

Risk management of seasonal influenza during pregnancy: current perspectives

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Abstract: Influenza poses unique risks to pregnant women, who are particularly susceptible to morbidity and mortality. Historically, pregnant women have been overrepresented among patients with severe illness and complications from influenza, and have been more likely to require hospitalization and intensive care unit admission. An increased risk of adverse outcomes is also present for fetuses/neonates born to women affected by influenza during pregnancy. These risks to mothers and babies have been observed during both nonpandemic and pandemic influenza seasons. During the H1N1 influenza pandemic of 2009–2010, pregnant women were more likely to be hospitalized or admitted to intensive care units, and were at higher risk of death compared to nonpregnant adults. Vaccination remains the most effective intervention to prevent severe illness, and antiviral medications are an important adjunct to ameliorate disease when it occurs. Unfortunately, despite national guidelines recommending universal vaccination for women who are pregnant during influenza season, actual vaccination rates do not achieve desired targets among pregnant women. Pregnant women are also sometimes reluctant to use antiviral medications during pregnancy. Some of the barriers to use of vaccines and medications during pregnancy are a lack of knowledge of recommendations and of safety data. By improving knowledge and understanding of influenza and vaccination recommendations, vaccine acceptance rates among pregnant women can be improved. Currently, the appropriate use of vaccination and antiviral medications is the best line of defense against influenza and its sequelae among pregnant women, and strategies to increase acceptance are crucial. This article will review the importance of influenza in pregnancy, and discuss vaccination and antiviral medications for pregnant women.

Keywords: antiviral medications, knowledge, vaccination

Introduction

Influenza is a potentially serious infectious disease that causes yearly outbreaks of respiratory illness. These outbreaks occur in all corners of the world in people of any age and are most commonly seen during the winter months. Significant morbidity and mortality can result, especially in certain populations. Persons aged 65 years or greater, young children, and persons of any age with underlying conditions, including pregnancy, are at higher risks for complications, including hospitalization or death.¹ In most influenza seasons, seasonal strains are the most prevalent, although pandemic strains can occasionally emerge, such as H1N1 influenza in 2009–2010. The combined use of vaccination and antiviral medications when appropriate can decrease the risks of influenza in pregnancy by reducing the likelihood of acquiring infection and ameliorating its effects in women who are infected. The objective of this paper is to

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present data on the risk management of influenza in pregnant women, including safety and efficacy data for vaccination and antiviral medications.

Risk of influenza in pregnancy

Risks of influenza in pregnancy to the pregnant woman

Pregnant women have consistently been found to be at a higher risk for morbidity and mortality from both seasonal and pandemic influenza compared to nonpregnant adults.^{2–18} Changes in physiology and immune function in pregnancy include: increased heart rate, stroke volume, and oxygen consumption; a decrease in lung capacity; and alterations in cell-mediated immunity. These physiologic and immune changes may lead pregnant women to be predisposed to more severe disease and/or worse outcomes from influenza infections relative to nonpregnant individuals.

In a surveillance study of 19 seasonal influenza seasons, pregnant women had a significantly higher rate of hospitalization due to an acute cardiopulmonary event during influenza season than women during the postpartum period.² In a study comparing hospital admissions for pregnant women during influenza season to the year before they were pregnant, pregnant women were up to five-times more likely to be admitted for a respiratory illness.³ In a Canadian study of national hospital admission records for pregnant women admitted with a respiratory illness during influenza season from 1994 to 2000, admission rates were 150/100,000.⁴ In an American series, the admission rate was 250/100,000 for pregnant women during the third trimester.² These rates are equivalent to those estimated for Canadian adults aged 65–69 years and 75–79 years, respectively.⁵ In general, all pregnant women (regardless of the presence of comorbidities) are at a higher risk for hospital admission related to influenza compared to nonpregnant women with comparable age and health, with the magnitude of increased risk ranging from four- to 18-fold.^{3,5} The degree of risk has also been demonstrated to rise with advancing gestational age and in the presence of any comorbidities.^{2,3,6}

Just as pregnant women have a higher risk for complications and admission to hospital with seasonal influenza, data during pandemics have also documented similar risks. In the 1918 H1N1 influenza pandemic, half of all pregnant patients in one study had pneumonia and there was a 27% case fatality rate among pregnant women.⁷ In the H2N2 influenza pandemic in 1957–1958, one half of women of reproductive age who died from pandemic influenza were pregnant.⁸

More recently, pregnant women were again overrepresented among cases of illness and death in the 2009 global H1N1 influenza pandemic. Although only roughly 1% of the population is pregnant at any given time, in a systematic review of 120 studies reporting on 3,110 pregnant women from 29 countries with H1N1 influenza, pregnant women accounted for approximately 6% of individuals who were hospitalized, were admitted to the intensive care unit (ICU), and died as a result of H1N1.⁹

In a case series from Canada, there were 78 pregnant women among a group of 1,479 patients admitted to hospitals over a 6-month period (April to September) in 2009 with laboratory-confirmed pandemic H1N1 influenza. The 78 pregnant women were more likely to require admission to the ICU (2.59 versus 0.33 per 100,000) or die (0.80 versus 0.05 per 100,000) compared to nonpregnant women of child-bearing age.¹⁰ In another Canadian series from Manitoba, 18 out of 30 pregnant women with pandemic H1N1 influenza were admitted to hospital and six required ICU admission.¹¹ Of those six, four were in their third trimester and two died. In a national surveillance study, the greatest number of hospital and ICU admissions and deaths occurred among pregnant women in the third trimester relative to earlier in pregnancy.¹²

In the United States, pregnant women accounted for approximately 5% of all deaths related to H1N1 in 2009.¹³ One of the earliest published series from the epidemic was published in the spring of 2009 and reported on 20 pregnant women with novel H1N1 influenza.¹⁴ Three of these women were admitted to hospital (two in the third trimester) and one died. A second series was then published with 34 pregnant women. Eleven of these required admission to hospital with six dying (one in the first trimester, one in the second trimester, and four in the third trimester). In this series, pregnant women had a greater than fourfold likelihood of hospitalization compared to nonpregnant adults (relative risk 4.3; 95% confidence interval [CI], 2.3–7.8).¹⁵ Similarly, in a report from New York City, the rate of hospitalization was significantly higher in pregnancy (55.3 compared with 7.7 per 100,000 population).¹⁶ Finally, among 94 hospitalized pregnant women in California in 2009, 95% were in the second or third trimesters. In this series, 18 women were admitted to the ICU with many requiring mechanical ventilation. Of these 18 women with more severe disease, 12 went into labor and gave birth while admitted to the ICU, and eleven of these had preterm labor. Six pregnant women in this published report died.¹⁷

Published data from Australia also showed that pregnant women had an increased risk for morbidity and mortality compared to the general population. From May to July 2009, 43 pregnant women were sufficiently ill to need hospital admission, and eight were admitted to the ICU.¹⁸ About one third of women hospitalized delivered while admitted, and roughly 50% had no risk factor for severe disease apart from pregnancy.

Risk of influenza in pregnancy to the fetus/newborn infant

Just as respiratory disorders and influenza lead to morbidity for pregnant women, so too are they linked with an increased rate of adverse pregnancy outcomes. The available evidence suggests that viremia is infrequent and, therefore, that transplacental transmission is rare.^{19,20} However, many studies have documented pregnancy loss and adverse fetal effects among women with both seasonal and pandemic influenza during pregnancy.

A Canadian population-based cohort study found that infants born to women who were hospitalized for a respiratory illness during influenza season over 13 years had a significantly increased risk of being born small for their gestational age (adjusted relative risk 1.66) and having a lower mean birthweight.²¹ In a case series from the 1918 H1N1 pandemic, one quarter of women with uncomplicated influenza and more than half of those with pneumonia had a pregnancy loss.⁷ A documented decline in the birth rate in the spring of 1919 (after the end of the pandemic) has been postulated to be a result of first trimester pregnancy losses in one out of ten women during the peak of the pandemic.²²

In pregnancies not affected by early loss, there has been an excess of adverse outcomes in women with influenza. In a Norwegian national registry study, there was an increased rate of fetal death among pregnancies complicated by 2009 H1N1 influenza.²³ In a United Kingdom series of 256 women with 2009 H1N1 influenza, there was an increased perinatal mortality rate (39 per 1000 births compared to 7 per 1000 in women without influenza), stillbirth rate, and a fourfold increased likelihood of preterm birth.²⁴ The highest risk for preterm labor occurred in women with infection in the third trimester, ICU admission, and pneumonia. Other studies of women from the United States and Canada with pandemic influenza have also found increased rates of preterm birth and low birth weight.^{11,25–27} In addition, in one study, infants born to mothers with severe influenza had an increased risk of admission to neonatal ICU and lower 5-minute

Apgar scores, whether they were delivered during the maternal hospital stay or after discharge.²⁵

Vaccination for influenza during pregnancy

Vaccination for influenza is still the most effective strategy to prevent severe infection and its sequelae, and pregnant women are considered a priority population for vaccination due to their increased vulnerability. Influenza vaccination has been recommended by national organizations in Canada since 2007 and in the United States since 2004 for all women who are pregnant during the influenza season, irrespective of gestational age.^{1,28} Immunization during pregnancy is important because of the proven benefits for both mothers and infants in terms of decreasing disease burden.

Seasonal influenza vaccine immunogenicity and efficacy for reducing disease burden among pregnant women and infants

Studies assessing immunogenicity have consistently shown that pregnant women mount a protective antibody response after vaccination, although many of these were nonrandomized or cohort studies. Two studies from 1976 showed that pregnant women had similar mean antibody titers when compared with nonpregnant women who were immunized,^{29,30} and later studies of both seasonal and H1N1 vaccines have also found protective antibody levels among pregnant women who were vaccinated.^{31–34} Some studies have demonstrated that actual geometric mean titers are lower in pregnant compared to nonpregnant vaccine recipients, although antibody levels were still in the protective range. In one study, 29 pregnant women vaccinated at all stages of pregnancy had lower mean titers postvaccination compared to 22 nonpregnant women, although the overall percentage of women who seroconverted was greater than 90% in both groups.³⁵ In another study of 239 pregnant women, seroconversion rates were lower among women vaccinated in the first trimester compared with later in pregnancy, and lower among women with a higher body mass index.³⁶ The Mother's Gift Project was a large randomized trial performed in 2004–2005 in Bangladesh and published in 2008.³⁷ Pregnant women were randomized to receive either the influenza (n=172) or pneumococcal vaccine (n=168). This trial differed from previous efficacy studies in that its main maternal outcome was clinical benefit of vaccination rather than immunogenicity. The results showed that pregnant

women who received the influenza vaccine were 36% less likely to develop a respiratory illness and fever compared to those women who received the pneumococcal vaccine.³⁷ Another trial that assessed clinical outcomes instead of immunogenicity was a case-control study showing that vaccination during pregnancy reduced the risk of acute respiratory illness associated with laboratory-confirmed influenza by about 50%.³⁸

Just as there is good data to document efficacy of maternal vaccination for preventing disease in pregnant women, so too have there been many studies^{37,39–41} proving that infants of women who received the influenza vaccine while pregnant have a lower risk of illness and infection after birth. In the Mother's Gift Project, among infants up to 6 months old whose mothers received influenza vaccination during pregnancy, there was a 63% reduction in the likelihood of a positive influenza test and a 29% decrease in febrile illnesses.³⁷ In a cohort study of 1,169 mother–infant pairs on Navajo and Apache Indian reservations, infants born to pregnant women who were vaccinated over three influenza seasons had a 41% reduction in the risk of laboratory-confirmed influenza (relative risk 0.59) and a 39% reduction in the risk of hospitalization (relative risk 0.61).³⁹ In a 2000–2009 case-control study from Connecticut of infants less than 6 months of age who were hospitalized for influenza, 2.2% of 91 infected infants had mothers who were vaccinated in pregnancy compared to 19.9% of 156 control infants whose mothers were not vaccinated, resulting in a 91.5% effectiveness of maternal vaccination for preventing infant hospitalization.⁴⁰ An American surveillance study from three states documented that 12% of mothers whose infants tested positive for influenza and 20% of mothers whose infants tested negative had received a vaccine in pregnancy, with a resulting 45%–48% decrease in infant hospitalization due to influenza.⁴¹

In addition to the data showing lower infection rates, there is also evidence of decreased adverse fetal outcomes among infants of vaccinated women. In a large Canadian database study of 9,781 pregnant women, the adjusted odds ratio for small for gestational age was 0.80 (95% CI, 0.65–0.95), and for low birth rate was 0.74 (95% CI, 0.58–0.95), among children born to women who received the vaccine during pregnancy compared to women who were not vaccinated.⁴² Rates of preterm birth and other adverse neonatal outcomes were also lower among vaccinated women, although not statistically significant. Other studies have documented decreases in preterm birth rates and the likelihood of small-for-gestational-age neonates among women given the vaccine during periods of influenza activity.^{43,44}

Pandemic H1N1 influenza vaccine immunogenicity and efficacy

Immunogenicity and efficacy data from the 2009–2010 influenza A (H1N1) pandemic were very similar among pregnant women when compared to seasonal influenza vaccination. Seroprotective titers were observed in populations of both HIV-negative and HIV-positive women who were vaccinated during pregnancy.^{45,46} In a cohort of 120 women, 89% also had seroprotective titers in cord blood at delivery, confirming transplacental transfer of antibody.⁴⁵ In a retrospective cohort study of 1,125 women who were vaccinated against H1N1 influenza during pregnancy compared to 2,202 women who did not receive the vaccine, infants of vaccinated women were significantly less likely to be born preterm (adjusted odds ratio, 0.63; 95% CI, 0.47–0.84) and had heavier birth weights.⁴⁷ In a recent Canadian study, infant outcomes among 23,340 pregnant women given the adjuvanted pandemic A/H1N1 vaccine were compared to 32,230 women who did not get vaccinated. The immunized mothers had lower chances of having a small-for-gestational-age infant (risk ratio, 0.90; 95% CI, 0.85–0.96), preterm birth <32 weeks (risk ratio, 0.73; 95% CI, 0.53–0.91), or fetal death (risk ratio, 0.66; 95% CI, 0.47–0.91).⁴⁸

Seasonal influenza vaccine safety

Despite decades of use of influenza vaccines in pregnancy, no study has demonstrated any harmful consequences of the vaccine among pregnant women or their infants. Historic data from the 1960s showed that, among 2,291 pregnant women who received trivalent inactivated vaccine, there was no increase in the rates of adverse events in mothers or the offspring.⁴⁹ In studies from the 1970s and 1980s, there were no serious side effects from influenza vaccine administration in pregnant women and no fetal, perinatal, or infant complications.^{29–31} In the Mother's Gift Project, no serious adverse events were reported in the mothers receiving vaccine, and there was no increase in pregnancy complications or adverse birth or neonatal events.³⁷ In a database study comparing 3,719 vaccinated women and 45,866 controls, there were no serious maternal adverse events and no difference in rates of cesarean section or preterm birth between the groups.⁵⁰ Reports from the Vaccine Adverse Event Reporting System (VAERS) provide safety data on large numbers of women who received influenza vaccines during pregnancy. Reports from 1990–2009 (over 11 million vaccinated women) and 2000–2003 (approximately 2 million vaccinated women) conclude that vaccination during pregnancy does not result

in an increased risk of adverse pregnancy outcomes when compared to background population rates.^{51,52}

Pandemic H1N1 influenza vaccine safety

Because pregnant women were quickly identified as a priority population for vaccination during the influenza A (H1N1) pandemic that began in 2009, thousands were vaccinated worldwide and were part of clinical trials to evaluate safety and efficacy. Published reports from many different countries reinforced that this vaccine was safe in pregnancy, although the exact formulations, dosages, and presence or absence of adjuvant differed. Studies of over 1000 women from Italy, France, Scotland, and the United Kingdom reported no serious adverse events among pregnant women or their neonates, with no significant differences in adverse birth outcomes and congenital anomaly rates compared with the background rates in the general population.^{53–56} A published review of reports to VAERS also concluded that there was no concerning pattern of maternal or fetal outcomes among women who were vaccinated during pregnancy or their children.⁵⁷

In Canada and in many European countries, the pandemic vaccine was formulated with an adjuvant. Adjuvants are used in vaccines to boost the immune response and provide broader protection. They can allow for the use of lower doses of antigen, resulting in more available doses of vaccine, which may be useful in times of high demand such as during pandemics. Aluminum-based adjuvants are commonly used in some vaccines (such as hepatitis A and B, diphtheria, tetanus, and pertussis) and many pregnant women have been vaccinated with such vaccines without an increased risk of adverse outcomes.⁵⁸ Pandemic H1N1 vaccines were formulated with newer adjuvants such as AS03 and MF59. Several studies showed that pregnant women vaccinated with adjuvant-containing vaccines had no increased risk of adverse events compared to those who received vaccines without adjuvants.^{53,56,59}

Vaccine uptake among pregnant women

It is unfortunate that actual vaccination rates among pregnant women remain low, even with the existence of national guidelines that advocate universal influenza vaccination. In one study from 2000, only 39% of surveyed American obstetricians administered the vaccine to pregnant women, even though almost 90% agreed that the risk of morbidity and mortality from influenza increases as pregnancy progresses.⁶⁰ A second survey from 2004 revealed that the likelihood of offering the vaccine was gestational-age dependent, with only 52% of obstetricians recommending it in the first trimester and 95% recommending it in the second and third

trimesters.⁶¹ In two different Canadian studies, less than 10% of pregnant women with comorbidities actually received the vaccine, and only 19% were even offered it.^{3,62} More recently, actual vaccination rates have been better, and this may be as a result of increased publicity and awareness associated with H1N1 influenza during the 2009–2010 pandemic. In different series, between 42% and 81% of pregnant women reported receiving the H1N1 influenza vaccine.^{63–65} Estimated vaccine coverage in the United States among pregnant women was 50% in the 2009–2010 influenza season, and these rates were sustained the following year (2010–2011 season).^{66,67}

There are myriad potential reasons why vaccination rates are suboptimal among pregnant women, despite clear guidelines that advocate vaccine administration. Both patient and provider barriers exist that can influence the likelihood of receiving a vaccine. Firstly, doctors need to believe that it is their responsibility to encourage vaccination. In North American surveys of prenatal care providers, obstetricians were significantly less likely than family doctors to believe that it was their responsibility to discuss, recommend, or actually administer influenza vaccines. They were also more likely to endorse that it was the responsibility of others (family doctors or the local public health unit) to vaccinate pregnant women.^{68,69} Nonphysician prenatal office staff can also be influential, with only two thirds of respondents in one study stating that they would recommend the seasonal influenza vaccine.⁷⁰ Many studies have documented that women are more likely to actually get vaccinated if it is strongly recommended by their prenatal care provider or health team.^{67,68,71} In one survey study, pregnant women who were offered the vaccine by their doctor were five-times as likely to be vaccinated as those not offered vaccination.⁶⁷ In a study of 1,325 postpartum women, provider recommendation was the most strongly associated factor with vaccine acceptance (odds ratio, 19.4; 95% CI, 12.7–31.1).⁷¹

Perhaps even more important than the attitude of the provider is the willingness of the patient to receive the vaccine. If women are skeptical or unwilling to consider vaccination, this can be very challenging to address. In many studies, being less willing to receive the vaccine was correlated with a lack of vaccine and/or influenza knowledge. Factual knowledge of influenza and the safety of the vaccine during pregnancy and breastfeeding, and understanding the recommendations for influenza vaccination for pregnant women, is poor among women during pregnancy. Surveys of pregnant women reveal that a significant proportion believe that the influenza vaccine can increase the risk of miscarriage, birth defects, and fever, and may be harmful during pregnancy or breastfeeding.^{62,71,72} Women with these beliefs are less likely to accept vaccination

during pregnancy, while women who believe that influenza in pregnancy poses a significant risk to either themselves or the pregnancy, and women who believe the vaccine is safe, are more likely to be vaccinated.^{63–65,71,73–75} Interventions to increase knowledge (such as patient education) have been shown to increase vaccination rates,⁷⁶ and newer technologies such as text messaging may show promise in promoting women to consider the vaccine.⁷⁷ Interventions to increase vaccination rates should be the focus of our time, effort, and new research in order to accomplish a significant change in the acceptance rates of vaccination among our pregnant patients.

Antiviral medications for influenza during pregnancy

The antiviral medications most widely used during pregnancy are the neuraminidase inhibitors oseltamivir and zanamivir. These agents are effective against both influenza A and B. Zanamivir is an inhaled drug and has little systemic absorption, while oseltamivir is an oral medication that is absorbed systemically. The recommended treatment and prophylaxis doses are presented in Table 1.

Antiviral agents should not be considered a substitution for vaccination, and administration of the influenza vaccine is still considered the first line of defense against infection.^{1,28} However, these drugs act as an important adjunct to immunization. They work most effectively early in the course of illness (within 12 hours), and should ideally be started within 24–48 hours of the onset of symptoms. These agents are not routinely recommended for people at low risk of complications from seasonal influenza as it is unclear if there is a benefit in this population. However, in cases of moderate or severe disease, and in high risk populations (including pregnant women), antivirals are recommended.^{78,79}

Efficacy and safety of antiviral medications in pregnancy

Antiviral medications were not routinely recommended for treatment or prophylaxis in pregnant women before the

2009–2010 H1N1 influenza pandemic. Prior to that time, it was believed that the safety of these agents during pregnancy had not been sufficiently proven, and, therefore, that they should only be used if the potential benefit outweighed the potential risks.¹

In controlled trials and a meta-analysis, it has been shown that antiviral medications reduce the duration, severity, and risk of complications in uncomplicated laboratory-confirmed influenza in healthy children and adults, as well as in higher risk populations including pregnant women.^{78,80–82} Some authorities recommend oseltamivir over zanamivir for pregnant women because it is systemically absorbed, although national guidelines in North America recommend either.^{78,79} The pharmacokinetics of oseltamivir do not change significantly in the different trimesters of pregnancy;⁸³ however, one study did demonstrate lower systemic levels of the active drug metabolite in pregnant compared to nonpregnant women.⁸⁴ Nonetheless, current dosing in pregnancy is the same as for nonpregnant women.^{78,79}

The neuraminidase inhibitors are all Food and Drug Administration Pregnancy Category C drugs because there have been no clinical trials specifically performed to evaluate their safety during pregnancy. However, limited data do exist suggesting that these agents are not teratogenic in humans.⁸⁵ In a Japanese teratogen information database, there was only one malformation (1.1%), a ventricular septal defect, among 90 women who received therapeutic doses of oseltamivir in the first trimester.⁸⁵ The rate of pregnancy loss in this series was 3.3%, which is less than that of the general population. For both oseltamivir and zanamivir, the breast milk concentrations are lower than doses used in children.⁸⁵ In addition to this data, studies from before the recent H1N1 pandemic, and many since, have confirmed that there is no increased risk for congenital anomalies or adverse birth outcomes among children exposed to antiviral medications while in utero. Series include 81 women from Sweden, 239 women from the United States, 669 women from Japan, and a database study of 1,237 women from Canada.^{86–89} In these studies, there was no association between antiviral use in pregnancy and congenital anomalies, preterm birth, premature rupture of membranes, low birth weight, low Apgar scores, neonatal seizures, stillbirth, or neonatal death.^{86–89}

Summary and conclusion

Influenza continues to be an important cause of morbidity and mortality for women during pregnancy. The cornerstones for prevention and management are vaccination of all women who are pregnant during influenza season, and the

Table 1 Oseltamivir and zanamivir treatment and prophylaxis regimens for pregnant women

Medication	Treatment (5 days)	Chemoprophylaxis (10 days)
Oseltamivir	75 mg twice daily	75 mg once daily
Zanamivir	10 mg (two 5 mg inhalations) twice daily	10 mg (two 5 mg inhalations) once daily

Note: Data from Aoki et al,⁷⁸ and the CDC.⁷⁹

use of antiviral medications to ameliorate disease. However, vaccination rates remain unacceptably low, and pregnant women's knowledge of the threat posed by influenza and of recommendations for vaccination in pregnancy is poor. In order to improve knowledge, patient education must become a priority in prenatal care settings. By educating women regarding the importance of vaccination and the appropriate use of antiviral medications as strategies to decrease the burden of influenza, we may be able to decrease rates of and complications from influenza in pregnancy. Providers must also realize that one of the most compelling reasons that pregnant women accept the vaccine is provider endorsement. More work is required evaluating the use and barriers to receipt of vaccines and antiviral medications among pregnant women. Research efforts must now focus on innovative strategies to improve knowledge and awareness among both patients and providers.

Disclosure

The author reports no conflicts of interest in this work.

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