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Pandemic Influenza A (H1N1) Virus Infection During Pregnancy

Gebelikte Pandemik İnfluenza A (H1N1) Virüs İnfeksiyonu

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SUMMARY

Human infection with novel influenza A (H1N1) virus was first reported in April 2009 in Mexico and then spread to the United States and other countries worldwide. Pandemic influenza A (H1N1) virus infection generally presents mild disease with symptoms similar to those of seasonal influenza A infection. Pregnant women are at higher risk for severe complications and death from influenza. Changes in the immune, respiratory and cardiovascular systems result in pregnant women being more severely affected by influenza. Influenza infections in pregnancy have been associated with adverse maternal and fetal outcomes, including preterm labor, preterm birth, preterm premature rupture of membranes, renal failure, pulmonary embolus, pneumonia, acute respiratory distress syndrome, and death. The rate of hospital admission for H1N1 infection in pregnant women is much higher than for non-pregnant women. Nearly one-third of the pregnant women with H1N1 influenza infection have been hospitalized during the current pandemic, and most of them had severe respiratory distress. Because of high complication rates, the Centers for Disease Control and Prevention (CDC) recommends that pregnant women be started on antiviral drugs as soon as possible after the onset of influenza symptoms. Treatment should not be delayed for laboratory confirmation. The benefit of treatment is greatest if started within 48 hours of onset. Pregnant women are in a high-priority group for pandemic influenza vaccine because of increased risk of morbidity and mortality. H1N1 monovalent vaccine can be given to pregnant women in any trimester.

Key Words: *Influenza A virus, H1N1 subtype, Pandemic, Influenza, Human, Pregnancy*

ÖZET

Gebelikte Pandemik İnfluenza A (H1N1) Virüs İnfeksiyonu

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İnfluenza A (H1N1) virüs infeksiyonu ilk kez Nisan 2009 tarihinde Meksika'dan bildirildi ve daha sonra Amerika Birleşik Devletleri ve diğer dünya ülkelerine yayıldı. Pandemik influenza A (H1N1) virüs infeksiyonu genellikle mevsimsel influenza A infeksiyonu gibi hafif seyirlidir. Gebelerde, influenzanın ciddi komplikasyon ve ölüm riski yüksektir. İmmün, solunum ve kardiyovasküler sistemdeki değişiklikler, gebelerin influenzadan daha şiddetli etkilenmelerine neden olmaktadır. Gebelikte influenza infeksiyonu erken doğum, erken membran rüptürü, renal yetmezlik, pulmoner emboli, pnömoni, akut solunum sıkıntısı sendromu ve ölüm gibi fetal ve maternal komplikasyonla-

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ra yol açmaktadır. Gebelerde H1N1 nedeniyle hastaneye yatış oranı gebe olmayanlara göre daha yüksektir. Pandemi sırasında, H1N1 infeksiyonu olan gebelerin üçte biri hastaneye yatırılmıştır. Çoğunda ciddi solunum sıkıntısı tespit edilmiştir. Yüksek komplikasyon oranından dolayı "Centers for Disease Control and Prevention (CDC)" gebelerde influenza semptomları başlar başlamaz antiviral tedavinin verilmesini önermektedir. Laboratuvar sonuçları beklenerek tedavi geciktirilmemelidir. İlk 48 saatte başlanan tedavinin etkinliği daha fazladır. Morbidite ve mortalite oranının yüksekliğinden dolayı gebe kadınlar ilk aşılanması gereken grupta yer almaktadır. H1N1 monovalent aşı gebeliğin herhangi bir döneminde yapılabilir.

Anahtar Kelimeler: *İnfluenza A virüsü, H1N1 subtipi, Pandemik, İnfluenza, İnsan, Gebelik*

Human infection with novel influenza A (H1N1) virus was first reported in April 2009[1,2]. The virus, which originated in Mexico, has since spread to the United States and other countries worldwide. On June 11, 2009, the World Health Organization (WHO) raised the pandemic alert to "Phase 6", which is the highest alert[3].

Currently, the circulating predominant influenza strain is influenza A (H1N1) virus[4]. The virus represents quadruple reassortment of 1 human, 1 avian and 2 swine strains of the influenza virus[5]. It is present in respiratory secretions of infected persons like other influenza viruses. Although respiratory droplets are the main route of virus transmission, it can be transmitted via contact with contaminated surfaces and by other body fluids. Infected patients are contagious from one day prior to the onset of symptoms until seven days after symptom onset. The incubation period ranges from one to seven days[6].

Pandemic influenza A (H1N1) virus infection generally presents mild disease with symptoms similar to those of seasonal influenza A infection. The hospitalization rate is up to 10% among confirmed cases. Mortality is below 1% and is higher in patients with comorbidities[7,8]. A significant proportion of hospitalized patients have pneumonia. The most common causes of death are pneumonia and acute respiratory distress syndrome (ARDS)[9,10].

The age distribution of incidence is different from that of seasonal influenza. Young adults are affected most; however, the mortality rate is higher in older ages. Though deaths have occurred in individuals with no known underlying disease, the presence of comorbidity poses a greater risk of death. Pregnant women are one of the risk groups for severe pandemic H1N1 influenza infection, and account for 7.7-23% of severe H1N1 infection cases[8-14].

PREGNANCY and INFLUENZA

During previous pandemics, pregnant women have increased morbidity and mortality from influenza infection compared with non-pregnant women. In the 1918 pandemic, about 50% of pregnant women developed pneumonia, and of these women, more than half died (overall fatality rate 27%). The mortality rate was highest in the third trimester. During the 1957 Asian flu pandemic, among women of reproductive age, 50% of deaths occurred in pregnant women. In the previous pandemics, high rates of pregnancy loss and preterm delivery were reported[15].

Pregnant women are at higher risk for severe complications and death from influenza. Changes in the immune, respiratory and cardiovascular systems result in pregnant women being more severely affected by influenza. These changes include decreased lung capacity and tidal volume and increased cardiac output and oxygen consumption. Impaired cell immunity in pregnancy also increases the serious influenza-related complications. The changes become most pronounced by the third trimester. In addition, the decreased colloidal oncotic pressure in the third trimester predisposes pregnant women to develop pulmonary edema. Thus, the complication rate is the highest in the third trimester[6,16,17].

Influenza infections in pregnancy have been associated with adverse maternal and fetal outcomes, including preterm labor, preterm birth, preterm premature rupture of membranes, renal failure, pulmonary embolus, pneumonia, ARDS, and death. The rate of hospital admission for H1N1 infection in pregnant women is much higher than for non-pregnant women. Nearly one-third of the pregnant women with H1N1 influenza infection have been hospitalized during the current pandemic, and most of them had severe respiratory distress[17].

CLINICAL PRESENTATION, COMPLICATIONS and OUTCOME

Signs and symptoms of influenza A (H1N1) infection are similar to those of seasonal influenza. Pregnant women with pandemic influenza A (H1N1) virus infection present with typical influenza-like illness. The symptoms are fever, cough, sore throat, rhinorrhea, myalgia, headache, and fatigue (Table 1). However, vomiting (18%) and diarrhea (12%) are more common than with seasonal influenza[6]. Patients could have respiratory symptoms without fever. Many pregnant women will proceed on a typical course of uncomplicated influenza. However, for some pregnant women, illness might progress rapidly and become complicated.

Pregnant women are at particularly high risk for morbidity and mortality from influenza. The primary life-threatening complications resulting in severe disease or death are pneumonia and ARDS requiring mechanical ventilation. Pregnant women were more frequently hospitalized for acute respiratory illness and cardiopulmonary events[6,18]. Thus, vital signs, oxygen saturation levels, and respiratory and mental status of the patient should be monitored closely[17,18].

The risk of complication and mortality from H1N1 influenza infection is higher among pregnant women, especially in the third trimester, than among non-pregnant women. While pregnant women represent 1% of the population in the United States, they accounted for 6% of the influenza-related deaths. The mortality rate among pregnant women with H1N1 infection was reported as high as 28%, with the highest rate in the third trimester[14]. Among hospitalized severe cases, pregnant women accounted for 11-15% of all patients[9,10].

Many pregnant women who have developed severe complications after H1N1 influenza A infection or who have died, had underlying medical conditions[18]. Comorbidities (type 1 diabetes, severe asthma, cardiac problems, immunosupression and obesity) increase the mortality rate compared to healthy pregnant women[6,11,17,18]. Advanced gestational age also affects prognosis of the infection. Women at term are five times more likely to be hospitalized than postpartum women or those at lesser gestational ages[6].

From April 15 to May 18, 2009, 31 confirmed and 3 probable cases of pandemic influenza A (H1N1) virus infection in pregnant women were reported to the Centers for Disease Control and Prevention (CDC) from 13 states in the U.S. Generally, symptoms reported by pregnant women were similar to those reported by non-pregnant women. However, shortness of breath was more likely to be reported by pregnant women (41% vs. 25%). Of the pregnant women with influenza A (H1N1) virus infection, 11 (32%) were admitted to hospital and 3 (9%) were followed in the intensive care unit. The estimated rate of admission was 4.3 times higher than in the general population (0.32 per 100.000 pregnant women vs. 0.076 per 100.000 populations at risk). Of the 45 deaths from H1N1 2009 influenza virus infection reported to the CDC between April 15 and June 16, 2009, 6 (13%) were among pregnant wo-

Table 1. Characteristics of influenza A (H1N1) in pregnancy (18)

Signs and symptoms of influenza A (H1N1)	Signs and symptoms in severe cases
Fever (> 37.8°C)	High fever not responding to acetaminophen
Chills	Difficulty breathing or shortness of breath
Cough	Pain or pressure in the chest or abdomen
Sore throat	Sudden dizziness or fainting
Rhinorrhea	Confusion
Headache	Decreased or no fetal movement
Myalgias and fatigue	Contractions
Nausea and vomiting	Abdominal cramping
Diarrhea	Vaginal bleeding

men. These patients were healthy before having influenza illness and 4 were in the third trimester. All had developed primary viral pneumonia and subsequent ARDS requiring mechanical ventilation. The length of time from onset of symptoms to beginning of antiviral medication ranged from 6 to 15 days (median 9). None of the 5 infants born to the women who died had any evidence of H1N1 influenza infection[15].

Using publicly available data from May to October 2009 in Australia, the relative risks of hospitalization, admission to the intensive care unit and death were estimated as 5.2, 6.5 and 1.4, respectively, for pregnant women[19].

Demographic and clinical data of H1N1-infected, reproductive-age women who were hospitalized or died were reviewed from April 23 through August 11, 2009, in California. Data were reported for 94 pregnant women, 8 postpartum women, and 137 non-pregnant women of reproductive age who were hospitalized with 2009 H1N1 influenza. Most pregnant patients (95%) were in the second or third trimester, and approximately one-third (34%) had established risk factors for complications from influenza other than pregnancy. Later antiviral treatment (administered > 2 days after symptom onset) was associated with admission to an intensive care unit or death (relative risk, 4.3). In all, 18 pregnant women and 4 postpartum women (22%) required intensive care and 8 (8%) died. The 2009 H1N1 influenza-specific maternal mortality ratio (the number of maternal deaths per 100.000 live births) was 4.3[10].

The EFFECT of INFLUENZA A (H1N1) VIRUS on the FETUS

Little is known about the effects of the pandemic influenza A (H1N1) virus on the fetus. In seasonal influenza, viremia seems to be rare, and placental transmission seems to occur infrequently[15]. Influenza viruses are not considered to be teratogenic in humans. Currently, there have been no reports of pandemic influenza A (H1N1) virus infection in the fetus transmitted via the placenta[20].

The fetus could be adversely affected by maternal hyperthermia, which has been associated with an increased risk for neural tube defects and congenital heart defects in the first trimester[6,15]. Maternal hyperthermia during labor is a risk factor for neonatal seizures, encephalopathy, cerebral palsy, and neonatal death. Thus, fever in pregnant women should be treated[15,18].

DIAGNOSIS

A number of different laboratory diagnostic tests can be used for detecting the presence of influenza viruses in respiratory specimens, including direct antigen detection tests, virus isolation in cell culture, or detection of influenza-specific RNA by real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) (Table 2). These tests differ in their sensitivity

Table 2. Comparison of available influenza diagnostic tests (21)

Influenza diagnostic tests	Method	Typical processing time	Sensitivity for 2009 H1N1 influenza	Distinguishes 2009 H1N1 influenza from other influenza A viruses?
Rapid influenza diagnostic tests (RIDT)	Antigen detection	0.5 hour	10-70%	No
Direct and indirect immunofluorescence assays (DFA and IFA)	Antigen detection	2-4 hours	47-93%	No
Viral isolation in tissue cell culture	Virus isolation	2-10 days	-	Yes
Nucleic acid amplification tests (including rRT-PCR)	RNA detection	48-96 hours	86-100%	Yes

and specificity in detecting influenza viruses. The sensitivity of the rapid test can range from 10% to 70%, and a negative rapid test does not exclude H1N1 virus infection. Direct immunofluorescence assays have variable sensitivity (range 47-93%) for 2009 H1N1 influenza virus, and a high specificity (≥ 96%). Nucleic acid amplification tests, including rRT-PCR, are the most sensitive and specific influenza diagnostic tests, but obtaining test results may take one to several days, and test performance depends on the individual rRT-PCR assay. As with any assay, false-negatives can occur. Not all nucleic acid amplification assays can specifically differentiate 2009 H1N1 influenza virus from other influenza A viruses. If specific testing for 2009 H1N1 influenza virus is required, testing with an rRT-PCR assay specific for 2009 H1N1 influenza or viral culture should be performed. Preferred respiratory specimens for diagnostic tests are nasopharyngeal swab or combined nasopharyngeal/nasal swab with oropharyngeal swab. In patients with pneumonia, endotracheal aspirate or bronchoalveolar lavage could be tested to improve the diagnostic yield[21].

TREATMENT

The present circulating pandemic influenza A (H1N1) virus is sensitive to oseltamivir and zanamivir. Antiviral resistance tests showed that among influenza A (H1N1) viruses, oseltamivir resistance rate is 0.6%, and all viruses tested are susceptible to zanamivir (4). In randomized controlled clinical trials, these drugs have reduced the severity of seasonal influenza if started within 48 hours of illness onset[15]. Data also suggest that oseltamivir can reduce mortality even if started more than 48 hours after symptom onset.

Pregnant women are at higher risk for severe complications from pandemic H1N1 influenza. The CDC recommends that pregnant women be started on antiviral drugs as soon as possible after the onset of influenza symptoms[22]. Treatment should not be delayed for laboratory confirmation. The benefit of treatment is greatest if started within 48 hours of onset. However, health-care providers or pregnant women may be reluctant regarding antiviral treatment because of pregnancy. As with most drugs, information about the safety of these antiviral drugs during pregnancy is limited[15]. In view of the expected effects of pandemic influenza A (H1N1) virus in pregnant women, the benefits of the treatment with these drugs are likely to outweigh potential risks to the fetus. The drugs can be taken during any trimester of pregnancy[23]. Health-care providers should give the information about the benefits and risks of antiviral drugs and about the increased risk of influenza complications in pregnant women.

Oseltamivir (Tamiflu®) is given orally and results in systemic absorption. The recommended dose is 75 mg capsule twice per day for 5 days. Zanamivir (Relenza®) is given by inhalation, and systemic absorption is lower (Table 3). Oseltamivir is the preferred drug in pregnants because of its systemic effect[22]. In patients requiring assisted ventilation, oseltamivir dose might be increased to 150 mg twice daily for a total of 10 days[17].

Hyperthermia is known to have adverse effects on the fetus. Thus, fever should be treated in pregnant women. Acetaminophen is the best option for treatment of fever during pregnancy. Aspirin and nonsteroidal antiinflammatory drugs are not recommended. Besides antipyretics, use of folic acid may reduce the neural tube defects[6].

SAFETY of OSELTAMIVIR and ZANAMIVIR in PREGNANT and BREASTFEEDING WOMEN

Oseltamivir and zanamivir are "Pregnancy Category C" medications. However, the available risk-benefit data indicate pregnant women with suspected or confirmed influenza should receive antiviral therapy[23].

There are more data on the safety of oseltamivir in pregnancy. A study using an ex vivo human placenta model showed that oseltamivir was extensively metabolized by the placenta. Transplacental transfer of the metabolite was incomplete with minimal accumulation on the fetal side[24]. Only 1 (1.1%) malformation (ventricular septal defect) was detected in 90 prospectively followed pregnant women who took therapeutic doses of oseltamivir (75 mg twice a day for up to 5 days) during the first trimester[25]. The rate of malformation (1.1%) is within the incidence of major malformations in the general population (1-3%). The data suggest that oseltamivir is not a major teratogen for humans. A study measuring the concentration of oseltamivir in breast-milk showed that

Table 3. Antiviral medication dosing recommendations for treatment or chemoprophylaxis of 2009 H1N1 infection (36)

Medication		Treatment (5 days)	Chemoprophylaxis (10 days)
Oseltamivir[1]			
		Adults	
		75 mg twice daily	75 mg once daily
		Children ≥ 12 months	
Body weight (kg)	Body weight (lbs)		
≤ 15 kg	≤ 33 lbs	30 mg twice daily	30 mg once daily
> 15 kg to 23 kg	> 33 lbs to 51 lbs	45 mg twice daily	45 mg once daily
> 23 kg to 40 kg	> 51 lbs to 88 lbs	60 mg twice daily	60 mg once daily
> 40 kg	> 88 lbs	75 mg twice daily	75 mg once daily
		Children 3 months to < 12 months[2]	
		3 mg/kg/dose twice daily	3 mg/kg/dose once per day
		Children 0 to < 3 months[3]	
		3 mg/kg/dose twice daily	Not recommended unless situation judged critical due to limited data on use in this age group
Zanamivir[4]			
		Adults	
		10 mg (two 5 mg inhalations) twice daily	10 mg (two 5 mg inhalations) once daily
		Children (≥ 7 years or older for treatment, ≥ 5 years for chemoprophylaxis)	
		10 mg (two 5 mg inhalations) twice daily	10 mg (two 5 mg inhalations) once daily

[1] Oseltamivir is administered orally without regard to meals, although administration with meals may improve gastrointestinal tolerability. Oseltamivir is available as Tamiflu® in 30 mg, 45 mg, and 75 mg capsules; and as a powder for oral suspension that is reconstituted to provide a final concentration of 12 mg/mL. If the commercially manufactured oral suspension is not available, the capsules may be opened and the contents mixed with a sweetened liquid to mask the bitter taste or a suspension can be compounded by retail pharmacies (final concentration 15 mg/mL). In patients with renal insufficiency, the dose should be adjusted based on creatinine clearance. For treatment of patients with creatinine clearance 10-30 mL/min: 75 mg once daily for 5 days. For chemoprophylaxis of patients with creatinine clearance 10-30 mL/min: 30 mg once daily or 75 mg once every other day, continuing for 10 days after the exposure.

[2] Weight-based dosing is preferred; however, if weight is unknown, dosing by age for treatment (give two doses per day) or prophylaxis (give one dose per day) of influenza in full-term infants younger than 1 year of age may be necessary: 0-3 months (treatment only) = 12 mg (1 mL of 12 mg/mL commercial suspension); 3-5 months = 20 mg once daily (1.6 mL of 12 mg/mL of commercial suspension), 6-11 months = 25 mg (2 mL of 12 mg/mL commercial suspension) once daily.

[3] Current weight-based dosing recommendations are not intended for premature infants. Premature infants may have slower clearance of Tamiflu due to immature renal function, and doses recommended for full-term infants may lead to very high drug concentrations in this age group. Very limited data from a cohort of premature infants receiving an average dose of 1.7 mg/kg twice daily demonstrated drug concentrations higher than those observed with the recommended treatment dose in term infants (3 mg/kg twice daily). Observed drug concentrations were highly variable among premature infants. These data are insufficient to recommend a specific dose of Tamiflu for premature infants.

[4] Zanamivir is administered by inhalation using a proprietary "Diskhaler" device distributed together with the medication. Zanamivir is a dry powder, not an aerosol, and should not be administered using nebulizers, ventilators, or other devices typically used for administering medications in aerosolized solutions. Zanamivir is not recommended for persons with chronic respiratory diseases such as asthma or chronic obstructive pulmonary disease that increase the risk of bronchospasm.

breast-milk concentration of oseltamivir is much less than the pediatric doses[26].

The bioavailability of zanamivir is 10-20% by inhalation. There are less data about its safety for pregnant women. Among four pregnant women taking zanamivir, one pregnancy was spontaneously abortus, one pregnancy was terminated and two women delivered a healthy baby[25]. The concentration of zanamivir in breast-milk is also lower than the recommended prophylactic inhalation dosage for children[27].

POST-EXPOSURE ANTIVIRAL CHEMOPROPHYLAXIS

The virus may be transmitted one day prior to the onset of symptoms and up to seven days after the initiation of illness. This period may be longer in children. Post-exposure antiviral chemoprophylaxis can be considered for pregnant women who are close contacts with suspected or confirmed cases. The drug of choice for prophylaxis may be zanamivir because of its limited systemic absorption. For women with respiratory problems like asthma, oseltamivir is the alternative drug. The recommended duration of prophylaxis is 10 days from the last known exposure to the virus[22].

VACCINATION

The H1N1 vaccines are available as a live, attenuated monovalent vaccine for intranasal administration and as monovalent, inactivated, split-virus or subunit vaccines for intramuscular injection[28]. Guidelines place pregnant women in a high-priority group for pandemic influenza vaccine because of increased risk of morbidity and mortality due to H1N1 influenza virus infection in pregnancy[15,29]. In addition to the protection of mothers, influenza vaccines are also beneficial for the infants. In a randomized study, influenza vaccination reduced laboratory-proven influenza illness by 63% in infants aged six months or younger[30].

The 2009 H1N1 monovalent vaccine can be given to pregnant women in any trimester and can be given at the same time as seasonal flu vaccine at different injection sites. Pregnant women should receive inactivated vaccine (flu shot) but should not receive the live attenuated vaccine (nasal spray). Postpartum women, even if they are breastfeeding, can receive either inactivated or live attenuated vaccines[31].

In adults, single-dose vaccine induces protective immune response in the majority of subjects aged between 12-65 years. However, lesser immune responses are seen after a single dose of vaccine in younger and older subjects. Thus, two doses of vaccine 21 days apart are recommended in children aged < 10 years[32-34].

The licensure and manufacturing processes for the monovalent H1N1 vaccines are the same as those used for seasonal influenza vaccines. Thus, the safety of pandemic H1N1 influenza A monovalent vaccine is expected to be similar to that of seasonal influenza vaccine. The most common side effects following vaccination are mild, such as soreness, redness, tenderness, or swelling at the injection site. Some might experience headache, muscle aches, fever, fatigue, and nausea. Through November 24, 2009 Vaccine Adverse Event Reporting System (VAERS) received 3783 reports of adverse events after receipt of H1N1 vaccine, of which 204 (5.4%) were categorized as serious, and 4672 reports after receipt of seasonal influenza vaccines, of which 283 (6.1%) were serious. The overall VAERS adverse event reporting rates were 82 per 1 million H1N1 vaccine doses distributed and 47 per 1 million seasonal influenza vaccine doses distributed. VAERS received 13 reports of deaths occurring after receipt of H1N1 vaccine. In nine of these deaths, significant underlying illness was present, and one death resulted from a motor vehicle crash. VAERS also received 10 reports of Guillain-Barré syndrome and 19 reports of anaphylaxis. Three of the Guillain-Barré syndrome cases and 15 of the anaphylaxis cases were coded as serious adverse events[28].

Safety of Inactivated H1N1 Influenza Vaccine in Pregnant Women

Pregnant women are not known to have an increased risk of side effects from the influenza vaccine. No study to date has demonstrated an increased risk of either maternal complications or adverse fetal outcomes associated with inactivated influenza vaccination. No teratogenicity was documented, and infants of vaccinated mothers did not differ from non-vaccinated offspring in physical or neurological assessments[16]. Licensed H1N1 monovalent vaccines were produced using the same manufacturing processes as seasonal influenza vaccines. Thus, it is anticipated

that they will have a similar safety profile. However, pregnant women had the lowest vaccine coverage level (14.4%). Concerns about vaccine safety are often cited by mothers as barriers to vaccinations[15].

Multi-dose vials of influenza vaccine contain the preservative thimerosal to prevent contamination. There is no scientific evidence that thimerosal is harmful to pregnant women or the fetus[16,35]. However, because some women are concerned about exposure to preservatives during pregnancy, manufacturers are producing preservative-free influenza vaccine in single-dose syringes. The CDC recommends that pregnant women receive flu vaccine with or without thimerosal[31].

Adjuvants are agents that are sometimes added to a vaccine to increase its effectiveness. They have been used for many years in numerous vaccines. In influenza vaccines, they can reduce the dose of antigen needed to produce the same immunological response and improve their ability to provide longer-lasting protection. Some pandemic vaccines contain squalene-based adjuvants and aluminium phosphate adjuvant. No safety concerns of clinical significance have arisen in more than 70 clinical trials with adjuvants. However, squalene-based adjuvants have been shown to induce more local or systemic reactions within three days of vaccination than non-adjuvanted vaccines, but no major reactions have been reported[35].

MANAGEMENT of PREGNANT WOMEN with H1N1 INFLUENZA INFECTION in INTRAPARTUM and POSTPARTUM HOSPITAL SETTINGS

Pandemic H1N1 influenza virus may be transmitted to the newborn by infected respiratory secretions of the infected mother at delivery and postpartum. Infants under 1 year of age are at risk of severe illness and death due to H1N1 virus infection. Thus, the following protective measures should be applied in hospital settings to prevent the transmission of the pandemic influenza A (H1N1) virus from mother to the newborn[20].

Antepartum

Pregnant women with suspected or confirmed H1N1 influenza virus should be placed in a private room. Contact and droplet precautions should be applied. Diagnostic testing and empiric antiviral treatment (oseltamivir or zanamivir) should be initiated immediately.

Intrapartum

During delivery, the mother should use a surgical mask, as tolerated. All persons should wear a surgical mask with face shield, gloves and gown. Upon delivery, the newborn should be separated from the mother immediately to reduce the risk of droplet exposure.

Postpartum

Providers should consider temporarily separating the infant from the mother until all of the following criteria are met:

• The mother has received antiviral therapy for at least 48 hours and;

• The mother is without fever for 24 hours without antipyretics and;

• The mother can control cough and respiratory secretions.

During this time, the newborn should be isolated in a separate room and infant care should be provided by a healthy person.

Newborn Care

Healthy term newborns of infected mothers with confirmed or suspected H1N1 infection should be considered exposed, not infected. They should be observed for signs of infection and if the symptoms develop, diagnostic tests for influenza should be done. Antiviral chemoprophylaxis for the infants is currently not recommended due to limited data on its safety and efficacy. Through the temporary separation from the mother, all feedings and care should be provided by a healthy caregiver until the criteria for close contact are met.

Breastfeeding

The risk for pandemic influenza A (H1N1) virus transmission through breast-milk is unknown. Viremia with seasonal influenza infection is rare, which suggests that the risk of the virus crossing in to the breast-milk is also probably rare. Thus, milk from an infected mother is not considered infectious. Antiviral treatment given to the mother is not a contraindication for breastfeeding[6,22]. Breastfeeding has many benefits for newborns. Breast-milk protects the

newborn against respiratory illnesses. Thus, breastfeeding should be encouraged, and the mother should be assisted to express her milk immediately fallowing delivery. The breast-milk should be fed to the newborn by a healthy caregiver until the criteria for close contact are met. When the mother and infant are able to initiate close contact, the following guidance is offered for mothers prior to feeding and caring for the infant:

• The mother should wash her hands with soap and water;

• The mother should wear a face mask;

• The mother should observe respiratory hygiene and cough etiquette.

These precautions should be followed for seven days after onset of symptoms or 24 hours after the resolution of symptoms. During this time, the infant should be brought to the mother's room for feeding and care.

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