INFLUENZA DURING PREGNANCY: AN IGNORED ASSOCIATION. PLEA FOR VACCINATION

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Abstract

Influenza during pregnancy exposes pregnant women at great risks with high morbidity and mortality, during pandemic influenza and non-pandemic seasons. Pregnant women are more susceptible in developing sever illness and complications of influenza because of the normal physiologic changes that occur during pregnancy.

During the H1N1 pandemic influenza from 2009-2010, there were many pregnant women who required hospitalization, with higher risk of death compared to non-pregnant women. The fetuses of pregnant women affected by influenza, are at greater risk of severe outcomes, such as: preterm birth, low birth weight, malformations and even death.

The most efficient way to prevent influenza is vaccination. This is recommended to all persons > 6 months of age, especially to women in preconception, antenatal and postnatal period. Despite this, the rate of vaccination is still low because the lack of recommendations from health care providers and the reluctance of patients. Antiviral medication represented by neuraminidase inhibitors is also recommended during pregnancy to diminish the severity of the disease.

The purpose of this review is to present the maternal and fetal risks during influenza and the importance of vaccination and antiviral medication.

Rezumat: Gripa în tipul sarcinii: O asociere ignorată. Pledoarie pentru vaccinare.

Gripa în timpul sarcinii expune mama la riscuri importante, cu morbiditate şi mortalitate crescute, atât în perioadele de pandemie cât şi în timpul gripei sezoniere. Femeile gravide sunt mai susceptibile în a dezvolta boală severă şi complicaţii ale gripei datorită modificărilor fiziologice care apar în timpul sarcinii.

În timpul pandemiei de gripă H1N1 din 2009-2010, a existat un număr crescut de gravide care au necesitat spitalizare, acestea având un risc mai mare de moarte comparativ cu femeile negravide. Feţii mamelor cu gripă apărută pe parcursul sarcinii, prezintă, de asemenea, un risc crescut de reacţii adverse severe, cum ar fi: naşterea prematură, greutatea mică la naştere, diferite malformaţii sau chiar decesul.

Cea mai eficientă metodă de prevenţie a gripei este vaccinarea. Aceasta este recomandată tuturor persoanelor peste 6 luni, în special femeilor aflate în perioada preconcepţională, antenatală şi postnatală. Cu toate acestea, rata de vaccinare a gravidelor este încă mică din cauza lipsei de recomandare din partea medicilor şi a reticenţei pacientelor. Medicaţia antivirală reprezentată de inhibitori de neuraminidază este, de asemenea, recomandată în timpul sarcinii pentru a ameliora severitatea bolii.

Scopul acestui articol este de a prezenta riscurile materne şi fetale în gripă şi importanţa vaccinării şi a tratamentului acesteia.

Cuvinte cheie: sarcină, făt, gripă, vaccinare, medicaţie antivirală.

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Introduction

Influenza is a potentially severe disease caused by infection with influenza A or B viruses. There are groups of people at great risk for developing severe illness with important complications: young children, persons aged 65 years or greater, persons with others comorbidities and pregnant women. The increased risk of pregnant women has been proved in many studies conducted during seasonal epidemics or during pandemics [1,2]. The fetuses and newborns are also at great risk for complications, such as: preterm deliveries, low birth weight or congenital anomalies [3,4,5].

The Center for Disease Control (CDC) and Advisory Committee on Immunization Practices (ACIP) have recommended vaccination during influenza season for pregnant women without regard to gestational age [6]. The vaccine protects pregnant women against severe disease and also increase neonatal outcome.

Antiviral medication reduces the duration, severity and risk of complications in influenza illnesses. The most used agent is Oseltamivir, a neuraminidase inhibitor. Studies have showed that the use of Oseltamivir is safe during pregnancy [7].

Influenza Virus

Influenza viruses are RNA viruses, classified within Orthomyxoviridae family. There are 4 types of viruses: A, B, C and D. Only A, B and C can affect people; the most common type is A, which is the most pathogenic and together with type B can cause seasonal epidemics; type C have been reported especially in children and cause a mild illness; type D is not known to affect people [8].

Influenza viruses structure is similar for all types: a central core which contains the viral RNA genome and a viral envelope containing two main types of glycoproteins. Influenza A viruses are divided based on two proteins located on the surface of the virus: hemagglutinin (H) and neuraminidase (N). There are 18 types of hemagglutinin and 11 types of neuraminidase. Influenza B viruses are not divided into subgroups [8]. Hemagglutinins are glycoprotein which helps the virus to connect with the cells host and facilitates the entry of the viral genome into the cell. Neuraminidases are glycoside hydrolase enzymes which offer mobility to the new virus particles and helps the virus to spread.

Influenza virus is capable of mutation and reassortment. Mutation, called antigenic drift, cause small changes in the H and N antigens, resulting in new strains that can cause an epidemic [9]. Reassortment, called antigenic shift, assume acquiring new antigens from mixing genetic material into new combinations in different individuals. The new virus will rapidly spread because everybody is susceptible, causing a pandemic [10]. The last century pandemics have been Spanish flu H1N1 (1918), Asian flu H2N2 (1957), and Hong Kong flu H3N2 (1968). The pandemic of this century was Swine flu H1N1 (2009).

Clinical manifestations and diagnostic

Influenza is an acute and contagious illness of the respiratory tract. It occurs mainly in the winter season. Transmission can be made in three main ways: direct transmission (the mucus from an infected person reach directly into the nose, eyes or mouth), airborne route (the aerosol from an infected person are inhaled) or contact (hand to eyes, hand to nose, hand to mouth) from contaminated surfaces or from personal contact (hand shake) [11]. Influenza viruses affects mainly some categories of persons which are more susceptible of developing a severe illness and complications: children under 5 years, persons older than 65 years, pregnant women, persons with other comorbidities [12].

Clinical manifestations of flu can be general manifestations, such as fever, myalgia, headache, fatigue and signs/symptoms of the respiratory tract as cough, sore throat, nasal congestion, sneezing. Most people experience a mild form of illness and they recover in several days to less than two weeks. The groups of people who are at high risk of developing complications, can require hospitalization and even admission in intensive care units. The most common complication is pneumonia either primary influenza pneumonia or secondary bacterial pneumonia. Other complications include encephalitis, meningitis, Guillain-Barré syndrome, myocarditis, pericarditis.

Laboratory testing include rapid antigen tests, immunofluorescence assay, reverse transcriptase polymerase chain reaction (RT-PCR) and viral culture [13].

Rapid antigens tests are qualitative tests that can identify viral antigens with results in approximately 15 minutes. The sensitivity of this tests is 62.3% and the specificity is 98.2%. [14]. Direct or indirect immunofluorescence detects the influenza antigens using immunofluorescent antibody. This test is a rapid one, with result within hours. RT-PCR is a confirmatory test that differentiates between specific types and subtypes of influenza viruses. RT-PCR is the most sensitive and specific test for influenza diagnostic [15]. Viral culture is a test used for public health surveillance and for confirming screening tests; although the test has been the gold standard for laboratory diagnosis, is not used for clinical management because it take 48 to 72 hours or even longer to have a result [15].

Effects of influenza viruses on pregnant women

Influenza during pregnancy exposes pregnant women at great risks with high morbidity and mortality, during pandemic influenza and non-pandemic seasons [1]. During pregnancy significant changes take place into the pathophysiologic mechanisms and immune function. A reduction in lung capacity with a decrease chest compliance, increased intra-abdominal pressure with elevation of the diaphragm, are changes that raise the risk for respiratory illnesses [16]. Pregnancy imply an immunosuppressive state with alteration in cell-mediated immunity [17]. Cytokine modifications (increased production in T helper 1 and 2 cells, decreased production in NK cell function) have a role in the process of maternal-fetal tolerance [18].

Pregnant women are more susceptible in developing sever illnesses and complications of influenza compared with the general population. They have a higher rate of hospitalization and admission to intensive care units [1]. A large study conducted during 19 influenza seasons, which included over 4 300 women, compared pregnant women with postpartum women. Pregnant women had a high rate of hospitalization for a cardiopulmonary illnesses as pregnancy progressed [2]. In an American series, the hospitalization rate during seasonal influenza for pregnant women that were in the third trimester, was 250/100 000 [2].

Another study that analyzed hospital admission for pregnant women during influenza season to the year before they were pregnant, concluded that pregnant women have a five time higher risk to be hospitalized for a respiratory illness [1]. Pregnant women have also high risks for complication and for hospital admission during pandemic influenza. During H1N1 influenza pandemic from 1918 and H2N2 influenza pandemic from 1957, pregnant women had important mortality rates.

In USA during H1N1 influenza pandemic from 2009, were reported 788 pregnant women of which 22.6% were admitted to an intensive care unit. Pregnant women who started treatment more than 4 days after symptom onset were more likely to be hospitalized to an intensive care unit compared with those treated within 2 days after symptoms begun [19]. The same study reported that pregnant women's death represent 5% of all deaths related to H1N1 in 2009.

Data from other studies shows that the risks for complications and death related to influenza virus, are greater in the second and third trimester of pregnancy [1,2]. Data collected from 2009 pandemic also shows that postpartum women are at greater risk for influenza associated complications [20].

During H1N1 pandemic in USA, 64.3% of all deaths occurred in the third trimester, 26.8% in the second trimester and 7.1% in the first trimester [19].

Effect of influenza viruses on the fetus

The fetuses of pregnant women affected by influenza are at greater risk of severe outcomes, such as miscarriage, preterm birth, low birth weight, malformations, perinatal mortality.

During influenza infection the spread of the virus beyond respiratory tract is unusual and viremia is rare; consequently, vertical transmission of the virus through the placenta is uncommon [21,22,23]. Despite all this findings, there was reported and documented a case of trans-placental transmission in a pregnant woman who was infected with H5N1 virus. The fetus was affected and died; on pathologic examination the

viral antigens and genome were found in the fetal lung's cell and in the placenta [24].

In USA in a study published in 2010, the preterm birth rate from H1N1 pandemic influenza was 30.2%, compared with the national preterm birth rate from 2007 (13%). This findings are related with data from previous pandemics, which also observed a high rate of preterm deliveries [19,25].

Pregnancy loss is another complication related to influenza infection. During H1N1 pandemic from 1918, there were 25% miscarriages among women with uncomplicated influenza and 50% miscarriages among those who had complications, such as pneumonia. A recent analysis of birth rate during 1918, reveal a decrease in the birth rate of the next year; the conclusion was that the influenza caused first trimester pregnancy losses [26].

A study conducted in Nova Scotia demonstrated that infants born to mothers who were hospitalized for respiratory illness at any time during pregnancy, through influenza season, are more likely to have lower mean birth weight and to be small for gestational age [4].

During H1N1 pandemic infants who were delivered during the mother's hospitalization had increased probability to be born premature or to have low birth weight, while the infants delivered after the discharge from the hospital were more likely to be small for gestational age [3]. A series of 256 women from United Kingdom were studied during 2009 H1N1 pandemic influenza; the outcome revealed a fourfold increased possibility of preterm birth, a high perinatal mortality rate (39/1 000 births by comparison with 7/1 000 in women without influenza) and an increased stillbirth rate [27].

Exposure to influenza virus in the first trimester of pregnancy was associated with an increased risk of congenital anomalies, such as neural tube defects, heart defects, cleft lip, limb reduction [5].

Others association have been made between exposure of the mother to influenza virus and adverse outcomes for the infant, such as childhood leukemia or schizophrenia [28,29].

Fever is a common symptom of influenza and has been associated with high risk for adverse infant outcome if the mother experiences fever during pregnancy. Associations between hyperthermia and neural tube defects or other congenital anomalies (orofacial clefts, heart defects) were found [30,31].

Influenza vaccination during pregnancy

Influenza vaccination is recommended for all persons over 6 months of age. Women in preconception, antenatal and postnatal period are at great risk for developing sever illnesses and complications with bad outcome for them and for their infant. Pregnant women are considered to be a priority population due to their vulnerability and vaccination is an important element of prevention for severe infection.

Since 2004, CDC and ACIP have recommended vaccination during influenza season for pregnant women without regard to gestational age and for women that will be pregnant during the season. They will receive inactivated influenza vaccine, both trivalent or quadrivalent [6]. Live, attenuated influenza vaccine is an intranasal spray which is not recommended for pregnant women, but can be used in the postpartum period [6]. The influenza vaccination reduces the maternal risk for influenza illness. A cohort study that included pregnant women with or without HIV infection, showed that vaccination provided partial protection against confirmed influenza in both groups [32].

Although the primary goal of the vaccination against influenza virus was to protect the pregnant women against severe disease during seasonal or pandemic influenza, advantages for neonates have also been shown through maternal antibodies witch passes to the fetus system and provides immunity [32]. The vaccination with inactivated influenza vaccine, determine a similar effect on the immune system as natural influenza infection, with production of IgG antibodies. The antibodies from the mother then pass throw the placental circulation to the fetus and provides the best protection during intrauterine life and 6 months after birth [33,34].

Antibodies placental transfer is demonstrated in a study of 69 maternal-infant pairs. All women had at birth an antibody titer at or above 1:40; 95.6% of infants had similar antibody titer at birth and at 2

months; at 5 months the titers diminished to 81.2% [35]. A randomized trial showed advantages for infants whose mothers had been immunized and reported up to 63% fewer influenza illnesses in infants as far as 6 months after birth and fewer respiratory cases with fever in mothers and infants [34].

Influenza vaccination improves fetal outcome. In a clinical trial from Bangladesh pregnant women received either influenza or pneumococcal vaccines. The results reveal that infants born to mothers who received influenza vaccines had an increase mean birth weight (3178 g vs 2978 g) and a lower proportion of them were small for gestational age (25.9% vs 44.8%) comparing with infants born to women who received pneumococcal vaccine [36].

Maternal immunization with influenza vaccine has proved to reduce the hospitalization for infants under 6 months old for influenza illnesses by 45-48% [37].

In a retrospective study that included 1 237 pregnant women, with 28.05% vaccinated women, demonstrated that adverse neonatal outcomes were lower in the vaccinated group: prematurity (9.1% compared with 17.6%), small for gestational age (8% compared with 14%) and low birth weight (6.3% compared with 10.4%). The same study showed that infants of unvaccinated mothers are at twofold increased risk for prematurity, 40% risk for small for gestational age and 30% risk for low birth weight.

The safety of the influenza vaccine was also proved; there were no increased birth defects among infants of vaccinated mothers [38]. A retrospective study compared 1 125 pregnant women who received influenza vaccine against H1N1 with 2 202 who did not received the vaccine; neonates of vaccinated mothers had 37% lower odds of being born preterm and they had heavier birth weights [39].

A Canadian study which compared 23 340 women vaccinated with H1N1 vaccine with 32 230 unvaccinated women, revealed that vaccination during the second and third trimester of pregnancy is associated with increased neonatal outcome; infants of vaccinated mothers had lower chances of preterm birth under 32 weeks, of being small for gestational age and lower chances for fetal death [40].

Although pregnant women are concerned about the safety of influenza vaccine, no studies have demonstrated an increased risk of complications or harmful consequences for mothers and their infants compared with the general population. Studies conducted in Europe during H1N1 pandemic, reported no side effects or adverse events through pregnant women who were vaccinated or through their infants, with no differences in congenital anomaly rates compared with general population [35,41].

Despite the guidelines recommendations, the rate of vaccination against influenza virus is still low among pregnant women. In two Canadian studies, only 20% of all pregnant women had been offered the vaccine and only 2.6% of all pregnant women and 6.7% of pregnant women with comorbidities were immunized [1,42]. During the H1N1 2009-2010 pandemic, the vaccination rate has increased and reached 50% [43].

Patients refuse the vaccine due to lack of information and anxiety, considering that vaccination can raise the risk of miscarriage or can harm the fetus. The vaccination rate needs to increase with help from health care providers which must recommend to all pregnant women the vaccine and with improving the population's education.

Antiviral treatment for influenza during pregnancy

Two classes of antiviral medication are available for prophylaxis and treatment of influenza: the neuraminidase inhibitors (oseltamivir, zanamivir) and the adamantanes (amantadine, rimantadine). The second class is active only against influenza A and have been considered first-line drugs for the treatment of influenza infection, but are not used anymore because of increased resistant of viruses [44].

Neuraminidase inhibitors are effective against both influenza A and B and are the most used antiviral agents now. Oseltamivir is orally administrated and is absorbed systemically crossing in a small amount the placenta and in breast milk, while Zanamivir is an inhaled drug, with no absorption into the blood stream and is active only in the respiratory tract [45]. Studies show that the placental transfer of Oseltamivir's metabolites is low [46,47].

The medication is the most efficient in the early course of the disease, within 12 hours, and should

be initiated within 24-48 hours after the onset of symptoms. This agents are recommended for high risk persons, including pregnant women or in case of moderate to severe disease [17,48,49]. It has been demonstrated that antiviral drugs are efficient if are used in general population and also in high risk population; it reduces the duration, severity and risk of complications in laboratory confirmed influenza [49,50,51].

There are no clinical trials to prove the safety of the neuraminidase inhibitors. However, there are studies proving that this agents are unlikely to cause adverse or teratogenic effects on fetuses [52].

A study conducted on 2 926 maternal exposures to Oseltamivir, concluded that the drug is unlikely to cause adverse pregnancy outcome or birth defects. The incidence of adverse pregnancy outcomes was: 2.9% spontaneous abortion, 1.8% therapeutic abortions and 4.2% preterm deliveries. This incidences are lower than in the general population [7].

Conclusions

Influenza virus is a RNA virus which belongs to Orthomyxoviridae family; there are 4 types, but only influenza A and B are the most common causing an acute and contagious disease of the respiratory tract. The virus can affect everyone, but there are groups at high risk, including pregnat women.

Pregnant women are more susceptible in developing sever illness and complications of influenza, with high rate of hospitalization and important mortality rates.

The fetuses of mothers affected by influenza virus are also at great risk of severe outcomes. Although, it is uncommon for the virus to pass throw the placental barrier, studies have shown that infants are more likely to be small for gestational age, to have a lower mean birth weight or to be born premature. Exposure to influenza virus was also associated with increased risk for congenital anomalies and high perinatal mortality rate.

Influenza vaccination with inactivated vaccine is recommended to all women that will be pregnant or are pregnant in the influenza season due to their increased vulnerability. The purpose of vaccination is to protect pregnant women against severe disease and improve fetal outcome. It was proved that vaccination of the mother protects the infant against influenza illnesses as far as 6 months after birth. The infants of vaccinated mothers had an increased mean birth weight, lower chances to be born preterm or lower chances for fetal death. The vaccine is proved to be safe during pregnancy with no harmful consequences for mothers or their fetuses.

Despite the recommendations, many patients refuse the vaccine due to lack of informations and anxiety. The vaccination rate need to increase and health care providers must recommend furtermore the immunization against influenza virus.

The most recommended antiviral medications in pregnancy are neuraminidase inhibitors. The drug must be administered early after the onset of symptoms. It reduce the severity, duration and risk of influenza complications. There are studies proving that antiviral medication is unlikely to cause teratogenic or adverse outcomes for fetuses.

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