The fetus and placenta might be perceived as nonself to the maternal immune system, which is considered to be altered to tolerate the fetus during pregnancy. One alteration is attenuation of cellular immunity, which can diminish resistance to viral infections in pregnant women [1]. In addition, physiological changes associated with pregnancy [2], such as increased oxygen consumption and ventilation, might explain the increased vulnerability to viral infections of the respiratory system. For these reasons, pregnant women are considered to be at high risk of influenza infection and influenza-related complications.

Major historical influenza pandemics such as Spanish influenza (H1N1) in 1918, Asian influenza (H2N2) in 1957 and Hong Kong influenza (H3N2) in 1968 suggested increased morbidity and mortality rates in pregnant women. In a series of cases from the 1918 pandemic influenza [3], approximately 50% of all pregnant women developed pneumonia, and more than half of these died, accounting for 27% of the total deaths. During the 1957 pandemic, 50% of women of reproductive age who died of influenza were pregnant [4].

In 2009, the novel influenza A (H1N1) virus infection was reported worldwide to be the cause of a widespread outbreak of acute febrile respiratory illness. Although the severity of this disease ranged from mild to severe, little was known about its impact on pregnant women. The CDC has summarized 34 cases of pregnant women with 2009 pandemic influenza A (H1N1) virus infection in the USA [5]. The rate of hospitalization for infection in pregnant women was higher than that in the general population. Six of the pregnant women died, and all of these had developed pneumonia and subsequent acute respiratory distress syndrome requiring mechanical ventilation. Therefore, medical staff should consider pregnant women to be at high risk of severe illness after infection with 2009 pandemic influenza A (H1N1) virus.


As pregnant women are at increased risk of influenza infection and influenza-related complications, immunization with inactivated influenza vaccine during the influenza season is recommended. Vaccination during pregnancy is considered to provide benefits for both the mothers and their young infants. In 2009, the novel influenza A (H1N1) virus was reported worldwide to be the cause of a widespread outbreak of acute febrile respiratory illness. The efficacy and efficiency of monovalent vaccine against 2009 H1N1 influenza virus during pregnancy has already been confirmed in several studies. This article provides further useful information regarding the persistence of maternal antibodies and the transplacental transfer of antibodies following vaccination by comparison with natural influenza infection.

**Keywords:** influenza • passive immunity • pregnancy • transplacental transfer • vaccination • 2009 pandemic influenza A (H1N1) virus
2009 H1N1 influenza virus during pregnancy (vaccinated) and ten control women without infection or vaccination (control) [6]. The infected group women were diagnosed by either the rapid antigen influenza A test or a PCR test on respiratory specimens during the 2009–2010 influenza season. The vaccinated group women did not develop influenza-like illness during pregnancy. Maternal and umbilical cord venous blood samples in each group were collected at delivery, and hemagglutination inhibition assays for 2009 H1N1 influenza virus were performed. Hemagglutination inhibition antibody titers ≥ 1:40 are regarded as effective.

The mean maternal antibody titers at delivery in both the infected and vaccinated groups were at or above the threshold. By contrast, control group women had antibody titers well below the threshold. Although four patients in the infected group were also vaccinated, their antibody titers were not significantly increased compared with either the total infected group or the vaccinated women.

The antibody to influenza virus generated after vaccination is generally short-lived, and maintenance of the antibody titer depends on the time elapsed since vaccination. There was a linear decline over time in maternal antibody titers after vaccination and natural infection. The rate of decline in antibody titers was similar in both the infected and vaccinated groups.

The antibody titers in the umbilical cord blood correlated with those in the maternal blood, suggesting efficient transplacental transfer of antibodies targeting the 2009 H1N1 influenza virus. This efficiency of transplacental antibody transfer was similar for both groups.

Discussion

Immunization with inactivated influenza vaccine is the most effective method to prevent influenza infection and influenza-related complications, particularly in pregnant women. The CDC’s Advisory Committee on Immunization Practices has recommended that all women who are pregnant or will be pregnant during influenza season should be vaccinated [7]. This recommendation was based on studies showing the increased risk of hospitalization for respiratory illness in pregnant women, as well as the demonstrated efficacy and safety of vaccination during pregnancy.

Regarding the use of vaccine against 2009 H1N1 influenza virus, the CDC’s Advisory Committee on Immunization Practices identified pregnant women as one of the five initial target groups for vaccination efforts [8]. A single dose of monovalent vaccine against 2009 H1N1 influenza virus showed a favorable immune response in pregnant women [9,10]. The efficiency of vaccination during pregnancy was not influenced by maternal immunological status or by the gestational stage when the vaccine was received [9]. The safety of vaccination against 2009 H1N1 influenza virus during pregnancy has been reported in a recent study [11]. There was no increase in spontaneous abortion or major malformations among the fetuses of women who were vaccinated at any time during pregnancy or ≤ 4 weeks prior to conception.

Maternal influenza vaccination might provide protection for not only the vaccinated women, but also the infants born to these mothers, via transplacental transfer of anti-influenza antibodies [12,13]. Seasonal influenza vaccine reduced the risk of influenza illness and hospitalization for an influenza-like illness among infants up to 6 months of age. Increased blood anti-influenza antibody titers were confirmed in infants through 2–3 months of age.

Data from stored serum samples from people who received vaccination with recent (2005–2009) seasonal influenza vaccines suggest that seasonal vaccines are unlikely to provide protection against 2009 H1N1 influenza virus [14]. Before vaccination, a cross-reactive antibody to the 2009 H1N1 influenza virus was detected in 6–9% of people aged 18–64 years and 33% of those aged > 60 years. In our study [9], the pre-vaccination antibody positivity rate among 124 pregnant women demonstrated a similar rate (7.2%). For the novel influenza A (H1N1) virus, few women of childbearing age had pre-existing antibodies and the initial vaccine formulation available was monovalent, in contrast to the trivalent seasonal vaccines. Therefore, the emergence of the 2009 pandemic influenza was a rare opportunity to evaluate the immunogenicity of the influenza vaccine without the influence of past vaccinations.

This study examines the persistence of maternal antibodies and the transplacental transfer of antibodies following vaccination among pregnant women. Unfortunately, the number of participants was rather small. The baseline antibody titers prior to vaccination were not measured and maternal blood samples were collected only once, at delivery. Each subject had a different period between vaccination and blood draw, depending on the gestational stage when the vaccine was administered. The mean maternal antibody titers in the infected and vaccinated groups were at least 1:40, but these antibody titers tended to decrease over time after infection and vaccination. Most of the women who received the vaccination more than 100 days before delivery did not have an effective antibody titer. The number of days taken for the antibody titer to fall below 1:40 was approximately 150 days in vaccinated women and 225 days in infected women. In terms of humoral immunity, vaccination would have an approximately 150-day period of effectiveness at preventing influenza infection. Considering the linear relationship between antibody titers in the maternal and umbilical cord blood, antibody transfer to the fetus would also decrease over time after vaccination. Our study findings demonstrated a similar tendency: antibody titers in the maternal and umbilical cord blood clearly fell more than 20 weeks after vaccination.

These data are helpful to evaluate whether maternal vaccination confers sufficient passive immunity to the newborn. As a result of inactivated influenza vaccine not being indicated for infants younger than 6 months of age, antenatal immunization might be a useful strategy.

Five-year view

Reports such as this are valuable because there might not otherwise be opportunities to see one-to-one correspondence between influenza virus and its vaccine. To understand in more detail the correlation between vaccination and natural infection, information about elevated antibody titers after infection and
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the presence or absence of antiviral medication in the natural infection group would be helpful. The efficiency of transplacental transfer of antibodies should be the same in both vaccinated and naturally infected pregnant women. If the antibody titer is low in the vaccinated women, additional vaccination during the antepartum period might be an efficient approach to protect young infants.

Key issues

- Pregnant women are at increased risk of severe complications from influenza infection, including the 2009 pandemic influenza A (H1N1) virus infection.
- Immunization with inactivated influenza vaccine is the most effective method to prevent influenza infection and influenza-related complications in pregnant women.
- Maternal influenza vaccination might provide protection for not only the vaccinated women, but also the infants born to these mothers, via transplacental transfer of anti-influenza antibodies.
- Because inactivated influenza vaccine is not indicated for infants younger than 6 months of age, antenatal immunization might be a useful strategy.
- To protect young infants most effectively, women vaccinated in early pregnancy might need an additional vaccination during the antepartum period.

References

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