

Pandemic H1N1 in Pregnancy

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Introduction

Pregnant women constitute a high risk group for disease-related morbidity and mortality during influenza season [1-3]. During the 2009 H1N1 pandemic, pregnant women had higher morbidity and mortality comparing to non-pregnant women. There have also been reports of an increased risk of miscarriage, birth defect and preterm delivery when pregnancy is associated with influenza infection [4-6]. The clinical presentation, diagnosis and management of H1N1 infection in pregnancy is described in this article.

Historical background

The first documented occurrence of swine-origin H1N1 influenza in human was during the 1918 pandemic that resulted in 40 to 50 million deaths worldwide. Since 1918, the largest swine-origin H1N1 outbreak was registered in Fort Dix, NJ in 1976; up to 230 soldiers were infected with 1 fatality [7]. Apart from that, there were 50 documented cases of swine-origin H1N1 infection reported between 1958 and 2005, with six cases (12%) resulting in death [8]. The second pandemic was declared by the World Health Organization (WHO) in June 2009. The pandemic alert was terminated on August 10, 2010 and during that interlude H1N1 caused an estimated 17,000 deaths worldwide, though the confirmed number was much less. Despite the fact that number of deaths from seasonal influenza in non-pandemic years is usually higher, due to disproportionally high number of young individuals with H1N1 the years of life lost was substantial [9].

H1N1 virology

Pandemic H1N1 influenza A virus is a quadruple reassortment of two swine strains, one human and one avian. It is transmitted via the respiratory route, and while placental transmission has been suspected [10,11], it is unlikely that it is of high clinical significance. The incubation period is 1.5-3 days [12]. Viral shedding begins one day prior to the development of clinical symptoms and lasts usually for 5-7 days, up to 14 days [13,14]. Early antiviral treatment is associated with shortening of viral shedding period [15].

Pregnancy outcomes during the 2009 H1N1 pandemic

Women: Pregnant patients with H1N1 had higher morbidity and mortality comparing to other patients with the same infection. Out of 788 cases of H1N1 influenza in pregnant women reported to the Centers for Disease Control (CDC) during April-August 2009, 509 were hospitalized, 115 required intensive care and 30 died [5]. An update of this report, which included ICU admissions among pregnant patients, though December 31, 2009, identified an additional 165 admissions and 26 deaths. The complications of H1N1 influenza were more prominent in advanced gestation. Among 56 deaths of pregnant women linked to H1N1 influenza in the US between April and December 2009, 36 (64%) occurred during the 3rd trimester.

Compared to non-pregnant women, pregnant women had a lower rate of underlying chronic medical conditions [16], which points to pregnancy per se being a high-risk factor. Other significant risk factors for lethal outcome were asthma (22.9% of pregnant women with H1N1 but 43.5% among maternal deaths) obesity (13.0% and 39.1% respectively), white race (22.7% and 44.8% respectively), and more than 4 days lag between initiation of treatment and the onset of symptoms

(15.9% and 80% respectively) [5]. Among severely ill pregnant patients a similar trend in relation between lag in treatment and death was observed [17].

In total, pregnant women suffered a considerably higher death rate from influenza; 6-10% of patients who died because of H1N1 influenza were pregnant, though in the same time pregnant women constituted only 1-2% of the population [5,12,18]. Callaghan et al. [19] (2010) found that while five maternal deaths related to influenza are reported annually in the US, in the 2009 pandemic the number was 56.

Fetus: Most of our knowledge about the effect of H1N1 infection on the developing fetus comes from extrapolation of data obtained from seasonal influenza. Transplacental transmission has been documented for influenza A virus [20], and there are case reports of H1N1 positive infants born from H1N1 positive mothers suggesting that there can be transplacental transmission of H1N1 as well [10,11]. At the same time, the largest reported cohort of infants born from critically ill H1N1 positive mothers and admitted to neonatal intensive care units found only two out of 20 tested positive for H1N1 infection [21]. A direct teratogenic effect of influenza is unlikely. Although an association between malformations, congenital abnormalities (cleft lip, neural tube defects, heart defects), miscarriage and preterm birth has been noted in association with influenza infection, it is probably related to febrile morbidity, not to a direct viral effect. [4,22]. Elevations in the rate of preterm deliveries have been noted [5,23], though definitive data are not available to determine if these outcomes were iatrogenic. Admissions to NICU were often reported for this category of patient, though more commonly for prematurity than for influenza [24].

Clinical presentation and diagnosis of H1N1 infection in pregnant patients

The clinical presentation of H1N1 infection in pregnant women is similar to that seen in other groups of patients. The hallmark symptoms are fever, cough, sore throat, rhinorrhea, and myalgia [25]. Pregnant women develop shortness of breath and dehydration more often than do other categories of patients [25,26]. Many patients with later confirmed H1N1 had been seen earlier when their symptoms, which were non-specific, had been attributed to a common cold, up to 30% of patients reported family members or close contacts with pneumonia or influenza-like illness [25].

Rapid antigen and immunofluorescent antibody diagnostic testing is available but can't distinguish between influenza A strains, and lacks the necessary sensitivity to rule out H1N1 infection. Real-time reverse transcriptase (PCR) is the most sensitive and specific test, and

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during the pandemic period referral to CDC was recommended for all specimens testing positive for influenza A by rapid tests (since most hospitals don't have equipment to perform the PCR) [27]. Nevertheless for pregnant patients the treatment should be initiated based on clinical symptoms rather than laboratory data. Failure to do so has been observed in multiple studies, and has been cited as one of the causes of higher mortality in pregnant patients [4].

Laboratory abnormalities associated with H1N1 include elevated liver function tests, anemia, leukopenia, leukocytosis, and thrombocytopenia [28]. Although severe abnormalities are more common among patients with more severe disease, their presence should not affect management, which is guided by the clinical presentation of the disease.

Imaging studies show infiltrative changes, patchy consolidations or ground glass opacities [18,29,30].

Management of H1N1 influenza in pregnancy

Management of H1N1 influenza in pregnancy is tailored to the patient's clinical presentation. In ambulatory settings, when a call is received from pregnant patients reporting symptoms suggestive of H1N1 it is appropriate to reschedule any existing appointment and call in a prescription for antiviral medications, recommend home quarantine and antipyretics if the temperature is in the 100-101 range [26,31]. Chemoprophylaxis for contacts should be considered. If the patient is unable to tolerate fluids, or has fever > 101, evaluation by a physician is recommended [26]. If available, separate waiting areas or scheduling changes should be arranged in order to separate sick from healthy patients. Face masks should be provided to everyone who will have contact with the patient [32].

Severe cases of H1N1 infection should be treated in a hospital. Signs suggestive of severe infection include, but are not limited to, shortness of breath, pulse oxygenation < 96% on room air, tachycardia > 110, and evidence of poor hydration status [26]. When presenting in hospital settings pregnant women with suspected or confirmed influenza should be managed utilizing the same institutional protocol used for other influenza patients (private room, droplet precautions). Droplet precautions should last for 7 days from the onset of symptoms or until 24 hours after the resolution of fever and respiratory symptoms, whichever is longer. In addition to antivirals and antipyretics, respiratory support may be required with supplemental oxygen, mechanical ventilation is necessary and ECMO in critical cases [24]. Antibiotic supplementation should be guided by the presence of pneumonia, and by guidelines for community-acquired pneumonia that are based upon patterns of resistance in the region [33]. Bacterial pneumonia was one of the major contributing factors to mortality during 1918 pandemic, but current reports suggest that due to the generous use of antibacterial agents in the current pandemic bacterial agents were not an important contributor to prognosis [34].

Pregnant women are considered at high risk for complications, and empiric treatment should be initiated based on symptoms rather than awaiting confirmation with laboratory testing; preferably within 48 hrs from the onset of symptoms since earlier treatment is associated with less severe disease [35,36]. In a report of H1N1 infection in pregnant women from April to August 21 by Siston et al. [5] (2010) (a total 788 cases) out of 219 patients who were started on antiviral treatment within 2 days of onset of symptoms only 1 died, compared to 20 out of 81 of those who initiated treatment more than 4 days after onset of treatment. Nevertheless even if the treatment is initiated more than 48 hours after the onset of symptoms it is still beneficial [36]. Vaccination status should not interfere with the decision to treat.

Almost all strains of H1N1 demonstrated resistance to adamantanes and susceptibility to neuraminidase inhibitors (oseltamivir and zanamivir) [37]. The treatment should continue for 5 days for both drugs. Oseltamivir is administered at a dose 75 mg oral twice a day. Zanamivir is administered through inhalations-two 5 mg inhalations (10 mg) twice a day; intravenous administration in critically ill patients was also reported during the pandemic [38]. Due to systemic absorption and more experience with oseltamivir, it is the preferred medication. Oseltamivir and zanamivir are both pregnancy category C drugs (clinical studies were not done to assess the safety of these drugs in pregnancy). The benefit of treating the influenza outweighs any theoretical risk to the fetus. There were no reports of increased rates of malformations during the pandemic period related to treatment with neuraminidase inhibitors. No adverse effects were reported in pregnancy or in infants exposed to these drugs in utero prior to the pandemic [4,39].

Hyperthermia has been associated with adverse neonatal outcomes; therefore antipyretics are recommended for treatment of fever during influenza. Since NSAIDs such as ibuprofen and aspirin are associated with adverse fetal and pregnancy outcomes, acetaminophen is recommended as a first line drug [31].

H1N1 influenza per se is not an indication for delivery, nevertheless cesarean section was often reported for patients with H1N1 infection. It was often performed to improve maternal oxygenation and respiratory function rather to salvage a compromised fetal status [5,18,23].

Management of H1N1 influenza in postpartum period

The higher risk of pregnant women extends to postpartum period [35]. Therefore the same approach to diagnosis and management is recommended for women in the immediate postpartum period including women having spontaneous abortions or termination of pregnancy.

Newborns born at term to H1N1 infected mothers are considered exposed but not infected. Temporary separation of the mother and newborn are advised. The CDC [40], has recommended the implementation of infection control measures that they developed though they are based on expert opinion, not scientific evidence. The mother needs to meet several criteria prior to being granted access to her newborn: she should be able to control her respiratory symptoms and secretions; use a mask; have received antivirals for at least 48 hours; and be afebrile for more than 24 hours without the use of antipyretics. During the separation feeding should be provided by a healthy person (other caregiver or healthcare professional). In cases when breastfeeding is desired, breast milk should be expressed and can be given to the infant. For both oseltamivir and zanamivir infant risk during lactation cannot be ruled out, but there is no empiric data demonstrating harm to breastfeed infants from these medications [39,41]. The benefits of breastfeeding greatly outweigh the risk of viral transmission through breast milk.

All individuals living or taking care of an infant younger than 6 months of age should be encouraged to be vaccinated against influenza, preferably prior to discharge of the infant home [42].

Prevention of H1N1 influenza in pregnant women

Vaccination: The recommended mode of prophylaxis for pregnant women (or women who will be pregnant during influenza season) regardless of gestation age is inactivated influenza vaccine. Due to the increased severity of influenza in pregnancy pregnant women are included in the highest priority vaccination group [43]. Despite this

recommendation, and multiple measures taken to implement them, pregnant women are notorious for being one of the worst groups in regard to compliance with vaccination; generally rates of influenza vaccination are less than 15-20%. Just a year before the pandemic (2009-2010 season) the median coverage of pregnant women with influenza vaccine was 11% [44]. For many reasons (unprecedented media coverage, publicity, education of medical providers) the 2010 season vaccination rate for H1N1 infection was one of the highest ever reported – 47% [45,46]. The recommendation by a provider that women obtain vaccination is strongly associated with acceptance of vaccination, and underlines the role of medical providers in ensuring appropriate coverage [45,47]. However, it should be noted that recall bias and “desire to look good” in the eyes of interviewer might provide a strong incentive for those who didn’t get vaccinated to “forget” their physician’s recommendation to be vaccinated. That could create a false association between recommendations and vaccinations. The “main” reasons reported in an online survey conducted by the CDC [47], for not receiving vaccination were concern for the safety of the fetus, concern about obtaining flu from the vaccine, concern regarding safety risks for oneself, and feeling that influenza is not a dangerous disease.

Providers should strongly encourage patients to obtain vaccination. One of the proven benefits of vaccination during pregnancy is prevention of influenza disease of the infant [48]. Poehling et al. [49] (2011) evaluated a cohort of hospitalized infants < 6 months old with upper respiratory symptoms during seven consecutive influenza seasons (2002-2009) all of whom had nasal swabs obtained to test for influenza. Children whose mothers reported having vaccine had a 6% influenza positive rate and those who did not have vaccination had an 11% influenza positive rate [49]. Both a lower rate of maternal infection and a transfer of protective antibodies could be responsible for infant protective effects [50,51].

One of the major factors that lead women to forgo vaccination is the fear of fetal side effects, particularly as related to the use of thimerisol as a preservative in some multidose vials. No studies have shown an increased risk of adverse fetal outcomes [52]. This information should be communicated to the patients. A study using the health belief model [53], to assess factors associated with H1N1 influenza vaccine acceptance showed that attitudes toward vaccination were positively associated with fear of disease and negatively associated with fear of side effects, which is in concordance with the CDC online survey [47]. Accordingly, explaining to pregnant patients that H1N1 influenza is associated with significant morbidity for them, as well as providing reassurance regarding the safety of the vaccine should increase the rate of vaccination.

Chemoprophylaxis was recommended for pregnant women with close contact with a confirmed or suspected case of H1N1 influenza [54]. Zanamivir (inhaled dry powder) has lower systemic absorption and thus can be a drug of choice for pregnant women. At the same time caution should be used due to reported respiratory distress [55], in patients with COPD and asthma. The regimen for prophylaxis with Zanamivir is 10 mg daily for 10 days. Oseltamivir is an alternative and is given as a 75 mg orally daily for 10 days for prophylaxis.

Conclusion

H1N1 infection disproportionately affects pregnant women leading to more common and more severe disease.

Routine vaccination is recommended, regardless of gestation age, for all women who are pregnant, will be pregnant or will be caring of infant less than 6 months old during the influenza season.

Initiation of antiviral treatment (oseltamivir 75 mg p/o BID x 5 days; zanamivir 10 mg inhalation BID x 5days) should be started as soon as possible based on symptoms alone.

Treatment of fever with acetaminophen is recommended.

In-hospital evaluation and management is recommended for patients with shortness of breath, pulse oxygenation < 96% on room air, tachycardia > 110, or evidence of poor hydration status.

Infection control measures should be implemented to assure protection of the newborn if the mother is infected.

Chemoprophylaxis is recommended if contact is suspected (oseltamivir 75 mg p/o daily x 10 days; zanamivir 10 mg inhalation daily x 10 days).

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