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SAFETY AND IMMUNOGENICITY OF SEASONAL TRIVALENT INACTIVATED INFLUENZA VACCINES IN PREGNANT WOMEN

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ABSTRACT

Pregnant women are at high risk for influenza virus infection and serious influenza-related complications and are recommended to receive inactivated influenza vaccine during the influenza season. Before 2009, although many attempts had been made to evaluate the efficacy of the vaccine, the strict evaluation had been difficult because of the presence of pre-existing antibodies and the antigenic mismatch between the vaccine strain and actual epidemic strain. Even within this context, however, the following findings have been identified: immunogenicity of the influenza vaccine in pregnant women is maintained; influenza vaccine is effective for protecting pregnant women from severe respiratory illness, and maternal antibodies are transferred to their fetuses via the placenta to protect the offspring from influenza infection and adverse infection outcomes. Beginning in 2009, when the A/H1N1pdm pandemic occurred, a more definitive evaluation of the efficacy of the vaccine from an immunological perspective was performed because vaccinated people had no or marginal pre-existing antibodies against the de novo A/H1N1pdm strain, and the formulation of the vaccine was monovalent at the time. It is suggested that influenza vaccination of pregnant women is an effective countermeasure to influenza virus infection is not only pregnant women, who constitute a high-risk group for influenza virus infection but also in their offspring.

KEYWORDS: Influenza vaccines, pregnant women.

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.[1]

Influenza is a common respiratory infectious disease, which operates in an epidemic model. It is responsible for secondary bacterial infections of lower respiratory tract causing a sharp increase in morbidity and mortality.[2]

Infants, young children, the elderly, pregnant women, but also individuals with chronic disease or underlying immunosuppression are considered at increased risk of death or complications from seasonal influenza.[3] In patients with cancer, influenza-associated infections because mortality estimated at 9%, which is significantly higher than the mortality in the general population. The overall case-fatality rate is considered to be low on average (o0.1%), but is higher in vulnerable populations like elderly people (approaching 1%) and in patients with chronic underlying conditions.[4]

In addition, infectious events may postpone the administration of chemotherapy, lowering dose intensity and thereby being detrimental to the care of cancer patients. Influenza vaccination is an effective means of preventing influenza and its complications. It allows a reduction of morbidity and mortality secondary to influenza and is cost-effective in healthy.[5] Influenza vaccines are mostly inactivated vaccines, composed of three influenza viruses' strains selected annually on the basis of epidemiological data by annual WHO recommendations, two influenza A and one B virus. A vaccine dose contains 15 mg of haemagglutinin for each strain and is given intramuscularly or subcutaneously. Influenza vaccination is recommended by several health authorities in immunosuppressed patients, including patients receiving chemotherapy.[6]

Influenza virus infection is a common cause of hospitalization and death, and worldwide the mortality from seasonal influenza virus infection is estimated to be 250,000 to 500,000 persons per year. Pregnant women are at increased risk for influenza-associated illness and death.[7]

Neuzil et al.[8] quantified influenza-related serious morbidity in pregnant women during predefined influenza seasons and found that the risk of influenza-related acute cardiopulmonary conditions was higher in pregnant women than in nonpregnant and postpartum women. In addition, the authors reported that the odds ratio (OR) was increased

about 3-fold for women at 37–42 weeks' gestation as compared with those at 14–20 weeks' gestation. Another study reported that pregnant women with asthma were at high risk for hospitalization during the flu season.[9] Furthermore, influenza infection in young infants often prompts hospitalization and can predispose the infants to pneumonia or death, especially in infants under the age of 6 months.[10]

Since no influenza vaccine has been licensed for use in infants less than 6 months of age, and the mortality and morbidity of influenza infection is high in pregnant women, maternal influenza immunization is a promising resolution for protecting both mothers and infants.[11] Influenza vaccine using the inactivated virus as the antigen had been proven safe for pregnant women and the fetus.[12] A study that included more than 2,000 pregnant women who received an inactivated virus influenza vaccine revealed no fetal malignancies. Deinard et al.[13] demonstrated no teratogenicity in the infants of 189 pregnant women immunized with the influenza A/New Jersery/8/76 virus vaccine. A retrospective study of pregnant women who received the influenza vaccine in the second or third trimester of gestation revealed no serious adverse effects in the perinatal period or in infants during the first 6 months of life. Other studies have also confirmed no adverse effects in infants when their mothers are administered inactivated virus influenza vaccines during the antepartum period.[14]

Immunization of pregnant women for influenza has also been shown to provide benefits for the infant. Zaman et al.[15] reported that administrating influenza vaccine in the third trimester could reduce influenza illnesses by 63% in infants up to 6 months of age, and avoid approximately 1/3 of respiratory illness in mothers and young infants. It has been demonstrated that vaccination or pregnant women with inactivated H1N1 virus can elicit an antibody response typically associated with protection against influenza infection, and result in the efficient transplacental transfer of antibody to the newborn.[16]

The World Health Organization (WHO) recommends that all pregnant women be immunized during the influenza season, while the United States (US) Centers for Disease Control and Prevention (CDC) also recommend that women who are or will be pregnant during the flu season get the flu vaccine. The American College of Obstetricians and Gynecologists (ACOG) concurs with this recommendation.[24] In Canada and many European countries vaccinating healthy pregnant women is also recommended.[17]

The Advisory Committee on Immunization Practices in Taiwan recommends and prioritizes pregnant women to receive influenza vaccination, regardless of the stage of pregnancy. We previously conducted a retrospective study to evaluate the incidence, nature, and seriousness of adverse drug reactions (ADRs) occurring after AdimFlu-S® influenza A (H1N1) vaccination in pregnant women in Taiwan, and reported that influenza A vaccination during pregnancy did not lead to a higher incidence rate of maternal or fetal adverse events.[18] Evaluation of the safety and immunogenicity of influenza vaccine in pregnant women may provide useful information to reduce the hospitalization rate of pregnant women during influenza seasons.

Background

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 the influenza virus (an Orthomyxoviridae family member), which is known to cause an epidemic annually. Transmitted mainly via droplets, influenza primarily manifests as high fever, often accompanied by shivering, headache, malaise, myalgias, and arthralgias. Subsequently, respiratory tract symptoms become more prominent.[19]

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, 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.[20] 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, 2005e2009 seasonal influenza vaccines were unable to protect against the 2009 H1N1 influenza virus.[21]

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 an 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.[22] Furthermore, Grund et al. showed in 2011 that the HI titer had a positive correlation with the neutralizing antibody titer. 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.[23]

Clinical significance of influenza vaccination for pregnant women

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. 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.[24] 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.[25] 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.

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.[26] 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[27], while the other demonstrated greater hospitalization burden and delivery complications (preterm labor, fetal distress, and cesarean delivery) in pregnant women. In the 2009 A/H1N1pdm pandemic[28], 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. Halberg 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.[29]

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. 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.[30] In addition, mothers' cardiopulmonary functions dramatically change during pregnancy. Oxygen consumption rises by 20% in pregnancy, about one-third of which is necessary for the 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.[31]

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.

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 the duration of symptoms, duration of hospitalization, and mortality compared with no treatment. Evidence also shows the safety and benefits of NA inhibitors in pregnant women. 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.[32]

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 those in non-pregnant women. Concurrently, it is also necessary to assess safety, the persistence of maternal antibodies, and the preventive effect of influenza infection or disease. Studies on the influenza vaccination of pregnant women have been limited until the 2009 A/H1N1pdm pandemic because of the low vaccination coverage rate and difficulty of evaluating the immunogenicity of the TIV due to pre-existing antibodies. Despite the recommendations of the Advisory Committee on Immunization Practices (ACIP), maternal influenza vaccination coverage remained low due to a shortage of scientific evidence. However, recent studies have addressed the safety and efficacy issues of vaccination in pregnant women and their fetuses and neonates.[33]

Notably, the data on the safety and usefulness/efficacy of the A/ H1N1pdm vaccine are now available. Moreover, with increased attention to influenza virus infection, immunization coverage in pregnant women has increased. Flore et al. reported that the seasonal influenza vaccination coverage among pregnant women increased from 15 to 25% during 2006e2008[34], and the United States Centers for Disease Control (US CDC) reported that the H1N1 vaccination coverage in 2009 was 38% in the US, which reached almost 50% in the 2011/2012 influenza season.[35]

Safety of influenza vaccination during pregnancy

Data suggestive of the adequate safety of influenza vaccination during pregnancy are available from the following epidemiological studies. Tamma et al. summarized the safety of influenza vaccination separately for maternal and infant outcomes[36] and reported no adverse effects of vaccination on either maternal outcome (i.e., adverse reactions in the mother and in pregnancy outcomes such as preterm delivery and Caesarean section) or infant outcome (i.e., congenital anomaly, gestational week of delivery, and body weight at birth).[37] Heinonen et al. reported the results of a collaborative perinatal project conducted in 1959 through 1965 in which more than 2000 pregnant women were enrolled. Of those women, nearly one third were vaccinated during the first trimester. Seven-year follow-up of the offspring revealed no increased incidences of stillbirth, congenital anomaly, malignancies, or neurocognitive disorder.

Assessing the safety of TIV at 3 and 42 days after vaccination in 75,906 vaccinated pregnant women with 147,992 unvaccinated counterparts, Nordin et al. showed that vaccination with TIV, even during the first trimester, did not increase vaccine-related major adverse events, particularly neurological disorders such as Guillain-Barre syndrome, optic neuritis, transverse myelitis, or Bell's palsy.[38] Kharbanda et al. found no increase in the risk of pregnancy-associated health problems (including proteinuria, urinary tract infection, gestational hypertension, preeclampsia or eclampsia, and chorioamnionitis) and a significant decrease in the risk of gestational diabetes by comparing 74,292 vaccinated pregnant women at 42 days after vaccination with 144,597 unvaccinated counterparts.[39] A recent integrative study, particularly utilizing a propensity score-matched cohort to avoid major confounding effects, showed that TIV during pregnancy had no influence on preterm or small for gestational age (SGA) births.

A major review by Moro et al. indicated that the A/ H1N1pdm monovalent vaccination does not affect the risks for preterm delivery, Caesarean section, miscarriage, and congenital anomaly, or increase the incidences of preeclampsia and intrauterine growth retardation.[40] Fell et al. suggested that vaccination protects the offspring from the H1N1 influenza virus, given the lower incidences of preterm delivery, fetal growth, and stillbirth in vaccinated than unvaccinated mothers. In another study, Moro et al. evaluated the safety of live attenuated A/H1N1 monovalent vaccine. The rate of pregnancy-specific adverse events in vaccinated women was similar or lower than that in unvaccinated controls. Analysis from the Organization of Teratology Information Specialists (OTIS) collaborative research group showed that inactivated monovalent A/H1N1pdm vaccination in 841 pregnant women did not increase the risk of major birth defects, spontaneous abortion, and SGA births as compared to 191 unvaccinated controls. While a marginal increase in the hazard ratio of preterm delivery was shown, the decrease in gestational age was only three days on average.[41] The Slone Birth Defects Study (BDS) found no correlation of inactivated monovalent A/H1N1pdm vaccination with congenital abnormalities. Colin et al. examined the safety of inactivated monovalent A/H1N1pdm vaccine in 10,376 pregnant women (4122 of whom [39.7%] received the vaccination during the first trimester) and their newborns and found no vaccine-associated adverse effects.[42] Pasternak et al. assessed the risk of adverse fetal outcomes in 330 infants exposed to the monovalent A/H1N1pdm vaccine in the first trimester and reported that the vaccine did not increase the risk of major birth defects, preterm birth, or fetal growth restriction.[43]

Immunogenicity of influenza vaccine during pregnancy

Multiple studies evaluated the immunogenicity of vaccines given to pregnant women. Murray et al. used a single dose of monovalent A/New Jersey/8/76 vaccine to evaluate immunogenicity in 26 pregnant women (all trimesters) and 18 non-pregnant women with the age-matched comparison at 6 weeks post-vaccination. An HI antibody titer of 1:40 or higher was achieved in 35% of pregnant women versus 44% of non-pregnant women and the titers were nearly comparable between pregnant and non-pregnant women.[44]

Englund et al. measured geometric mean antibody titers (GMT) at delivery (approximately 5 weeks post-vaccination) in 13 pregnant women vaccinated with the TIV during the third trimester, and showed antibody titers against A/H1N1, A/H3N2, and B were 4.6-, 3.4-, and 1.6-fold higher than before vaccination, respectively.[45] In 45 and 27 pregnant women vaccinated with TIV at the second and third trimesters, Yamaguchi et al. demonstrated an HI antibody titer higher than 1:40 at 1 month after TIV vaccination in 91.8% and 87.1%, respectively, confirming that vaccination during these trimesters can elicit HI antibody titers that are high enough to reduce the risk of influenza infection or disease.[46]

A study of 128 pregnant women receiving A/H1N1pdm monovalent vaccine revealed that 87.7% and 88.7% of vaccinees attained a more than 4-fold rise at HI antibody titers (seroresponse) after the first and second doses, respectively.[47] Horiya et al. explained that the boosting effect of the second dose was marginal and nonresponders to the first dose responded poorly also to the second dose. When antibody positivity was defined as an HI antibody titer greater than 1:40, the antibody positivity rate before vaccination was 6.5% and increased to 89.5% after the second dose. Another study in pregnant women also reported that single vaccination resulted in 91% of the subjects having more than 4-fold increase in antibody titer, and in 89% of the subjects attaining >1:40 HI antibody titers. These studies revealed that pregnant women were able to respond to the influenza vaccine in a manner equivalent to nonpregnant women. Concurrently they suggest that pre-existing anti-influenza virus antibodies may interfere with the immunogenicity of influenza vaccine.[48]

Protective effects of vaccination during pregnancy on influenza infection or influenza-related complications

It is difficult to strictly assess whether vaccination has preventive effects on influenza infection and adverse infection outcomes. Most surveillance studies have been based on the incidence of visits to medical institutions. From the milieu of previous evidence, the

preventive effect of influenza vaccination in pregnant women should not so different from those in non-pregnant women. Therefore, many surveys have alternatively focused on the acquisition of symptomatic infection or severe outcomes in the offspring to score the protective effects of vaccination. For example, Black et al. reported no significant difference in the risk of respiratory infection requiring a visit to a medical institution between TIV-vaccinated and unvaccinated pregnant women.[49] In a study in Bangladesh, TIV's preventive efficacy was assessed during 2004e2005 in pregnant women. Enrolled subjects were randomly assigned to receive influenza (n ¼ 176) or control pneumococcal polysaccharide vaccine (n ¼ 168), and were followed up. The incidence of respiratory illness with fever was 36% lower in the influenza vaccination group than in the control group, providing evidence for the benefit of vaccination in pregnant women. In turn, a cohort study using the A/H1N1pdm monovalent vaccine was conducted on high and low HI titer groups.[50] The study enrolled 119 pregnant women with a post-vaccination HI antibody titer greater than 1:40, and 16 pregnant women with the value of less than 1:40. The rate of visits to medical institutions was higher in pregnant women with low HI antibody titer than in those with high HI antibody titer (31% vs 11%, respectively). The hospitalization rate was 6% and 8%, respectively. These studies, however, have some limitations. Firstly, it is not known whether symptoms such as fever and respiratory illness are actually due to influenza virus infection. Secondly, the detection of vaccine efficacy was greatly affected by the scale of influenza pandemics and the antigenic match between the pandemic and vaccine virus strains. On the other hand, the evidence of vaccine effectiveness for non-pregnant subjects was consistent. Hardelid et al. reported that in their cohort study of 3152 individuals, 4 (4.7%) of 85 vaccinees and 870 (28.4%) of 3067 non-vaccinees were infected with A/ H1N1pdm. The resulting vaccine effectiveness for infection prevention was 88%.[51]

Methods

In this prospective, randomized clinical study, 200 pregnant women, 20-30 years of age and ≥14 weeks gestation received a single intramuscular dose of H3N3 and H1N1.

The sample was divided into groups of two groups receiving the drug and a control group that did not receive anything.

Injection site and systemic reactions were recorded for 6 days after vaccination and serious adverse events (SAEs). Serum samples collected before and 28 days after vaccination were tested for hemagglutination inhibition (HAI) antibody levels.

RESULTS AND DISCUSSION

The results of the study showed that the reactions of the women towards the vaccine were normal, and their attitudes regarding the location of the injection were mild and limited to the value of the level of significance 0,123 significance 0.110 in all side effects.

Table 1.

	P value	
Anemia of pregnancy	**0,102**	
Chronic genitourinary infections	**0,1233**	
Thyroid disorders	**0,432**	
Neuro-circulatory dystonia syndrome	**0,11**	
Threatening miscarriage	**0,12**	

Clinical safety of vaccination the clinical course of the early post-vaccination period in pregnant women vaccinated against influenza is reflected in the table. It should be noted that the difference between the vaccinated and placebo groups in the development of local reactions was for reactions that did not require the prescription of any medication and disappeared on their own after several days, without causing disruption of the patient's activity. The incidence of systemic reactions in the first week after vaccination was higher than that of local reactions, but was comparable between vaccinated groups and did not exceed the values obtained in the placebo group. The appearance of a cough or sore throat in all groups of patients characterized the appearance of a respiratory infection. The late post-vaccination period in pregnant women was characterized mainly by the registration of systemic reactions, without significant differences among the observed groups. At the same time, the probability of occurrence of such symptoms as fatigue, headache, dizziness, and abdominal pain prevailed over other common symptoms that characterize the well-being of pregnant women.

Table 2.

	Group 1=100	**Group2=50**	**Group 3=50**
Local reactions Pain at the injection site	4	32	21
Hyperaemia at the injection site	12	6	16
Sealing at the injection site	4	3	14
Systemic reactions Enhanced temperature	3	6	17
Fatigability	1	3	23
Arthralgia	4	5	12
Myalgia	2	1	17
Headache	5	9	15
Dizziness	3	8	11
Nausea	2	3	13
Infection Cough	1	4	14
Pain in the throat	1	1	14

Assessment of the clinical picture of pregnant women subject to vaccination, as well as placebo groups, showed the presence of concomitant somatic pathology, which does not differ from the indices of other authors Injection site and systemic reactions were recorded for 6 days after vaccination and serious adverse events (SAEs) and pregnancy outcomes were documented. Serum samples collected before and 28 days after vaccination were tested for hemagglutination inhibition (HAI) antibody levels. These indicators in the post-vaccination period were not taken into consideration. Similar premorbid backgrounds were observed in the two study groups, which permitted a comparative qualitative analysis of the clinical tolerability and immunological efficacy of the influenza immunization. There was the same high proportion of women with underlying comorbidities in both groups, but these women were not registered in any clinics as patients with chronic diseases. There were no outbreaks of these diseases during pregnancy. If we assume that these comorbidities could influence the efficacy of vaccination, the data would be affected in both groups.

The introduction of subunit vaccines to pregnant women, regardless of the production technology, was accompanied in the first week by the development of local reactions more often than in the placebo group.

At the same time, the frequency, severity, and duration of these reactions did not differ between the compared vaccinated groups. However, it is important to note that these reactions were rare when the placebo phosphate-buffered saline solution was administered. The frequency of development of systemic reactions did not differ between groups of pregnant women vaccinated with unadjusted and adjuvant preparations against influenza, and these systemic reactions were often subjective in nature and their interrelation with immunization is unlikely.

The emergence of systemic reactions in the late post-vaccination period can be regarded as background symptoms accompanying the course of pregnancy. In addition, they differ little from those that occurred in the early period after immunization. Cough or sore throat signified the appearance of respiratory infections, which proceeded in a mild form; the treatment consisted mainly of local application of decongestants or irrigation of the oral cavity with antiseptic solutions, without the development of complications. The described symptoms and complaints made by pregnant women were not regarded as side-effects of vaccination and did not affect the subsequent course of pregnancy.

Despite the differences in the concentrations of initially protective levels of antibodies to influenza A(H1N1) and B virus strains in the observed groups, after immunization the growth of specific antibodies to all vaccine strains, regardless of the drug administered, was noted. It should be emphasized that pregnant women who received an adjuvant vaccine had antibody levels to the A(H3N2) influenza virus than subjects immunized with a non-adjuvanted vaccine. The levels of antibodies to the strain of influenza B virus were registered higher by 16.3% at 5–6 months after vaccination of pregnant women with an unadjusted vaccine, but after 8–9 months these differences were leveled. Nevertheless, by analyzing the levels of protection against influenza in vaccinated pregnant women with one of the two vaccines, a fairly strong seroprotection can be observed within 8–9 months after immunization.

The study of the average geometric antibody titers in the observation dynamics showed differences in the values of the A(H3N2) influenza virus among pregnant women vaccinated with an immunoadjuvant preparation, in which they were higher in comparison with the pregnant women receiving the unadjusted vaccine. Conversely, the average geometric titers of antibodies to the influenza B virus strain were higher at all observation times in subjects vaccinated with a conventional subunit vaccine. It is important to note that these differences disappear 8–9 months after immunization, regardless of the vaccine used. It is interesting that there were no differences between the groups according to the average geometric titers of antibodies to the strain of the A(H1N1) virus.

Despite the fact that the levels of seroprotection, determined at 1 month and 8–9 months after immunization, did not differ statistically, except for the A(H1N1) strain in group I, the average geometric amount of antibodies received in 8–9 months was lower, regardless of the vaccine used, except for the A(H3N2) virus strain in group I and A(H1N1) in group II, which corresponded to the antibody level after 1 month after vaccination.

The level and seroconversion factor reflecting the increase in antibody titers after immunization against influenza were high during the first month after vaccination in both study groups, although there were some differences (a relatively lower increase in antibody titer after the first month after immunization against influenza A(H3N2) in group I).

Thus, the administration of subunit influenza vaccines to women in the second and third trimester of pregnancy does not lead to the development of unusual phenomena that cause a complicated course of pregnancy. In the post-vaccination period, an asymptomatic complex

of systemic reactions was most often associated with the psycho-emotional state of pregnant women, due to the fear of the possible development of an adverse effect of vaccination. After vaccination, antibodies to all strains of the influenza virus were observed at a conventionally protective level with an increase to 64.8–94.5% after immunization with the subunit vaccine and to 72.5–90.0% after the administration of the immunoadjuvant vaccine. Although the number of cases of seropositive pregnant women declined in the post-immunization period, we demonstrated that the majority of subjects immunized against influenza were still protected from three strains of the influenza virus 8–9 months after vaccination (the proportions changed to 51.3–72.9% in group I and to 54.2–74.2% in group II). Another interesting result was that during the epidemic season, there were no cases of influenza among the immunized.

In conclusion, the most advanced trivalent subunit anti-influenza vaccines, Agrippal S1, and Grippol Plus are an effective means of specifically preventing influenza for pregnant women, in full compliance with the requirements of the CPMP. The immunogenicity of subunit influenza vaccines in pregnant subjects is confirmed by the fact that 1 month after vaccination, a high level of seroprotection, seroconversion and high intensity of influenza immunity are provided. After the introduction of an immunoadjuvant vaccine with a reduced number of antigens (5 μg of each of the influenza virus strains), the criteria for CPMP were fully met for all strains of the influenza virus included in the vaccine.

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