

Anti-Influenza Antibody Level in Mother-Infant Pairs Depending on Trimester of Vaccination of Pregnant Women Using Immunoadjuvant Vaccine

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Abstract

Introduction: Anti-influenza vaccination of pregnant women using a subunit vaccine is an effective method to prevent pregnancy complications and fetal disorders. The efficacy of immunoadjuvant vaccines, as well as the production of IgG antibodies depending on the vaccination trimester requires further investigation.

Materials and Methods: 48 mothers were vaccinated against influenza in the II and III trimesters. Grippol plus vaccine was used. Each dose of the vaccine contains antigens of A and B strains and adjuvant Polyoxidonium 500 µg. Hemagglutinine-inhibiting antibodies level (HIAb) were evaluated in sera of mothers and babies at different time points after vaccination using a standard reaction of hemagglutination inhibition, in accordance with criteria developed by the committee for proprietary medicinal products (CPMP).

Results: Within 1 month after vaccination, the seroprotection rate against all influenza strains was above the threshold level of 140 in more than 70% of pregnant women. After delivery, the seroprotection level in the group vaccinated in the III trimester was similar for A/California/7/2009/H₁N₁/v and A/H₃N₂ strains, and differed for B strain. The percentage of infants with seroprotection was 55.5%-59.3%, while in their mothers, the respective value was 74.1%-81.5% ($p < 0.05$). Within 3 months, the number of infants with seroprotection against influenza strains in mother-infant pairs was decreased: A/California/7/2009/H₁N₁/v, A/H₃N₂, B. In infants and the seroprotection level disappeared completely by 6 months. The time of vaccination of pregnant women had no effect on these parameters. In mothers, the protective levels against vaccine strains were found in 46.2%-65.4% of cases after delivery.

Conclusion: Vaccination of pregnant women in the II and III trimesters using Grippol plus results in production of antibodies at levels complying with CPMP criteria. No difference in production and transplacental transfer of IgG antibodies against influenza was found in mother-infant pairs vaccinated in different trimesters of pregnancy.

Introduction

In 2009-2010, the pandemic of influenza demonstrated that pregnant women are still very susceptible to severe complicated infection with unfavorable pregnancy outcome and impact on infants. Among the available methods of prevention, vaccination is the most effective one. Recent literature reviews demonstrate safety and efficacy of influenza vaccination in pregnant women using inactivated vaccines, thus confirming previous recommendations related to extensive introduction of vaccination into healthcare practice and the need in further studies for improvement of the immune-based prophylaxis technologies in this population [1,2]. The epidemiologic efficacy of influenza vaccine was demonstrated in pregnant patients: infant's hospitalization rate during the first months of postnatal period was decreased by 45-48% as compared to those born by non-vaccinated mothers [3]. The level of influenza protection in infants is influenced by multiple factors mediating the placenta transfer of maternal IgG antibodies [4]. One of these factors is the amount of general and specific IgG to particular vaccine antigens in pregnant patients. Influenza vaccination is recommended in the II and III trimesters of pregnancy, or even during the first months of normal pregnancy under certain conditions; therefore the levels of trans-

placental specific IgG antibodies in infants, as well as their persistence in future will vary.

The objective of this study was to determine the influenza antibody levels in mother-infant pairs depending on the trimester when vaccination was performed.

Materials and Methods

48 pairs of mothers and infants were monitored: mothers were vaccinated against influenza in the II (27 females) and III (21 females) trimesters of pregnancy in 2010-2011 and 2011-2012 using vaccines with similar levels of antigens of A and B influenza strains. Grippol plus vaccine, a trivalent, inactivated, polymeric subunit vaccine (manufactured by Petrovax Pharm LLC, Russia), was used for immunization. Each dose of vaccine (0.5 ml) contains antigens of the following strains: A/California/7/2009/H₁N₁/v-like (5 µg), A/H₃N₂/ (Victoria)-like (5 µg) and B/Brisbane-like (5 µg) flu, as well as a water soluble adjuvant Polyoxidonium (azoxymere bromide) (500 µg). The vaccine contains no preservatives.

In Russia, due to high risk of complications and increased maternal and antenatal mortality rate associated with the current pandemic,

influenza vaccination or pregnant women was officially recommended in 2009. Raw data on the effect of Grippol Plus on pregnant women and the fetus were based on animal studies alone. Similar approach to vaccination in pregnancy was adopted in other countries [5].

The study was conducted according to the Clinical Studies Protocol approved by the I.I.Mechnikov Scientific Research Institute of Vaccines and Sera under the Russian Academy of Medical Sciences (Moscow, Russia). It was a single-arm, blind, placebo-controlled, parallel-group and comparative study of 48 pregnant women (aged 23.3 ± 0.4 years old).

Normal, physiological course of pregnancy was established both prior to vaccination and after it. Physiologic labors occurred at gestation weeks 39-40. Cases of miscarriage were not reported. Clinical condition of newborns (Apgar scale) was 8-9 scores in 42 neonates (87.5%). Mean body weight of neonates was 3546.9 ± 168.7 g, their body length was 50.8 ± 0.94 cm.

Hemagglutinine-inhibiting antibodies level (HIAb) was evaluated in mothers' and infants' sera at different time points after vaccination using a standard hemagglutination inhibition reaction technique. According to criteria developed by Committee for Proprietary Medicinal Products (CPMP) (Protocol CPMP/BWP/214/96) [6], the following parameters were used to evaluate the antigen activity of the vaccine.

Seroprotection rate – evaluation of percentage of patients with HIAT protective titer $\geq 1:40$ prior to vaccination and after it (target level $\geq 70\%$ within 21 days after vaccination)

Seroconversion rate or vaccine immune activity – relative number of vaccinated patients with a 4-fold increase HIAT level within 21 days after vaccination compared to baseline found in all immune protected patients (target level $\geq 40\%$)

Seroconversion factor (mean geometric titer) – elevation of mean geometric HIAT titers by day 21 compared to baseline level, expressed as a grade of increase (target level ≥ 2.5)

Serum positivity level – total number of patients with HIAT titers $\geq 1:20$

The dynamics of antibody levels was evaluated by the change of mean geometric titer of antibodies log (log₂ mean geometric titer) in compared groups.

Statistical software AtteStat 10.2 integrated into Microsoft excel 2003 was used for statistical data analysis. Significance of numeric difference was based on a 0.95 confidence interval; Wilcoxon's non-parametric criteria were used to calculate difference in non-related samples (W).

Results

No adverse events that could possible affect health were found during the follow up of women immunized in the II and III trimesters of pregnancy.

Immunogenicity parameters evaluation demonstrated that the seroconversion rate and the seroconversion factor to 3 strains of influenza within 1 month complied with CPMP criteria. Prior to vaccination, the seroprotection rate to various influenza strains was detected in 3.7%-22.2% women in the II trimester and in 8.7%-26.1% women in the III trimester.

Within 1 month after vaccination, an increase of seroprotection level was reported reaching the target level recommended by CPMP. At that, in women vaccinated in the II trimester, the seroprotection rate almost did not change 3 months later. Graduated decrease in the seroprotection rate against all 3 influenza strains was reported in postpartum period in both groups; statistically significant difference was reached within 6 months ($p < 0.01$).

In infants the transplacental protective levels of antibodies against vaccine strains were detected within 2-3 days after delivery: they were 52.3% to 61.9%, irrespective of the trimester when the vaccination was performed. Within 3 months, the decreased seroprotection rate was reported: it reached 14.2%-24.0% for all vaccine strains, and no significant difference between groups was reported. At the age of 6 months, no demonstrated an antibody level of $1 \geq 40$. It should be taken into consideration, that the described criterion for evaluation of the antibody protective level against the influenza virus is a standard for vaccination of adults. A conditionally protective titer $1 \geq 20$ against all influenza strains found in 16.7%-38.8% of infants at the age of 6 months may be considered a protective titer for this category of infants.

Evaluation of the mean geometric antibody titer in pregnant patients prior to vaccination demonstrated comparable low levels. 1 month later, the increase in antibody levels against all vaccine influenza strains was reported in pregnant women. In women vaccinated at the III trimester, the mean geometric antibody level against A/California/7/2009/H₁N₁/v strain was higher ($p < 0.05$) as compared to that in women vaccinated at the II trimester. Subsequent slow decrease of mean geometric antibody level was reported; at that, no significant difference between groups was found.

In infants, similar mean geometric antibody levels against all influenza strains were found within 2-3 days after birth; they were lower as compared to levels found in mothers ($p < 0.05$). One mother-infant pair was an exception: the mother in a subgroup evaluating antibody levels against influenza strain B was vaccinated at the II trimester, and no significant difference was found. Later the mean geometric level of antibodies against all vaccine strains decreased in all infants, irrespective of the vaccination trimester (from 7.23 ± 0.22 to 8.49 ± 0.20 –II trimester, from 7.94 ± 0.18 to 11.22 ± 0.19 –III trimester; $p > 0.05$).

Discussion

While comparing the immunogenicity of influenza vaccine depending on the vaccination trimester based on the seroconversion rate and the conversion factor, we found no significant difference for studied viral strains.

The seroprotection rate against all influenza strains in both groups of vaccinated females within 1 month exceeded the $1 \geq 40$ in more than 70% of patients; therefore, this parameter complied with CPMP requirements. In postpartum period, similar decrease of seroprotection against 3 strains was reported irrespective of the vaccination trimester.

Evaluation of the seroprotection rate in mother-infant pairs demonstrated similar levels of protection against A/California/7/2009/H₁N₁/v and A/H₃N₂ strains in the group vaccinated at the III trimester within 2-3 days after labors. The percentage of infants with seroprotection born by mothers vaccinated at the II trimester was over 50%. However, it was lower ($p < 0.05$) as compared to their mothers. Within 3 months, similar decrease of number of infants with

seroprotection against all influenza strains was reported in mother-infant pairs irrespective of the vaccination trimester. The seroprotection rate in infants was 2.5-fold lower as compared to their mothers ($p < 0.01$); disappeared completely by 6 months, however, it was still found in 20% of infants, thus confirming data reported by other authors [7]. Within 6 months after birth, the number of seropositive infants against vaccine strains A was 24.0%-38.8%, while the number of seropositive babies against strain B was 16.7-20.0%. The time of vaccination had no effect on these parameters.

Analysis of relative distribution of influenza antibody levels into low (1:20-1:40), medium (1:80) and high ($\geq 1:160$) titers demonstrated that only in 7% of infants born to mothers vaccinated at the II trimester have high levels of antibodies against strain A/California/7/2009/H₁N₁v and strain B, and in 3.5% of these infants, high levels of antibodies against strain A/H₃N₂ were detected. No other differences in antibody levels in mother-infant pairs were found.

Evaluation of mean geometric antibodies titers in studied groups of pregnant patients demonstrated significant level increase during the post-vaccination period as compared to baseline. Despite early vaccination during the II trimester, the mean geometric antibodies level in these females was similar to that found in females vaccinated in the III trimester. During the next 6 months, gradual decrease of mean geometric antibody level against all influenza strains was reported irrespective of the time of vaccination.

In mother-infant pairs, the mean geometric antibody levels in infants was lower; the difference becomes more pronounced by months 3 and 6 after birth irrespective of the time of vaccination ($p < 0.01$).

Therefore, vaccination in the II and III trimesters results in similar development and maintenance of mean geometric antibody levels against vaccine influenza strains. Conditionally protective levels are detected within 6 months. In infants, the mean geometric antibody titers were lower as compared to maternal ones and conditionally protective levels were found within 3 and 6 months after birth.

Therefore, anti-influenza vaccination in the II and III trimesters of pregnancy using an immunoadjuvant vaccine Grippol plus with 3-fold decreased (5 μ g each) viral antigens level is associated with synthesis of antibodies at similar levels which comply with CPMP criteria.

Evaluation of post-vaccination antibodies levels in mother-infant pairs demonstrated no significant difference in antibody level maintenance. However, single cases of high levels of HIAt placenta transmission ($\geq 1:160$) were reported in infants born to mothers vaccinated in the II trimester. During the first days after birth, protective levels of antibodies were found in a half of infants, while within 3 months, it was found in 1/5 of infants only. Despite the lack of protective antibody levels (1:40) in infants at the age of 6 months, seropositivity to various influenza vaccine strains was found in 16.7%-38.8% of these infants (titers $\geq 1:20$) irrespective of the time of vaccination of their mothers. In women, protective titers against vaccine strains were found in 46.2%-65.4% of cases within 6 months of postpartum period; therefore, they were found approximately in one half of vaccinated females irrespective of the vaccination trimester.

Therefore, no difference in IgG antibodies production and placenta transfer was found in mother-infant pairs vaccinated during different trimesters of pregnancy.

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