

## Vaccination against influenza in pregnant women

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**Pregnancy places otherwise healthy women at an increased risk of complications arising from an influenza infection. It is suggested that physiological changes such as immunological changes, increased cardiac output and oxygen consumption, as well as lung tidal volume might increase the susceptibility to influenza complications if infection occurs during pregnancy. Immunization of pregnant women against influenza is currently recommended in many countries and has been proven to be safe and effective in reducing rates and severity of the disease in vaccinated mothers and their children. Influenza vaccination is also cost-effective. Nevertheless, influenza vaccine coverage remains low in pregnant women. This might stem from the lack of healthcare workers' education, a feeling among the general public that influenza is not a serious disease and a failure of prenatal care providers to offer the vaccine. In order to protect pregnant women and infants from influenza related morbidity and mortality an educational programme targeting healthcare workers in charge of pregnant women should be implemented.**

**Key words:** influenza, vaccination, pregnancy

**Received:** 18 May, 2014; **revised:** 12 August, 2014; **accepted:** 12 August, 2014; **available on-line:** 08 September, 2014

### INFLUENZA IN PREGNANT WOMEN AND THEIR INFANTS

Pregnant women form a special group of patients that, although infected with influenza with similar frequency as general population, display complications more frequently. Pregnant women are more often admitted to hospitals with cardiac complications in the course of influenza than women in the postpartum period. The risk of complications depends on the pregnancy stage and is higher at 37–42 weeks of gestation compared with 21–26 weeks of gestation (Neuzil *et al.*, 1998). Interesting data come from observations made during the last influenza pandemic: 32% of pregnant women suffering from the flu required hospitalization, whereas the appropriate rate in the general population was 8% (Jameson *et al.*, 2009). Furthermore, 9% of pregnant women hospitalized due to influenza required treatment in the intensive care unit (ICU), 20% of whom were diagnosed with pneumonia that in some patients led to the development of acute respiratory distress syndrome (Jameson *et al.*, 2009). Pregnant women were over 7 times more often hospitalized, and 4.3 times more likely required treatment in the ICU when compared with the general population (Creanga *et al.*, 2010). It was also calculated that among

all deaths from influenza in 2009–2010, 4–13% of them concerned pregnant women (Creanga *et al.*, 2010; WHO, 2010). Factors increasing the risk of severe course of influenza in pregnant women are associated with physiological changes occurring mainly in the third trimester of pregnancy, including debilitating changes in the immune system, increased cardiac ejection fraction, increased oxygen consumption and reduced lung volume (Puck *et al.*, 1980; Creanga *et al.*, 2010; Steinhoff *et al.*, 2010).

The effect of influenza virus infection on the fetus is not fully understood. Fetus viremia in the course of infection with influenza virus is rarely ascertained, but transplacental transmission of influenza viruses is possible, as evidenced by descriptions of the disease in newborns (Fisher *et al.*, 2012). It is known that infection during pregnancy increases the risk of miscarriage and premature births and stillbirths. This also applies to infections caused by the influenza virus (Stanwell-Smith *et al.*, 1994; Louie *et al.*, 2009; Leick-Courtois *et al.*, 2011). Some researchers have suggested there is a relationship between mother's influenza virus infection and the incidence of fetal birth defects such as a cleft palate, neural tube development disorders or congenital heart defects (Stanwell-Smith *et al.*, 1994). However, it seems that the influenza virus has no direct teratogenic effect and damage to the fetus may be caused by a fever. Indeed, it has been shown that if fever occurs in women in the third trimester of pregnancy, it is associated with the occurrence of neural tube defects of the fetus and seizures in the neonatal period (Nishiura *et al.*, 2009).

It should be emphasized that currently registered and available influenza vaccines are meant for individuals over 6 months of age and when outbreaks of influenza occur in younger infants they carry a high risk of complications, hospitalization and death. Indeed, outbreaks of infections caused by influenza virus have been described in neonates (Pierce *et al.*, 2011). Data from the season 2003/2004 in the United States indicate that the death rate from influenza in infants aged 0–6 months was 88/100 000, with only one third of deaths that could be attributed to chronic diseases such as bronchial asthma, chronic lung disease or cardiovascular conditions (Glass *et al.*, 2009). The question is “How can we protect newborns and young infants from influenza virus infections?”. Undoubtedly, a protective role is played by maternal antibodies transferred transplacentally (IgG antibodies) and during lactation (IgA antibodies) to the

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**Abbreviations:** ACIP, Advisory Committee on Immunization Practices; ACOG, American College of Obstetricians and Gynecologists; ICU, Intensive Care Unit; TIV, Trivalent Influenza Vaccine; VAERS, Vaccine Adverse Event Reporting System; WHO, World Health Organization.

child (Englund *et al.*, 1993). Duration of passive protection seems to depend on the concentration of the antibody in the cord blood and is believed to operate up to 6 months of age (Englund *et al.*, 1993). Accordingly, children with higher levels of antibodies in the cord blood had flu occurring at a later age, and less severe than in children with lower levels of antibodies derived from the mother (Puck *et al.*, 1980).

#### **INFLUENZA VACCINATION IN PREGNANT WOMEN, PROOFS OF SAFETY AND IMMUNOGENICITY, EFFECT ON INFANTS**

Influenza vaccines (inactivated split virion vaccine or subunit vaccine) were given to millions of pregnant women in the world with no harmful effects on either the mother or the child. During the 2000–2003 season, an estimated 2 million pregnant women were immunized and only 20 adverse events among women who received TIV were reported to Vaccine Adverse Event Reporting System (VAERS), including nine injection-site reactions and eight systemic reactions (e.g. fever, headache and myalgia). In addition, three miscarriages, not known to be causally related to the vaccination, were reported (Is-cander *et al.*, 2006). The incidence of adverse reactions was similar among vaccinated and unvaccinated women (Munoz *et al.*, 2005), and there was no increased risk of obstetric complications during pregnancy (Sumaya *et al.*, 1979; Sheffield *et al.*, 2011) or more cesarean deliveries in vaccinated women, including the risk of the preterm delivery (Black *et al.*, 2004; Englund *et al.*, 1993; Zaman *et al.*, 2008). Importantly, the efficacy of pregnant women vaccination in reducing the number of respiratory infections with fever and reducing the number of cases of influenza and hospitalization due to influenza in children born to mothers vaccinated against influenza during pregnancy has been extensively demonstrated.

One of the first published papers aimed to determine the effectiveness of influenza vaccination in pregnant women was a randomized controlled study conducted by Zaman and coworkers (2008), which involved more than 300 patients in Bangladesh in the season 2004/2005. The authors proved a reduction in the number of infections with influenza-like symptoms and fever in mothers by 36% and demonstrated that 88% of vaccinated women produced protective levels of antibodies after vaccination (Zaman *et al.*, 2008). Later study by Thompson and coworkers (2014) provided further substantial evidence on the effectiveness of the vaccination against influenza in pregnant women demonstrating that influenza vaccination of pregnant women reduced the risk of getting the flu by 50%.

Vaccination of pregnant women against influenza protects their infants. Benowitz and coworkers (2010) indicated 92% effectiveness of vaccination during pregnancy in preventing hospitalization due to influenza in children 12 months after delivery. Poehling and coworkers (2011) demonstrated that infants of mothers vaccinated during pregnancy had a reduced risk of hospitalization due to flu by 45–48%. Eick and coworkers (2011) also showed that children born by vaccinated mothers had the risk of influenza reduced by 41% and the risk of hospitalization arising from infection with influenza-like symptoms reduced by 39%.

Influenza vaccines administered during pregnancy did not show any harmful effects on fetuses, newborns and infants. No differences have been observed in the development of infants during their first 6 months of age

(Munoz *et al.*, 2005; Sheffield *et al.*, 2011). No differences in the incidence of preterm births, incidence of low birth weight among two groups have been revealed (Zaman *et al.*, 2008). Omer and coworkers (2011) showed a lower risk of intrauterine immaturity and hypotrophy among infants of vaccinated women.

#### **RECOMMENDATIONS FOR INFLUENZA VACCINATION OF PREGNANT WOMEN**

Recommendations for influenza vaccination of pregnant women in the second and third trimester of pregnancy using inactivated virus have been implemented in the United States and Canada for over 10 years. They were first published by the U.S. Advisory Committee on Immunization Practices (ACIP) in 1997; in 2004 these recommendations were expanded, recommending influenza vaccination not only in the second and third trimesters, but also in the first trimester of pregnancy (in both healthy women and those affected by chronic diseases, which might constitute a risk factor for severe and complicated course of the flu) (ACIP, 2005). The WHO in 2005 recommended vaccination for all pregnant women during an epidemic season (WHO, 2005). Vaccination against influenza in pregnant women has also been recommended by the American College of Obstetricians and Gynecologists (ACOG, 2004). Despite the official recommendations of experts, the level of vaccinations against influenza in the population of pregnant women is very low and varies from 2 to 20% (CDC, 2010). The reasons of low influenza vaccination rates among pregnant women can be such as: lack of physicians' recommendation, difficulties with access to vaccinations in obstetric and gynecological wards, insufficient knowledge about influenza and its complications in pregnant women and medical professionals, scarce knowledge concerning safety and efficacy of influenza vaccination both in pregnant women and medical staff, the common belief expressed by patients that the flu is not a serious disease, lack of reimbursement of vaccination, or even the misconception that vaccination against influenza can cause flu (Panda *et al.*, 2010; Tong *et al.*, 2010; Yudin *et al.*, 2011). Indeed, some studies indicate insufficient medical knowledge concerning influenza vaccination in pregnancy: 40% of surveyed doctors and nurses did not know that pregnant women were in the high risk group for complicated and severe course of influenza and only 65% were aware of recommendations for influenza vaccinations for this group of patients (Panda *et al.*, 2010; Tong *et al.*, 2010; Yudin *et al.*, 2011). All this shows that intensive educational efforts should be directed toward medical staff, especially those taking care of women of childbearing age, in order to improve the influenza immunization status among this patient population. Vaccines-related topics, including vaccination against influenza among pregnant women, should be implemented into the national courses for medical and nursing students (pre-graduate educational level) and also should be a part of postgraduate continuous medical education. Researchers need to monitor vaccination-related intentions, attitudes, and behaviors among patients. Psychometrically validated tools also must be developed and implemented in longitudinal studies in order to capture and measure baseline attitudes to vaccination and then track their evolution in near real time (Thompson *et al.*, 2012).

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