

Influenza infection during pregnancy

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Abstract

Influenza is the acute viral infection of respiratory system which is seen commonly and usually self-limiting. In some specific cases such as pregnancy, the complications of the disease tend to be seen more common compared to the general population. During influenza season, the admission to the hospital, hospitalization requirement and intensive care need due to acute respiratory distress in pregnant women because of influenza infection is significantly higher than the women who are not pregnant. Seasonally, the first cases with influenza infection are reported in October, with an increase in the reports during January and February, and the cases are reported until May. During the period between October and May, known as the influenza season, inactive influenza vaccination is recommended for pregnant women. Inactive influenza vaccination can be done at any period of pregnancy. Although live attenuated influenza vaccines can be used during postpartum period, it should not be used during pregnancy. The diagnosis of influenza infection is usually established clinically. Empiric treatment is recommended for pregnant women in case of clinical suspicion, without waiting for the results of diagnostic tests particularly in pandemic conditions. The pregnant women with hospitalization indication, who are suspected or confirmed for influenza infection, should be hospitalized and appropriate antiretroviral treatment should be initiated as soon as possible without waiting for the results of diagnostic tests. During pregnancy, the use of neuroaminidase inhibitor antiviral medications is indicated for the treatment and prophylaxis after influenza exposure for patients who have suspected or confirmed influenza infection. Oseltamivir is an outstanding neuroaminidase inhibitor to use in the treatment and prophylaxis of influenza infection during pregnancy as the resistance rate of influenza strains is low, its systemic absorption is well and clinical experience regarding this medication is high.

Keywords: Influenza, influenza vaccine, oseltamivir, pregnancy.

Özet: Gebelikte influenza enfeksiyonu

İnfluenza virüs enfeksiyonu sık görülen ve genellikle kendini sınırlayan solunum sisteminin akut viral enfeksiyonudur. Gebelik gibi bazı özel durumlarda genel topluma oranla hastalığın komplikasyonları daha sık görülmeye eğilimindedir. İnfluenza sezonu boyunca gebe kadınlarda influenza enfeksiyonu nedeniyle hastaneye başvuru sayısı, hastaneye yatış ihtiyacı ve akut respiratuar distres nedenli yoğun bakım ihtiyacı gebe olmayan kadınlara oranla anlamlı oranda yüksektir. İnfluenza enfeksiyonunda mevsimsel olarak ilk olgular genelde Ekim ayı gibi bildirilmeye başlanmakta, Ocak-Şubat aylarında olgu sayılarında ciddi artış olmakta ve Mayıs ayına kadar olgular bildirilmeye devam etmektedir. İnfluenza sezonu olarak bilinen Ekim-Mayıs ayları arasında gebe olan kadınların inaktif influenza aşısı ile aşılanmaları önerilmektedir. İnaktif influenza aşısı gebeliğin herhangi bir zamanında uygulanabilir. Canlı, atenüe influenza aşıları postpartum dönemde kullanılabilse de gebelik döneminde kullanılmamalıdır. İnfluenza enfeksiyonu tanısı daha çok klinik olarak konur. Özellikle pandemi durumlarında tanılmal testlerin sonucu beklenmeden klinik şüphe durumunda gebelere ampirik tedavi önerilmektedir. İnfluenza enfeksiyonu şüphesi olan veya influenza enfeksiyonu olduğu doğrulanmış, hastaneye yatış endikasyonu olan gebeler hastaneye yatırılmalı ve uygun antiretroviral tedavi, tanılmal testlerin sonuçları beklenmeden hızlıca başlanmalıdır. Gebelik sırasında nöraminidaz inhibitörü antiviral ilaçların kullanımı, şüpheli veya kanıtlanmış influenza enfeksiyonu bulunan hastaların tedavisi ve influenza maruziyetinden sonra profilaksisi için endikedir. Oseltamivir, influenza şüphesinde direnç görülme oranının düşük olması, sistemik emiliminin iyi olması ve bu ilaçla ilgili klinik deneyimin yüksek olması nedeniyle gebelikte influenza enfeksiyonu tedavisi ve profilaksisinde kullanılması önerilen seçkin bir nöraminidaz inhibitörüdür.

Anahtar sözcükler: Gebelik, influenza, influenza aşısı, oseltamivir.

Introduction

Influenza is the acute viral infection of respiratory system which is seen commonly and usually self-limiting. The transmission rate of influenza viruses is quite high

and it may affect people of all ages. In some specific cases such as pregnancy, the complications of the disease tend to be seen more common compared to the general population.^[1] Although it seems that the risk

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for influenza infection is limited with the third trimester of pregnancy and the first 4 weeks of postpartum period, the evidence level of the data on this matter is not high.^[2] The reasons for severe progress of influenza infections during pregnancy are associated with the physiological changes of pregnancy such as the increased heart rate and oxygen consumption during pregnancy, reduced pulmonary capacity due to the elevated diaphragm and decreased cellular immunity as a result of the shift from Th1 to Th2 with the effects of estradiol and progesterone.^[3] During influenza season, the admission to the hospital, hospitalization need, hospitalization duration and the need for hospitalization in the intensive care unit due to acute respiratory distress in pregnant women because of influenza infection is significantly higher than the women who are not pregnant.^[4] It was reported that pregnant women admit to hospitals for influenza infection 6.8 times higher (relative risk: 3.5–25.3) and their intensive care requirement is 6.5 times higher than normal population.^[5,6]

Epidemiology

Seasonally, the first cases with influenza infection are reported in October, with an increase in the reports during January and February, and the cases are reported until May. Although high mortality rates were reported associated with the pandemic seasonal influenza infections in the years 1918–1919 and 1957–1958, high mortality rates seen in 2009 H1N1 pandemic which is never seen before attracted the attention.^[7] While the influenza virus infections were accounted for 5% of all deaths in 2009 in the USA, 12% of maternal deaths were associated with H1N1 pandemic. While maternal mortality rate was 2.9/million in seasonal influenza infections, it was reported 20/million in 2009 pandemic.^[5] Since 2009, H1N1-associated maternal deaths which can be prevented have still been reported all over the world.^[8] According to the data of Turkish Ministry of Health, 272 patients died during H1N1 pandemic in 2009 in Turkey. According to the report of Pandemic Coordination Unit of Turkish Ministry of Health dated January 5, 2010, 6.1% of the patients who died of Influenza A H1N1-2009 infection were pregnant and puerperal women.^[9] These data clearly show the importance of vaccination against influenza during pregnancy and postpartum periods.

Pathogenesis

Influenza virus is a RNA virus from *Orthomyxoviridae* family and it has three antigenic types. These are Type A, Type B and Type C. Types A and B are responsible for many clinical diseases. A and B are the types causing important clinical issues and seasonal epidemics while Type C is the type mostly causing seasonal mild upper respiratory tract diseases. Influenza A is categorized according to two glycoproteins it carries on its surface. These are hemagglutinin (HA) and neuroaminidase (NA) antigens and it is known today that HA may have 16 different sub-types and NA may have 9 different sub-types, and they may establish a great number of combinations. Influenza B has no sub-type.^[10]

Diagnosis and Clinical Progress

The diagnosis is established with the presence of unexplained fever exceeding 38°C or fever together with at least one of the complaints of common body pain, sore throat, headache, nasal flow, cough, respiratory distress, vomiting and diarrhea. The final diagnosis is confirmed by the detection of virus by real-time polymerase chain reaction (PCR) or virus culture in one of the reference laboratories.^[11] Empiric treatment is recommended for pregnant women in case of clinical suspicion, without waiting for the results of diagnostic tests in pandemic conditions. There are many diagnostic tests providing rapid results. Most of them are qualitative tests and they provide positive or negative result. In these tests, specificity is between 85% and 100% while sensitivity is between 45% and 62%. Therefore, even though the result of rapid diagnostic test is negative, clinically suspicious cases should also be treated.^[12]

The incubation period of influenza infection is 1–4 days. Most of the cases know who transmits the disease. This is either a family member or a colleague. The most common symptoms are cough, fever (rarely above 40°C, <2%), myalgia, nasal flow, sore throat and headache, and tachycardia. Many symptoms recover within a week; however, cough and malaise may continue up to two weeks.^[13]

Maternal Effects

Influenza infection has a more severe clinical progress in pregnant women compared to the general population.^[14] The risk tends to increase especially during third trimester and within first 4 weeks of postpartum period.^[2] The clinical progress during pregnancy may vary

depending on the immunization against influenza. The most common and severe complication of influenza infection during pregnancy is pneumonia and it can develop due to primary viral or secondary bacterial reasons. Since both viral and bacterial pneumonias developing during pregnancy and early postpartum periods may have an adverse progress, early diagnosis should be established and empiric antiviral treatment should be initiated as soon as possible if the influenza infection is symptomatic.

Fetal Effects

Although the transplacental transmission of influenza virus is rare, this transmission was shown in the case with fatal avian influenza (H5N1) infection.^[15,16] It should not be ignored that influenza infection may have fetal effects even in cases where there is no transplacental transmission. Based on some observational studies and case reports, it was argued that influenza infection is associated with congenital anomalies (cleft lip, neural tube defect, hydrocephaly and congenital heart disease), spontaneous abortion, preterm labor, low birth weight and fetal death.^[17-19] Besides, it is suggested that hyperthermia developing as a result of infection is a risk factor for the development of fetal anomalies, and the use of antipyretics would reduce this risk.^[20]

The rate and severity of fetal complications is in proportion to the severity of maternal disease. In ambulatory patients, gestational outcomes are similar to the general population. However, the rates of preterm labor, birth weight small for gestational age (SGA) and fetal death increase in hospitalized patients.^[1] In a study showing the UK national data after 2009 influenza A H1N1 pandemic, perinatal mortality was found 39/1000 (7/1000 in non-infected women), and there were 4-fold increased preterm labor risk, newborn intensive care need ($p < 0.001$) and secondary pneumonia ($p < 0.001$).^[21] Another study reported that there was no difference between pregnant women with H1N1 infection and the control group in terms of perinatal outcomes. However, the patients with severe infection were compared with the control group in the sub-group analysis, and the risk of group with severe infection was found higher in terms of SGA (18.8% vs. 7.4%) and preterm labor (25% vs. 11.6%).^[22]

Vaccination and Prophylaxis

The Centers for Disease Control and Prevention (CDC) recommends to vaccinate ≥ 6 -month pediatric group and all

adult population including pregnant women, all who have no contraindication, annually against influenza.^[19] American College of Obstetricians and Gynecologists Influenza vaccine in pregnancy is categorized as Category-B and C which there is no any evidence to cause any harm for the fetus while there is limited data about that its use is safe in first trimester in pregnancy. But CDC is recommending influenza vaccination before or during any influenza season.^[19] American College of Obstetricians and Gynecologists (ACOG) also recommends vaccination for pregnant women regardless of their weeks of gestation.^[7] Vaccinating pregnant women, as soon as inactive influenza vaccine is available, between October and May which is known as influenza season is important particularly. Inactive influenza vaccination can be done at any period of pregnancy. Besides, October is considered as the most appropriate time for vaccination. When the time of vaccination delayed to November, a decrease is seen in the activity of vaccine.^[12] Post-immunization protective immune response is provided within 14 days. It was reported that no increase in the fetal anomaly risk was observed and stillbirth risk decreased in pregnant women who were vaccinated with first trimester trivalent (triple vaccine) inactive influenza vaccine.^[23] Independent from the week of gestation for vaccination, it was reported that there was a decreased risk for stillbirth, neonatal death and preterm labor by vaccination. Although live attenuated influenza vaccines can be used during postpartum period, it should not be used during pregnancy. Two types of influenza vaccine are available, which are quadrivalent (two vaccines containing influenza A virus and two vaccines containing influenza B virus) and trivalent (two vaccines containing influenza A virus and one vaccine containing influenza B virus).^[24] The Centers for Disease Control and Prevention did not recommend any specific vaccine among these two types of influenza vaccines as there are no studies comparing the impacts of these two vaccine types on wider populations, and reported that any of the vaccine types can be used for immunization. Although the rates of vaccination against influenza by pregnant women were very low previously, this rate reached up to 54% in the USA with the influences of national studies after 2009 pandemic.^[25] It has been showed that the rates of influenza vaccination are higher when healthcare professionals, especially those providing gestational healthcare, inform and provide recommendation about vaccination. Therefore, it is important to inform about the significance of influenza vaccination by healthcare professionals.

In their Cochrane review, Demicheli et al. showed that 2009/2010 monovalent pandemic H1N1 vaccination reduced the rates of influenza-like diseases by 89% in pregnant women, and seasonal inactive vaccine reduced the rates of influenza-like diseases by 24%.^[26] Another review conducted in 2015 showed that influenza vaccination during pregnancy was associated with the decrease in stillbirth rates although it did not have any impact on low rates.^[27] On the other hand, it is known that influenza vaccination during pregnancy protects the newborn for a long time after birth. Antenatal immunization stimulates the production of anti-influenza-specific serum immunoglobulin G (IgG) and this immunoglobulin passes through placenta during fetal period and through breast milk during newborn period.^[28,29] Therefore, maternal immunization during antenatal period is an effective strategy to reduce morbidity and mortality associated with influenza in newborns, and it is also important for the protection against the infection in this group, which has no chance for vaccination in their first 6 months of life and under risk in terms of severe influenza infection.^[30]

The contraindications of the vaccine are similar to those of all other vaccines. It should be avoided in case of allergy and high fever against the substances of vaccine. Although many pregnant women have concerns about the adverse effects on fetus, there are many studies showing that influenza vaccine does not increase the complication risk in pregnant women and fetuses.^[31,32] In addition, like in all other vaccines, adverse effects such as Guillain-Barre syndrome were also reported very rarely in influenza vaccine.^[33] However, no specific risk was shown on pregnant women, fetuses and newborns.

Taking standard precautions, which is the basic factor for the prevention of all infections as well as vaccination, is also significant to prevent influenza infection. Among these precautions are hand hygiene (washing hands with water and soap) and respiratory hygiene (keeping mouth closed when coughing, preventing contact with respiratory secretions etc.).^[34]

Treatment

The pregnant women with hospitalization indication, who are suspected or confirmed for influenza infection, should be hospitalized in a special room and appropriate antiretroviral treatment should be initiated as soon as possible without waiting for the results of diagnostic tests. Cases with severe or persistent symptom(s), those espe-

cially with respiratory symptom(s) and patients who do not exhibit any recovery within 7 days despite the standard precautions and antiviral treatment are the patient group which should be hospitalized and monitored. Ambulatory patients should be monitored properly in terms of respiratory findings. Antiretroviral treatment should be initiated promptly for patients who are suspected for influenza during pregnancy and postpartum periods. There are two groups of agents for antiviral treatment. M2 inhibitors, amantadine and rimantadine, as the agents in the first group, are only used for the treatment and prophylaxis of influenza A. These agents have not been recommended in the primary treatment since 2005–2006 influenza season due to high resistance. Neuroaminidase inhibitors such as oseltamivir, peramivir and zanamivir, as the agents in the second group, are effective for both influenza A and influenza B. This group has been recommended in the primary treatment since 2006.^[35]

In the past, both CDC and ACOG were cautious for antiviral treatment in pregnant women due to the lack of insufficient data. However, after 2009 season, CDC recommends antiviral treatment for both prophylaxis and treatment.^[35] Most of the influenza viruses are sensitive against neuroaminidase inhibitors such as oseltamivir, peramivir and zanamivir. Oseltamivir is an outstanding neuroaminidase inhibitor as the resistance rate of influenza strains is low, its systemic absorption is well and clinical experience regarding this medication is high. As in non-pregnant women, the dose is 75 mg twice per day for 5 days. During the prophylaxis, 75 mg per day for 10 days is recommended. In severe influenza infections, it can be used in higher doses for a longer period. It also can be used during lactation period. It reaches to a specific concentration in breast milk; however, it is below the treatment dose for newborn. Zanamivir is an inhaler agent and can be used by pregnant women. It is important to reduce the fever since hyperthermia during first trimester increases congenital malformation risk such as neural tube defects and is a risk factor during the labor in terms of neonatal encephalopathy, seizure, cerebral palsy and neonatal death, and the use of acetaminophen is recommended since the side effect profile as an antipyretic agent is lower than other antipyretic agents.^[36–40] In cases with severe progress, the treatment should be decided by virological PCR test. In cases which cannot be administered oseltamivir in particular, intravenous peramivir and inhaler zanamivir can be administered. Although effective results are obtained by initiating the treatment

particularly within the first two days when symptoms are observed, treatment should be recommended without considering the duration of symptoms as recovery is observed in the progress of the disease in patients whose treatments are initiated in later phases.

There is no guideline published for fetal monitoring during and after maternal influenza infection in pregnancy. Fetal follow-up frequency and type should be individualized according to each patient and should be carried out in accordance with the decision of physician.

Conclusion

Influenza infection is a common viral respiratory tract disease affecting a significant part of the population during influenza season. The pregnancy prominently increases the risks associated with influenza infection and severe disease and death are seen more frequently in pregnant women compared to the general population. Influenza diagnosis should be established clinically without waiting for the results of diagnostic tests. Influenza vaccination is an effective method to prevent influenza infection. All women who are pregnant or about to deliver during influenza season should be vaccinated by trivalent or quadrivalent influenza vaccine independent from the trimester of pregnancy. While vaccination during pregnancy is a safe and cost-effective method, it also provides neonatal protection against influenza due to the partial transplacental transfer of protective antibodies. During pregnancy, the use of neuroaminidase inhibitor antiviral medications is indicated for the treatment and prophylaxis after influenza exposure for patients who have suspected or confirmed influenza infection.

Conflicts of Interest: No conflicts declared.

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