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RESEARCH PAPER

Prospective randomized open-label comparative study of immunogenicity after subunit and polymeric subunit influenza vaccines administration among mothers and infants

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ABSTRACT

Pregnant women are risk group for influenza infection. Results of new subunit vaccines application have not been studied enough. Prospective, randomized, open-label comparative study of subunit (Agrippal) and polymeric subunit (Grippol plus) vaccines. 42 pairs of mothers-infants were participated in the study. Protective antibodies (≥ 1:40) to different influenza strains were registered on day 1 after the birth on the same level as 53% of cases in pairs mothers-infants after immune adjuvant polymeric subunit and subunit vaccines administration. There were the same level of protective antibodies (AB) among mothers after 3 month, but transplacental antibodies decreased among infants and registered in the 13–22% cases of Grippol plus group and 31–43% cases in Agrippal S1 group. AB titre to influenza virus A/H1N1/pdm09 and A/H3N2/in pairs mothers-infants were the same in both groups in first days after birth, but AB levels to B strain were lower among infants without regard to vaccine. There is no difference in AB titres among infants of both groups at 3 month of age, but their levels were twice lower versus initial data. An immune adjuvant polymeric subunit as well as subunit vaccines application in pregnant women forms protective AB in pairs mothers-infants.

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vaccine; influenza; polymeric-subunit; pregnant women

Introduction

Influenza is one of the most common viral infections resulting in pregnancy complications (premature birth), foetal disorders (congenital abnormalities, central nervous and respiratory systems disorders) and disorders of postnatal development (fetal growth retardation).[1] Therefore, prophylactic vaccination of pregnant patients is a priority adopted by the WHO and other scientific and medical organizations from various developed countries.[2] Polymeric immune modulate medicine "Polyoxidonium" (Azoximera bromide), which can increase antibody response, was added in dose of 500 mcg to a subunit vaccine to enhance it's efficacy. Thanks to Polyoxidonium the content of virus antigens was decreased up to 5 mcg, which is three times lower compare with other manufacturing vaccines. However, the efficacy remains high, among at-risk groups for influenza disease. Previous findings demonstrating the safety of vaccination in pregnant patients and the high immunogenicity of inactivated vaccines, similar to the findings for non-pregnant patients, were supported by recent studies.[3–5] Similar post-vaccination levels of antibodies to influenza were found in the mothers and infants.[6] The correlation between the level of serum IgG antibodies to influenza in infants and the time of influenza infection in the mother was demonstrated.[7] Therefore, the trans-placental transmission of antibodies targeting various strains of influenza can protect infants throughout their first months of life. Infants younger than 6 months old with a confirmed diagnosis of influenza born to vaccinated mothers have been shown to have a 91% lower risk of hospitalization compared to infants born to non-vaccinated mothers.[8]

The level of protection against influenza in infants younger than 6 months is most likely associated with baseline maternal antibody levels prior to labour. The administration of modern subunit vaccines during pregnancy is associated with the transplacental transmission of antibodies to the infant; however, their levels depend on multiple factors, including placental conditions, trimester when vaccinated, and the vaccine used. The administration of new adjuvant vaccines has been associated with better specific immunity in infants (6–36 months) and adults (18–64 years) with chronic diseases.[9–11] The search of articles, published in the period from 2002 till 2012 based on key words influenza vaccination, pregnancy, immunoadjuvant vaccines, in "Pubmed" system on June 2012 didn't reveal such publications. The adaptive immunity to influenza in pregnant patients received subunit vaccines, the ratio of mother-to-infant trans-placental antibodies and the preservation of these antibodies in infants throughout the first months of life have not yet been described enough in publications.

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Study objective

Evaluation of post-vaccination immunity to influenza in mothers and infants after the administration of an adjuvant polymeric subunit vaccine and a subunit vaccine during pregnancy.

Results

We registered the incidence of influenza-like respiratory infection in 79 mother-infant pairs. No difference in infection frequency was found during follow up in these pairs – both during pregnancy and within 3 months after birth.[12]

The results of the study showed that initially before administration of immunoadjuvant vaccine in group I of pregnant women antibody titre ≥ 1:40 to strains A/California/7/2009 (H1N1)pdm09-like virus, A/Perth/16/2009 (H3N2)-like virus, B/Brisbane/60/2008-like virus was registered respectively in 9.5%, 19.0%, 23.8% cases, and in group II of pregnant women – in 16.2%, 18.9%, 48.7% cases. It means that these women could come through the influenza before impregnation, but everyone denied influenza illness as well as vaccination against influenza one year before the present pregnancy. At 1 month after immunization antibodies in protective means among pregnant women to the corresponding influenza strains were 72.5%, 87.5%, and 90.0%, that indicates the immunogenicity of the vaccine. In the group II of vaccinated with non-adjuvanted vaccine post-vaccination antibodies also increased to the corresponding strains A/California/7/2009 (H1N1)pdm09-like virus, A/Perth/16/2009 (H3N2)-like virus, B/Brisbane/60/2008-like virus (75.6%, 68.8% and 94.5% respectively). However, post-vaccination antibodies to strain A/Perth/16/2009 (H3N2)-like virus did not reach the level of immunogenicity (at least 70%) corresponding to the recommended by CPMP.

Antibodies for protection against three strains of influenza virus were evaluated in hemagglutination inhibition reaction. The serum evaluation for group I (motherinfant pairs vaccinated with Grippol Plus during pregnancy) at days 2–3 after birth demonstrated similar levels of protective antibodies (≥ 1:40) for all influenza strains, ranging from 53.1% to 78.4% (Table 1). The number of children with protective levels of antibodies was lower than the number of mothers with protective levels; however, the difference was not significant ($p \geq 0.05$).

Similar changes in the protective antibody levels were demonstrated in group II (mother-infant pairs vaccinated with Agrippal S1), ranging from 57.7% to 91.9% for various influenza strains (Table 1).

Three months later, in group I, the post-vaccination levels of protective antibodies against 3 influenza strains, detected in hemagglutination inhibition reaction, in the mothers were similar to the levels detected within 2–3 days after birth (54.3%, 71.4% and 74.3%, respectively) ($p > 0,05$). The number of infants with protective levels of antibodies decreased from 53.1% to 21.9% ($p < 0,01$) for the A/H1N1/pdm09 strain, from 62.5% to 12.5% ($p < 0,01$) for the A/H3N2/strain, and from 59.4% to 15.6% ($p < 0,01$) for the B strain. It demonstrates the physiological decrease of mother's antibodies due to their catabolism.

Three months later, in group II, the post-vaccination levels of protective antibodies against the 3 influenza strains in the mothers were similar to the levels detected within 2–3 days after birth (62.2%, 51.4% and 72.9%, respectively) ($p > 0,05$). A similar decrease in the number of infants with a protective antibody titre was found: strain A/H1N1/pdm09, from 61.5% to 34.6% ($p < 0,01$); strain A/H3N2/, from 57.7% to 30.8% ($p < 0,05$); and strain B, from 80.8% to 42.3% ($p < 0,01$). This decrease of antibodies level is physiological too.

Therefore, on the first day after birth, the titres of protective antibody targeting various influenza strains were found in 53.1% of patients from group I (who received the polymeric subunit influenza vaccine during trimesters II and III) and in 57.7% of patients from group II (who received the subunit influenza vaccine during trimesters II and III); no significant difference was found for the mother-infant pairs. Within 3 months after birth, similar levels of protective antibodies were found in the mothers from both groups; for the infants, the titres of the trans-placental post-vaccination antibodies to all of the influenza strains were decreased due to physiological catabolism, independent of the vaccine used. In group I (vaccinated with polymeric subunit vaccine), protective antibodies against various influenza strains were found in at least in 12.5% of infants; in group II (subunit vaccine was administered), the percentage of infants was at least 30.8% ($p < 0.05$).

The rate of increase in the mean geometric antibody titre and the duration of its persistence are important parameters of vaccine immunogenicity, detected in hemagglutination inhibition reaction (Table 1). Regarding the mean geometric antibody titres within 2–3 days after birth for the mother-infant pairs receiving Grippol Plus during pregnancy, similar levels of antibodies to the influenza strains A/H1N1/pdm09 and A/H3N2/were found. However, for the infants, the mean geometric antibody titre for influenza strain B was lower than that in the mothers ($p < 0,05$).

In females receiving the Agrippal S1 vaccine during pregnancy, similar changes of antibodies titres as in Grippol plus group were detected.

Within 3 months after birth, in group I, a decrease in the mean geometric titre for antibodies for each of the strains was found only in the children [12.59 ± 0.22 ($p < 0.01$) for the A/H1N1/pdm09; 14.47 ± 0.18 ($p < 0.01$) for the A/H3N2/strain; 13.50 ± 0.21 ($p < 0.01$) for strain B] (Table 1). No significant changes in the mean geometric titre was found for the mothers compared with the early post-natal period; for the children, the titres of antibodies to each influenza strain were lower than those in the mothers ($p < 0.05$).

Within 3 months after birth, in group II (women who received the Agrippal S1 vaccine during pregnancy), the mean geometric titres for the antibodies to each influenza strain were decreased compared with the initial level [27.32 ± 0.38 ($p < 0.05$) for the A/H1N1/pdm09; 23.78 ± 0.59 ($p < 0.05$) for the A/H3N2/strain; 47.57 ± 0.45 ($p < 0.01$) for the B strain]. Similar decreases in the mean geometric titres of the antibodies for the influenza strains were found in the children [20.0 ± 0.55 ($p < 0.05$), 10.91 ± 0.44 ($p < 0.01$) and 18.34 ± 0.4 ($p < 0.01$)]. Despite

Table 1. Post-vaccination anti-influenza immunity in the mother-infant pairs.

		Group I – Grippol Plus (n = 42)						Group II – Agrippal S1 (n = 37)					
		A/California/7/2009 (H1N1)pdm09-like virus		A/Perth/16/2009 (H3N2)-like virus		B/Brisbane/60/2008-like virus		A/California/7/2009 (H1N1) pdm09-like virus		A/Perth/16/2009 (H3N2)-like virus		B/Brisbane/60/2008-like virus	
Parameter	Time	Mother	Infant	Mother	Infant	Mother	Infant	Mother	Infant	Mother	Infant	Mother	Infant
Seropositive level (%) (hemagglutinin inhibition titre ≥ 1:40)	2–3 days after birth	64.8	53.1	78.4	62.5	75.7	59.4	67.6	61.5	62.2	57.7	91.9 ×	80.8 ×
	3 months after birth	54.3	21.9 **/Δ	71.4	12.5 **/ΔΔ	74.3	15.6 **/ΔΔ	62.2	34.6 **/Δ	51.4 ×	30.8 ×/*/Δ	72.9	42.3 ×/**/Δ
Geometric mean antibody titre (log_2)	2–3 days after birth	38.19± 0.24	25.78± 0.26	45.95± 0.25	31.74± 0.17	54.01± 0.27	31.02± 0.19 Δ	42.38± 0.39	37.03± 0.65	34.82± 0.68 ×	23.78± 0.40	85.74± 0.28 ×	33.64± 0.50 ΔΔ
	3 months after birth	30.31± 0,26	12,59± 0.22 **/Δ	30.31± 0.21	14.47± 0.18 **/Δ	44.89± 0.23	13.50± 0.21 **/Δ	27.32± 0.38 *	20.00± 0.55 *	23.78± 0.59 *	10.91± 0.44 **/Δ	47.57± 0.45 **	18.34± 0.40 **/Δ

Notes:
×- $p < 0.05$ – comparing the groups
* – $p < 0.05$ ** – $p < 0.01$- for the intra-group changes
Δ – $p < 0.05$; ΔΔ- $p < 0.01$ – for mother-infant differences

of mother's antibodies levels, the levels of transplacental, post-vaccination antibodies to the influenza strains A/H3N2/and B in the infants were significantly lower than the maternal levels ($p < 0.05$), what is a consequence of their physiological catabolism.

Discussion

The Grippol Plus vaccine has been used in Russia for 20 years for vaccination of children from 6 months, adolescents, adults, elderly people and immunocompromised patients. An assessment of its safety and effectiveness was carried out in numerous studies.[13–27] Unlike other domestic vaccines it was the first vaccine which was recommended by the Ministry of Health of the Russian Federation in 2009–2010 for the mass vaccination of pregnant women on II and III trimester of gestation initially as a monovalent (containing only a pandemic strain of the influenza virus) and then as a trivalent vaccine. Prior to the current study the vaccine had not been tested on pregnant women, just pre-clinical studies in pregnant animals in which its safety and no teratogenic effect on fetal development were proved. Clinical observations of the trivalent Grippol Plus vaccine for the mass vaccination of pregnant women in the Russian Federation from 2010 till present time demonstrated no one case of a serious unusual reaction associated with the administration of the drug. With regard to assess its impact on biochemical indicators, the cytokine profile, pregnancy hormones, fetoplacental complex, intrauterine fetal development, the state of health of newborns, physiological development of children of the first 6 months of life it was studied in accordance with the protocol of the study and is reflected in many publications.[28–40] In this article only the immunogenicity of the vaccine in mother-child pairs is described that is rarely found in the world publications.

It is important to explore the problem of protective action of new class of polymeric subunit vaccines against influenza to pregnant women and their infants. We conducted open-label comparative randomized study focused on changes of antibodies titres against influenza (strains A(H1N1)pdm09, A/H3N2/and B) among pregnant women, who was vaccinated in the II and III trimester of pregnancy with polymeric subunit vaccine "Grippol plus" and subunit vaccine "Agrippal S1". Blood samples collected from mothers after vaccination and birth as well as their infants on 2–3 day after birth and 3 month later. Study design have been chosen to characterize the changes of mother's antibody levels ant their catabolism in infants.

Obtained results are the similar to previous data regarding the immunogenicity of influenza vaccines among pregnant women compare with non-pregnant women.[3–7] Despite of less antigen content, polymeric subunit vaccine "Grippol plus" demonstrated not less efficacy than subunit vaccine "Agrippal S1".

Transplacental antibodies to all strains of influenza virus were registered on protective level in infants on the moment of birth and in early postnatal period as well as in mothers regardless of vaccine type. Both groups demonstrated the same level of protective antibodies, apart from higher level of women and infants in pairs of group II. It is demonstrated the same mechanism of action for both vaccines focused on B-cell stimulation and antibodies forming. The range between vaccinations was about 1 month, because blood samples were collected from mothers during childbearing, and all children were born at time. The antibodies level became on maximum level by that time, therefore this range didn't influence in obtained results.

As it was described early in studies of other authors[3-7] there is a decrease of protective antibodies level against influenza after birth up to their total disappearance by 6 month. It is related to the fact that a half-life period of IgG is about 3 weeks, their uptake with mother's milk cant supply their deficit, but speed down the concentration rate. At the same period the decrease of protective antibodies concentrations in mothers blood was slowly: not significant in group of "Grippol plus" vaccinated, there is decrease to all influenza

strains in "Agrippal S1" group. A maintenance of high level of influenza antibodies is important for support of specific insensibility of mothers and their protection of children from influenza-like virus infections. In the meantime it is an advantage of "Grippol plus" vaccine for its application in pregnant women.

This study focused only on special aspects of antibody-mediated immunity (Bcell part of immune system). 3-month interval of supervision had been chosen due to the fact, that there are significant changes in antibodies levels in this time period. It is known, that influenza vaccines induce changes in T-cell part of immune system. The study of these changes is assumed more complex methods of diagnosis, but their clinical perspective is not so clear, therefore we didn't try to assess them in frames of this study.

Obtained results of this study are important for the reasonable choice of medicine for vaccination of pregnant women against influenza, as it is recommended in national vaccination Schedule.[41] Future investigations should be focused on the cellular component of immune system to find the explanation for the difference between two vaccines immunity from this study.

Materials and methods

It is a prospective randomized open-label comparative study of immunogenicity after subunit and polymeric subunit influenza vaccines administration among mothers and infants.

Patient description

In total, 79 mother-infant pairs, which meet to inclusion criteria (physiological gestation course, ability to participate in the study, signed patient informed consent form) were included in this study.

Inclusion criteria

Healthy pregnant women aged 20–40; volunteers capable of fulfilling the protocol requirements (i.e., able to fill in the selfobservation diary and turn up for the scheduled visits); signed informed consent of the volunteers to participate in the clinical study.

Exclusion criteria

History of leukemia, oncologic conditions or positive tests for HIV, hepatitis B and C; volunteers who had received the immunoglobulin preparations or blood transfusions within the last three months prior to the study;long-term (more than 14 days) administration of immunodepressants or other immunomodulating drugs within the last six months prior to the study;any confirmed or suspected immunosuppressive or immunodeficiency disorder; history of chronic alcohol abuse and/or substance abuse; presence of respiratory or cardiovascular insufficiency, hepatic or renal impairment revealed during physical examination or by laboratory tests at visit 1; severe congenital defects or serious chronic diseases including any clinically significant diseases of lungs, kidneys, cardiovascular system, nervous system, psychiatric diseases or metabolic disorders confirmed by anamnestic data or objective clinical examination; presence of acute infectious and/or non-infectious diseases at the time of enrollment in the study; migrated influenza and influenza-like diseases, as well as vaccination against influenza within 1 year before the onset of pregnancy; pregnancy via IVF procedure.

Table 2. Comparative characteristics of infants.

Characteristic	Group I (Grippol plus) (n = 42)	Group II (Agrippal S1) (n = 37)
Gestation age (children)	Full-term (39–40 weeks)	Full-term (39–40 weeks)
Weight, g	3277,5 ± 253,9	3347,2 ± 201,3
Height, cm	51,11 ± 0,82	50,89 ± 0,73
Head circumference, cm	34,79 ± 0,52	34,44 ± 0,12
Chest circumference, cm	33,52 ± 0,42	33,59 ± 0,16

Vaccination was conducted at gestation week 16 – 30. 42 pair (pregnant women aged 23.3 ± 0.4 years) received the Grippol Plus vaccine (NPO Petrovax Pharm LLC, Russia) (group I), and 37 pairs (pregnant women aged 27.8 ± 0.6 years) received the Agrippal S1 vaccine (Novartis Vaccines and Diagnostics, Italy) (group II) over the same gestation period, based on the Study protocol. The main number of pregnant women from group I accounted for the first-born young women – 13 (30.9%), from group II – 12 (32.4%). At the same time, 16 (43.2%) women already had 2 or 3 pregnancies in the anamnesis, mostly ending with childbirth. It was noted that 27 (72.9%) pregnancies in this group were planned. All pregnant women were caucasian. The characteristics of the observed groups of children are reflected in Table 2. As can be seen from the table, the compared parameters were the same in both groups of children born from vaccinated with different preparations pregnant women.

Sealed code envelope method of randomization was used: each women received sealed envelope with the number of study group. Since the moment of vaccination during the entire period of pregnancy and after childbirth women and their infants were followed for 3 months under close assessment of the clinical status by obstetrician-gynecologist, neonatologist, pediatrician and a researcher. The study protocol was approved by the Ethics Committee at the Governmental University of Ulyanovsk (№18 dated 10.02.2010). This project as a prospective, randomized, open-label comparative study in parallel groups of pregnant women and their infants. The study was conducted according to the Russian Federation National Standard Protocol ГОСТР 52,379–2005 «Good Clinical Practice» and International GCP standards.[42] The study was based on the ethical principles and recommendations of the WHO and the Russian Ministry of Health.[41,43] All women signed the patient informed consent form for the participation in the study before the beginning of this research.

Vaccines

For vaccination were used commercial influenza vaccines, compound of which was the same. The antigen content of the study drugs was compliant with the WHO and EU recommendations for the seasonal vaccines for 2010–2011. The work was carried out in the 2010–2011 season (A/

California/7/2009 (H1N1)pdm09-like virus; A/Perth/16/2009 (H3N2)-like virus; B/Brisbane/60/2008-like virus). Single-dose vaccination was performed according to the manufacturer's instructions. The patients from group I (n = 42) received the trivalent inactivated polymeric subunit vaccine Grippol Plus (NPO Petrovax Pharm LLC, Russia). A Grippol Plus dose contains 5 mcg of influenza H-antigens and the watersoluble high-molecular immune system adjuvant Polyoxidonium (500 mcg in 0.5 ml in 1 vaccination dose).

Characteristics of the adjuvant used in the vaccine

Polyoxidonium (PO) properties are world apart from all adjuvants developed previously and those under the development today by researches all over the world.

PO is the high molecular derivative of heterochain polyamines, synthesized by professor Arkadiy Nekrasov and patented in Russia, EU and USA. PO structure is defined, stable and easily reproducible in batch to batch manufacture. According its chemical structure, PO is the copolymer of N-oxide of 1,4-ethylene piperazine and (N-carboxymethyl)-1,4-ethylene piperazinium bromide with molecular mass about 80 kDa (INN: Azoximer bromide). This high molecular compound is analogue of natural wide-spread physiologically active N-oxide polymers having strong physiological and pharmacological properties including immune tropic potency.

PO is a water soluble, non-toxic biogenic compound that degrades and eliminates from the organism by natural metabolic way. Due to structure organization peculiarities, PO is safe because does not provokes immediate and delayed side effects, that was confirmed by many-years product application in clinical practice as independent immune modulating and detoxicating drug.

PO clinical implementation was started in 1996. PO as an immune modulator and detoxicant in the dose of 6 mg was approved for application in such fields of clinical practice as immunology, allergology, oncology, surgery, pulmonology, gynecology. PO is approved for children and adults in the form of injections, intravenous infusions, suppositories and tablets. Medicine was registered in Russian Federation, CIS countries, Slovakia, Cuba.

For more than 20 years of PO clinical application as independent drug, mechanisms of its immune modulating action were studied in many respects. PO possesses expressed immune modulating effects acting first of all on autarcesis factors such as monocytic-macrophagal system cells, neutrophils and NK-cells and inducing them activation under initially reduced functions. Flow cytochemistry data showed that PO does interact with three lymphocyte subclasses, predominantly binds with monocytes and neutrophils and to a lesser extent with lymphocytes, enhancing intracellular H2O2 production. Hydrogen peroxide being the secondary messenger activates the transcriptional NF-kB factor that is the participant of the cytokines synthesis regulation. The enhancement of the pro-inflammatory cytokines IL-1β, IL- 6, TNF-α synthesis takes place. Activation by PO cells of monocytic-macrophagal cluster and natural killers promotes mobilization of both cellular and humoral immunity. Finally all immunity starts up for adequate response development similarly to that as it occurs in natural way.[44]

Besides its own clinical application as independent drug, Polyoxidonium is used as immunoadjuvant in new generation vaccines and is a compound in subunit adjuvanted Grippol family vaccines since 1997 when first Grippol® vaccine was registered in Russian market. Due to Polyoxidonium, all Grippol family vaccines contain 3-times lower antigen content in one immunizing dose – 5 mcg per strain, in comparison to 15 mcg per strain in other subunit and split influenza vaccines. This provides Grippol family vaccines with higher safety profile.

Today Grippol vaccines are approved and especially recommended for vaccination of cohorts that previously were considered to be not vaccinated (patients with allergic conditions, subjects with chromic somatic diseases, individuals with different immune deficiencies), and children from 6 months of age, and pregnant women. These recommendations were made based on relevant clinical trials results followed by many years practical mass vaccine application experience.[45,46]

The patients from group II (n = 37) received the standard tri-valent subunit vaccine Agrippal S1 («Novartis Vaccines and Diagnostic», Italy), which contains 15 mcg of influenza H-antigens per dose.

Blood samples

The blood samples obtained from 42 (group I) and 37 (group II) mother-infant pairs were evaluated on days 2–3 and 3 months after birth.

Laboratory methods

The antibody levels against the influenza A and B strains were evaluated using a hemagglutination inhibition reaction and a 0.75% chicken RBC mix with prior warming of the study serum up to 56 C for 1 hour to remove the nonspecific inhibitors and improve the sensitivity of the reaction. It should be noted that this test is recognized as specific for the evaluation of the immunogenicity of influenza vaccines. To determine specific antibodies were used antigens of the A/California/7/2009 (H1N1)pdm09-like virus, A/Perth/16/2009 (H3N2)-like virus, B/Brisbane/60/2008-like virus, recognized by WHO as seasonal and included in the compound of influenza vaccines in 2010– 2011 and 2011–2012 years.

Criteria for evaluating influenza vaccine immunogenicity in pregnant patients and newborns are not available; therefore, we used the criteria developed by the Committee for Proprietary Medicinal Products (CPMP) for adult patients. The same criteria were used in previous studies.[9–11] We used only two criteria in this study:

(1) Seroprotection level – percentage of vaccinated patients with a hemagglutinininhibiting antibodies titre (HIAT) over 1:40 by post-vaccination day 21 (reference level – over 70%).
(2) Seroconversion factor or mean geometric increase – increase in the mean geometric titre of hemagglutinin-inhibiting antibodies by post-vaccination day 21

compared to baseline – expressed as an increase ratio (reference level – over 2.5-fold).

The mean geometric antibody level enables the reliable determination of the seroconversion increase or decrease, reflecting the decrease in the intensity of immunity to influenza in infants during the early post-natal period.

The efficacy and immunogenicity of the vaccine is considered to be satisfactory if the vaccine meets at least one of these criteria.

Statistical analysis

Descriptive statistics were used to analyze the results with Thompson's rule for preliminary processing. The significance of the different numerical parameters was evaluated using the non-parametric Wilcoxon's criteria for non-related samples (W). AtteStat10 software was used. The log of the mean geometric data (antibody titre) was used to calculate the seroconversion factor. Microsoft Excel 2003 software was used.

Conclusion

The dynamic of influenza antibodies after the administration of [polymeric subunit vaccine] "Grippol plus" was investigated in frames of this study for the first time. The originality of this study is a description of antibody response and it's dynamic among pregnant women and their infants during pregnancy and 3 month after birth. Obtained results demonstrated than polymeric subunit vaccine "Grippol plus" corresponds to needed requirements in forming of protective antibodies among pregnant women and provides protection of mothers and their children after birth. Therefore, this vaccine can be administered to pregnant women for influenza prophylaxis as it is described in recommendations of National Vaccination Schedule.[41] Represented data confirm results of foreign studies regarding vaccination of pregnant women against influenza. An advantage of "Grippol plus" vaccine application among pregnant women is longer period of protective antibodies level maintenance after childbearing compare with "Agrippal S1". But there is a need in investigation of the cellular component of immune system after influenza vaccines application to find the explanation for the difference in their actions.

The administration of a polymeric subunit influenza vaccine and subunit influenza vaccine during trimesters II and III resulted in the development of protective antibodies (≥ 1:40) against different strains of influenza within several days after birth in more than 53% of cases. Three months later, similar levels of protective antibodies were reported in the mothers, while in the children, the levels of trans-placental antibodies decreased. The percentage in group I was 13 – 22% (Grippol Plus), and the percentage was 31 – 43% in group II (Agrippal S1).

The geometric mean antibody titres for the A(H1N1) pdm09 and A/H3N2/influenza strains for the mother-infant pairs after birth were similar; however, for the infants, the antibody titres for strain B were lower, independent of the vaccine used during pregnancy. This effect is likely associated with the mechanism of trans-placental transmission. Vaccination during trimesters II and III with a polymeric subunit vaccine containing the immune adjuvant Polyoxidonium helped to maintain the geometric mean antibody titre throughout the first three months after birth, while administration of a standard subunit vaccine resulted in decreased antibody levels for various influenza strains. In both groups, a similar decrease in the geometric mean antibody titre was reported in the infants, with a mean 2-fold decrease. This result reflects the decrease in specific influenza immunity due to physiological catabolism of the trans-placental antibodies.

Therefore, the administration of a polymeric subunit immune adjuvant vaccine with a 3-fold deceased amount of the viral strains during pregnancy resulted in the development of protective antibodies in mother-infant pairs, similar to the administration of the standard subunit vaccine. Three months later, the number of infants with protective antibody levels and the geometric mean antibody titre decreased, independent of the vaccine used. In contrast, for the mothers, no significant changes in influenza protection were observed; however, the decrease in the geometric mean antibody titres in the women vaccinated with Agrippal S1 during pregnancy was more prominent.

Disclosure of potential conflicts of interest

The authors declare no conflict of interest.

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References

1. Romanovskaya AV, Davydov AI, Maleev VV. Influenza and acute respiratory virus infections among pregnant women: clinical findings and hemoreological disturbances. Questions Gynaecol Obstetrics Perinatol. 2014;13(5):22–26.
2. ECDC scientific advice on seasonal influenza vaccination of children and pregnant women: ECDC Technical report. European Centre for Disease Prevention and Control. ECDC scientific advice on seasonal influenza vaccination of children and pregnant women. Stockholm (Sweden): ECDC; 2012. p. 68.
3. WHO Influenza (Seasonal). World Health Organization; 2009 Apr accessed 2011 May 9. http://www.who.int/mediacentre/factsheets/fs211/en/index.html.
4. Eick AA, Uyeki TM, Klimov A, Hall H, Reid R, Santosham M, O'Brien KL. Maternal influenza vaccination and effect of influenza virus infection in young infants. Arch Pediatr Adolesc Med. 2011;165(2):104–111. doi:10.1001/archpediatrics.2010.192.
5. Cherdantsev AP, Kostinov MP, Kuselman AI, Dagil Y. Post-vaccination immunity to A/California/7/2009(H1N1)v influenza

strain in pregnant patients after immunization. Med Immunol. 2012;14(6):527–532. doi:10.15789/1563-0625-2012-6-527-532.
6. Steinhoff MC, Omer SB, Roy E, Arifeen SE, Raqib R, Altaye M, Breiman RF. Influenza immunization in pregnancy – antibody responses in mothers and infants. N Engl J Med. 2010;362 (17):1644–1646. doi:10.1056/NEJMc0912599.
7. Puck JM, Glezen WP, Franf AL, Six HR. Protection of infants from infection with influenza A virus by transplacentally acquired antibody. J Infect Dis. 142;1980:844–849.
8. Benowitz I, Esposito DB, Gracey KD, Shapiro ED, Vazquez M. Influenza vaccine given to pregnant women reduces hospitalization due to influenza in their infants. Clin Infect Dis. 2010;51 (12):1355–1361. doi:10.1086/657309.
9. Vesikari T, Pellegrini M, Karvonen A, Groth N, Borkowski A, O'Hagan DT, Podda A. Enhanced immunogenecity of seasonal influenza vaccines in young children using MF59 adjuvant. Pediatr Infect Dis J. 2009;28(7):563–571. doi:10.1097/INF.0b013e31819d6394.
10. Baldo V, Baldovin T, Floreani A, Carraro AM, Trivello R. Family medicine group of Pianiga. MF59 – adjuvanted influenza vaccine confers superior immunogenicity in adult subjects (19-60 years of age) with chronis diseases who are at risk of post – influenza complication. Vaccine. 2007;25:.3955–3961. doi:10.1016/j.vaccine.2007.02.045.
11. Baldo V, Baldovin T, Floreani A, Fragapane E, Trivello R. Response of influenza vaccines against heterovariant influenza virus strains in adults with chronic diseases. J Clin Immunol. 2007;27(5):542–547. doi:10.1007/s10875-007-9100-4.
12. Kostinov MP, Cherdantsev AP, Savisko AA, Tarbaeva DA, Slovyova IL. True and false reactions in pregnant women to introduction of influenza vaccine. Gynaecol Obstetr Perinatol. 2011;10(6):44–48.
13. Kostinov MP. New in clinics, diagnostics and vaccine prevention of the governed infection. Moscow (Russia): Medicine for everybody; 1997.
14. Kostinov MP. Vaccination of children with impaired state of health. Practical guideline for doctors. 2nd ed. Moscow (Russia): Medicine for everybody; 2000.
15. Kostinov MP, Ozeretskovskiy NA. Clinico-immunological effectiveness of immunobiological preparations: directory. Moscow (Russia): Miklosh; 2004.
16. Chebykina AV, Kostinov MP, Magarshak OO. Estimation of safety and efficiency of vaccination from a flu at patients with chronic obstructive lung syndrome. Epidemiol Vaccinal Prev. 2010;6(55):50–53.
17. Kostinov MP, Lavrov VF, editors. New age vaccines for prevention of infectious diseases. 2nd ed., renewed. Moscow (Russia): MDV; 2010.
18. Protasov AD, Ryzhov AA, Zhectkov AV, Kostinov MP. The influence of comlex vaccination against pneumococcus, haemophilus influenzae type B infections and influenza in the clinical course of chronic obstructive pulmonary disease. Bulletin Contemporary Clin Med. 2012;5(2):22–24. doi:10.20969/VSKM.2012.5(2).22-24.
19. Protasov AD, Ryzhov AA, Zhectkov AV, Kostinov MP. Vaccination of adults with bronchopulmonary pathology. In: Kostinov MP, editor Guideline for doctors. Moscow (Russia): Art Studio "Sozvezdie"; 2013.
20. Kostinov MP.Vaccination of children with weak health. In: Kostinov MP, editor Practical manual for doctors. 4th ed. Moscow (Russia): Medicine for everybody; 2013.
21. Khaitov RM, Ilyina NI, editors. Allergology and immunology: national guidance. Moscow (Russia): GEOTAR-Media; 2014.
22. FGBU NIIVS named after I.I. Mechnikov. Vaccines and vaccination. In: Zverev VV, Chaitov RM, editors. National guidance. Brief publication. Moscow, Russia: GEOTAR-Media; 2014.
23. Kostinov MP, Chuchalin AG, editors. Guidance for Clinical Immunology in Respiratory Medicine. 1st ed. Moscow (Russia): LLC ATMO; 2016.
24. Chuchalin AG, Yasnetsova VV, editors. Federal guidelines for the use of medicines (Formular System, Reference Edition) Issue XVII. Chapter 19 "Vaccines". Moscow (Russia): LLC "Vidox"; 2016.
25. Tarasova AA, Kolbasina EV, Lukushkina EF, Kuzmichev Yu G, Kostinov MP. Immunogenicity and safety of a trivalent subunit immunoadjuvant influenza vaccine in children with type 1 diabetes: results of a prospective comparative study. Curr Pediatrics. 2016;15(5):487–497. doi:10.15690/vsp.v15i5.
26. Rusnak FI, Kostinov MP.Infections of the urinary system in children. In: Dlin VV, Osmanov. IM, Chugunova OL, editors. Practical manual for doctors. 2nd ed. Chapter 14 Vaccine prevention of governed infection in children with urinary tract infection. F.I. Rusnak, M.P. Kostinov. Moscow (Russia): Overlay; 2017.
27. Protasov AD, Ryzhov AA, Zhectkov AV, Kostinov MP. Respiratory medicine. In: Guidelines. Vol. 2. 2nd ed., revised and enlarged. Section 9. Respiratory infections. 9.10. Vaccination; 2017. p. 173–183.
28. Cherdantsev AP, Kuselman AI, Sinitsyna MN, Shalyagina ME, Kostinov MP, Tarbaeva DA. Study of the clinical safety of vaccination against influenza in pregnant women. Medical Almanac. 2011;4(17):120–122.
29. Cherdantsev AP, Kostinov MP, Kuselman AI, Voznesenskaya NV. Vaccination against influenza A (H1N1) in pregnancy. J Microbiol Epidemiol Immunobiol. 4;2011:46–50.
30. Cherdantsev AP, Kuselman AI, Kostinov MP, Lyutaya ZA, Deryabina EV, Azizova RS, Melnik RK. Post-natal development of children born by women vaccinated against flu. Ulyanovsk Medico-Biol J. 3;2012:80–84.
31. Cherdantsev AP, Kostinov MP, Kuselman AI, Lyutaya ZA, Kutbutdinova MH. Analysis of anteand postnatal fetal development after influenza vaccination of pregnant women. Russian Bulletin Perinatol Pediatrics. 2013;58(2):30–34.
32. Cherdantsev AP, Kostinov MP, Kuselman AI, editors.. Vaccine prevention of influenza in pregnant women. In: Guidelines for doctors. Moscow (Russia): 4Mpress; 2013.
33. Cherdantsev AP, Kostinov MP, Kuselman AI, editors.Vaccine prevention of influenza in pregnant women. In: Guidelines for doctors. 2nd ed., enlarged. Moscow (Russia): MDV Group Art Studio "Sozvezdie"; 2014.
34. Kostinov MP, Cherdantsev AP, Semenova SS, Tarbaeva DA, Savisko AA, Serova OF, Iozefson SA, Akhmatova NK, Kostinova TA, Praulova DA. Obstetric and perinatal outcomes among pregnant women after influenza vaccination and after transferred respiratory infection. Gynecol. 2015;17(4):43–46.
35. Kostinov MP, Cherdantsev AP, Praulova DA, Kostinova AM. Influenza vaccination is a safe way to protect pregnant women and newborn infants from sequels of infection. Russian Bulletin Obstetrician-Gynecol. 2015;15(5):69–74.
36. Zverev VV, Kostinov MP, Cherdantsev AP, Kuselman AI, Kiselev OI, Erofeeva MK, Krasnopolsky VI, Novikova SV, Serova OF, Briko NI, editors. Vaccination against influenza in pregnancy. Federal clinical guidelines. Remedium. 2015.
37. Kostinov MP, Cherdantsev AP. Health state of children born from pregnant women vaccinated against influenza. Pediatria J Named After GN Speransky. 2016;95(1):67–71.
38. Kostinov MP, Cherdantsev AP. The clinical and immunological safety of inactivated immunologic adjuvant influenza subunit vaccine for pregnant women. Obstet Gynecol. 2;2016:64–69.
39. Kostinov MP, Cherdantsev AP, Praulova DA, Kostinova AM, Polishchuk VB. Analysis of safety for fetus of immunoadjuvant influenza vaccines in pregnant women. Pediatria J Named After

GN Speransky. 2017;96(1):91–96. doi:10.24110/0031-403X-2017-96-1-91-96.

40. Khromova EA, Akhmatova EA, Kostinova AM, Cherdantsev AP, Savisko AA, Akhmatova NK. Impact of influenza vaccination on the course of pregnancy and on fetal and neonatal development. Obstet Gynecol. 7;2017:12–17.
41. Recommendations for organization and conduction of influenza strain A (H1N1) vaccination in pregnant patients and in post-labor period. http://www.minzdravsoc.ru/docs/mzsr/letters/161
42. Good Clinical Practice. Russian federation national standard, GOSTR 52379-2005/Moscow 2005. http://www.medtran.ru/rus/trials/gost/52379-2005.htm
43. Botina AV, Medvedeva TG, Neznanov NG. Ethical concerns of clinical studies in females of childbearing potential. Good Clin Pract. 3;2003:43–46.
44. Dyakonova VA, Dambaeva SV, Pinegin BV, Khaitov RM. Study of interaction between the polyoxidonium immunomodulator and the human immune system cells. Int Immunopharmacol. 2004;4 (13):1615–1623. doi:10.1016/j.intimp.2004.07.015.
45. SavelyevaGM,SukhikhGT,SerovVN,ManukhinIB,RadzinskyVE, editors. Gynecology. In: National Guideline. 2nd ed. Moscow (Russia): GEOTAR-Media; 2017.
46. Boytsov SA, Loukianov MM, Platonova EV, Gorbunov VM, Romanchuk SW, Nazarova OA, Belova OA, Kravtsova EA, Dovgalevsky P, Furman NV, et al. Efficiency of influenza vaccination in patients with circulatory system diseases under dispensary observation in outpatient clinics: prospective follow-up monitoring data. Rational Pharmacother Cardiol. 2016;12(6):703–710. doi:10.20996/1819-6446-2016-12-6-703-710.