transfer of antibodies following vaccination protected newborn infants against influenza infection. With reports showing the effectiveness of influenza vaccine during pregnancy, it is suggested that influenza vaccination benefits both mothers and their young infants.

1. Introduction

Pregnant women are at high risk for influenza infection and influenza-related complications and, in most countries, are recommended to receive an inactivated vaccine. Although previously vaccination tended to be avoided during the first trimester to ensure safety, its risks and benefits have been established and vaccination is now recommended at any stage of gestation. This review summarizes issues relevant to both the trivalent inactivated influenza vaccine (TIV) and A/H1N1pdm monovalent vaccine including clinical significance, safety and immunogenicity of influenza vaccine in pregnant women; persistence of maternal antibodies and transplacental transfer of antibodies following vaccination; and the effectiveness of vaccination for protecting mothers and their infants from influenza infection and adverse infection outcomes.

2. Influenza virus and vaccination

Influenza viruses possess a negative-sense, single-stranded RNA genome with envelope, and are classified according to the antigenicity of M1 protein and nucleoprotein into types A, B, and C. Human influenza is mainly caused by types A and B. Influenza virus type A is divided into subtypes based on the antigenicity of hemagglutinin (HA) and neuraminidase (NA), both of which protrude through the viral envelope. HA enables entry of the virus into the host cell cytoplasm by membrane fusion within endosomes and is highly immunogenic. NA cleaves sialic acid on the infected cell surface to facilitate progeny virion release from the plasma membrane [1,2].

Influenza infection is caused by influenza virus (an *Orthomyxoviridae* family member), which is known to cause an epidemic annually. Transmitted mainly via droplets, influenza primarily

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manifests as high fever, often accompanied by shivering, headache, malaise, myalgias, and arthralgias. Subsequently, respiratory tract symptoms become more prominent. In severe cases, pneumonia, acute respiratory distress syndrome (ARDS), secondary bacterial infection and neurologic complications such as encephalopathy and encephalitis can occur [3]. Historic pandemic outbreaks of influenza infection include Spanish flu (A/H1N1) in 1918–1919, Asian flu (A/H2N2) in 1957–1958, Hong Kong flu (A/H3N2) in 1968–1969, and influenza caused by swine-origin A/H1N1pdm in 2009 [2].

Influenza vaccination is particularly important for people who are at high risk for developing serious influenza-related complications. These high risk groups include: children younger than 5, particularly those younger than 2 years old; adults 65 years of age and older; pregnant women; and people who have underlying medical conditions such as asthma, diabetes, heart disease, cancer, and HIV infection [4].

TIV is annually used for induction of 3 seasonal strain-specific neutralizing antibodies, including 2 influenza A virus subtypes (ex. H1 and H3) and 1 influenza B virus. Currently, a quadrivalent formulation is available. Seasonal TIV induces limited cross-reactive neutralizing antibody responses. Consequently, 2005–2009 seasonal influenza vaccines were unable to protect against 2009 H1N1 influenza virus [5]. Since the influenza virus is highly prone to mutate, the epidemic influenza virus subtype or strain varies from year to year, and an annual vaccination suitable for epidemic strain is required for effective prevention.

There are several measures of whether an influenza vaccine has induced adequate immunity. The most commonly used assay is the HA inhibition test (HI test). Influenza virus binds to animal erythrocytes via HA and agglutinates it. Anti-virus antibody in serum, if present, reacts with virus antigen to inhibit this process. Parren et al. suggest that the HI titer represents the host defense against influenza virus infection [6]. Furthermore, Grund et al. showed in 2011 that the HI titer had a posirtive correlation with the neutralizing antibody titer [7]. Thus, it is conceivable that the HI titer serves as one of the measures of influenza vaccine effectiveness. An HI titer of 1:40 or higher is considered to be the level necessary for >50% reduction in the risk of influenza infection or disease [8].

3. Clinical significance of influenza vaccination for pregnant women

3.1. Pregnant women are at high risk for influenza infection and serious influenza-related complications

Severe cases of influenza infection in pregnant women were first reported in the 1918 Spanish flu pandemic, which led to death in 49% of the pregnant women who suffered from pneumonia [9]. It was also reported that half of the women of child-bearing age who died of influenza in the 1957 Asian flu pandemic were pregnant [10–12]. Subsequently it has been reported that pregnant women infected with seasonal influenza or pandemic influenza are generally at high risk for developing serious influenza-related complications [13–21]. Notably, Neuzil et al. demonstrated that hospitalizations for acute cardiopulmonary events during the influenza season are more prevalent in pregnant women than in postpartum women. The risk tended to be increased in the later period of gestation, with an odds ratio of 1.06 (95% confidence interval [CI]: 0.68–1.67) in the 1st to 7th weeks of gestation, 2.52 (1.74–3.65) in the 21st to 26th weeks of gestation, and 4.67 (3.42–6.39) in the 37th to 42nd weeks of gestation [15]. Dodds et al. reported that the proportion of women who were hospitalized for respiratory illness in the influenza season was higher during pregnancy, compared with the preceding year [16]. It has also been reported that pregnant women with comorbidities, including diabetes mellitus, respiratory disease, heart disease, renal disease, and anemia, appear to be at particularly high risk. Of the two studies on hospitalization of pregnant women for respiratory illness in the influenza season, one denied increased adverse perinatal outcomes [17], while the other demonstrated greater hospitalization burden and delivery complications (preturm labor, fetal distress, and cesarean delivery) in pregnant women [18]. In the 2009 A/H1N1pdm pandemic [19], pregnant women were more likely to be hospitalized for influenza infection, and some infected pregnant women died of pneumonia and subsequent ARDS [20,21]. As for the fetus, after the 2009 influenza pandemic, the risk of fetal death with or without vaccination was evaluated in 117,347 pregnancies. Haberg et al. concluded that the influenza virus infection was associated with increased risk of fetal death, and vaccination might reduce the risk of influenza-related fetal death [22].

3.2. Pregnancy-associated maternal physiological changes

The immune system of the mother develops tolerance to fetal non-self antigens. This is explained by the suppression of cellular immunity in pregnant women, leading to increased susceptibility to viral infections. The changes involve predominance of T helper 2 (Th2) and relative reduction in T helper 1 (Th1) in the decidual tissue and peripheral blood [23–25]. Yamaguchi et al. demonstrated that while the Th1/Th2 ratio in maternal blood varied among individuals during the first trimester, it tended to decline as pregnancy progresses [25]. In addition, mothers' cardiopulmonary functions dramatically change during pregnancy [26]. Oxygen consumption rises by 20% in pregnancy, about one-third of which is necessary for metabolism of the fetus and placenta. The increase in oxygen consumption is associated with a marked increase in ventilation of 40%, leading to a reduction in PaCO2 levels. This is presumably regulated by progesterone, and effective alveolar ventilation is increased by a reduction in residual volume. These physiological adaptations to pregnancy likely explain the vulnerability to viral infections of the respiratory system.

3.3. Use of anti-influenza virus agents during pregnancy

Anti-influenza virus agents are used to treat and prevent illness due to influenza. Especially in the initial stage of a new pandemic before a suitable vaccine becomes available, the use of these drugs could be effective means of protection against influenza virus. Currently, two classes of anti-influenza drugs are available: M2 ion channel blockers (amantadine and rimantadine) and NA inhibitors (zanamivir, oseltamivir, peramivir, and laninamivir). Several disadvantages, including the global prevalence of drug-resistant viruses and limitation on treatment efficacy to influenza A strains, preclude common use of adamantanes in clinical practice. Systematic reviews of general population studies show that treatment with NA inhibitors may reduce duration of symptoms, duration of hospitalization, and mortality compared with no treatment [27]. Evidence also shows the safety and benefits of NA inhibitors in pregnant women [28–34]. The use of NA inhibitors during pregnancy might be expected to prevent the spread of influenza infection as well as serious influenza-related complications in mothers.

4. Evaluation of safety, immunogenicity, and efficacy of influenza vaccination for pregnant women

To evaluate the effectiveness of influenza vaccination during pregnancy, it is essential to investigate whether vaccination for pregnant women can induce immune responses comparable to