

# Effects of influenza on pregnant women and infants

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**I**nformed decisions regarding the use of influenza vaccine during pregnancy must include consideration of both the benefits and the potential risks of the vaccine. To fully understand the benefits of influenza vaccine during pregnancy, we must examine the complications that are associated with influenza virus infection during pregnancy that include those in the woman and her infant. In addition, because observational studies and 1 randomized trial have shown that influenza vaccination protects infants <6 months old from influenza,<sup>1-3</sup> the influenza-associated disease burden among young infants also must be considered. Here, we review data on the effects of influenza virus infection on pregnant women and infants <6 months old.

## Effects of influenza during pregnancy on the pregnant woman

Pregnant women are more likely to experience severe complications that are associated with influenza compared with the general population, based on data from seasonal influenza epidemics and pandemics.<sup>4</sup> During pregnancy, immunologic alterations and physiologic changes

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Influenza vaccination during pregnancy has been shown to decrease the risk of influenza and its complications among pregnant women and their infants up to 6 months old. To adequately assess the benefits and potential risks that are associated with the use of influenza vaccine during pregnancy, it is necessary to examine the influenza-associated complications that occur among pregnant women and their children. Pregnant women have been shown to be at increased risk for morbidity and death with influenza illness during seasonal epidemics and pandemics. Newborn infants born to mothers with influenza during pregnancy, especially mothers with severe illness, are at increased risk of adverse outcomes, such as preterm birth and low birthweight. Infants <6 months old who experience influenza virus infection have the highest rates of hospitalization and death of all children. Here we review the risks for influenza-associated complications among pregnant women and infants <6 months old.

**Key words:** infant, influenza, pandemic, pregnancy, seasonal

that affect respiratory, cardiovascular, and other organ systems place women at increased risk for certain infections and associated complications. A woman's immune system adapts during pregnancy to tolerate a genetically foreign fetus. How this adaptation occurs is not well understood, but it appears that a shift away from cell-mediated immunity and toward humoral immunity occurs. This immunologic adaptation results in increasing the risk for complications that are associated with certain infections, which includes infection with influenza viruses.<sup>5</sup> Changes in the cardiovascular and respiratory systems that include increased heart rate, stroke volume, oxygen consumption, and decreased lung capacity also put women at increased risk for severe influenza illness.<sup>6,7</sup>

Data suggest that pregnant women are at increased risk of hospitalization related to complications from seasonal influenza compared with nonpregnant women. Using data from the Tennessee Medicaid program for the years 1974-1993, Neuzil et al<sup>8</sup> showed that pregnant women were more likely to be hospitalized with an acute cardiopulmonary illness during seasonal influenza epidemics compared with postpartum women. The highest rate of hospitalization was during the third trimester of pregnancy, at which time pregnant women were 3-4 times more likely to be hospitalized with

a cardiopulmonary illness during influenza season compared with postpartum women.

Cox et al<sup>9</sup> examined data from a nationally representative hospital discharge database for the years 1998-2002 and showed that the proportion of hospitalizations among pregnant women with respiratory illness was substantially higher during influenza season (3.4 per 1000 pregnancy hospitalizations, compared with 1.8 per 1000 during the rest of the year). Pregnant women with comorbid conditions (ie, chronic cardiac disease, chronic pulmonary disease, diabetes mellitus, chronic renal disease, malignancies, and immunosuppressive disorders) were >3 times more likely to be hospitalized for respiratory illness during influenza season than women without these comorbid conditions.

A study from Nova Scotia also demonstrated an increased risk for influenza-associated complications during pregnancy.<sup>10</sup> Compared with the year before pregnancy, pregnant women without comorbid conditions were 1.7 (95% confidence interval [CI], 1.0-2.8), 2.1 (95% CI, 1.3-3.3), and 5.1 (95% CI, 3.6-7.3) times more likely to be hospitalized for respiratory illness during the influenza season during the first, second, and third trimesters, respectively. Pregnant women with  $\geq 1$  comorbid conditions (defined as preexisting diabetes mellitus,

pulmonary disease that included asthma, heart disease, renal disease, and anemia) were at substantially higher risk of hospitalization during all 3 trimesters, with rate ratios of 2.9 (95% CI, 1.5–5.4) in the first trimester, 3.4 (95% CI, 1.9–6.0) in the second trimester, and 7.9 (95% CI, 5.0–12.5) in the third trimester of pregnancy, compared with the year before pregnancy.

Among a case series of pregnant women with laboratory-confirmed influenza A at Parkland Memorial Hospital in Dallas, Texas, during the 2003–2004 influenza season,<sup>11</sup> 62% of the women were hospitalized, and 1 in 8 experienced pneumonia. Symptoms of influenza among pregnant women were similar to those in nonpregnant adults, except that pregnant women were more likely to have nausea and vomiting. A substantial proportion of women in this cohort experienced a profound tachycardia that failed to respond to hydration or antipyretic medications.

Human infections with highly pathogenic avian influenza (HPAI) A (H5N1) virus were first identified in Hong Kong during 1997<sup>12</sup> and again in early 2003 in family members who had traveled to southern China.<sup>13</sup> HPAI H5N1 virus has received considerable attention in recent years because of high mortality rates among human cases and extensive spread among poultry populations of many countries since 2005; concern about the virus prompted extensive pandemic preparedness activities worldwide. As of May 2, 2012, 603 laboratory-confirmed human cases of HPAI H5N1 virus infection have been reported to the World Health Organization since November 2003, with a 59% cumulative case fatality proportion.<sup>14</sup> Published information on the effects of HPAI H5N1 virus infection in pregnant women is limited. A review paper that was published in 2008 noted that 4 of 6 pregnant women with HPAI H5N1 virus infection died and that the 2 women who survived had spontaneous abortions.<sup>15</sup> Detailed clinical and pathologic data have been reported on 1 of the women who died.<sup>16,17</sup> Her illness progressed rapidly to multiorgan failure and death, despite intensive supportive care. Pathologic analysis demonstrated widespread extrapulmonary dissemination of HPAI H5N1 virus in several tissues, including

in fetal lung cells, that documented transplacental transmission to her fetus.<sup>16</sup>

Data from previous pandemics (which includes the pandemics of 1918, 1957, and 2009) suggest that pregnant women have higher rates of morbidity and mortality. In one report from the 1918 H1N1 influenza pandemic ( $n = 1350$ ), one-half of all pregnant patients had pneumonia; approximately one-half of these patients died, which yielded a case fatality proportion among pregnant women of 27%.<sup>18</sup> Among a case series of 86 pregnant women who were hospitalized with pandemic influenza in Chicago during 1918, 41 women (45.5%) died.<sup>19</sup>

Pregnancy was also identified as a risk factor for severe disease during the 1957 H2N2 influenza pandemic. In a study in Minnesota in 1957–1958, pandemic influenza was the leading cause of death during pregnancy; nearly 20% of deaths that occurred during pregnancy were due to influenza. During this time period, one-half of the women of reproductive age who died from pandemic influenza were pregnant.<sup>20</sup>

More recently, the influenza A(H1N1)-pdm09 (2009 H1N1) pandemic provided further evidence that pregnant women are at high risk for severe influenza complications. When the data for pregnant women were compared with nonpregnant women of reproductive age or with the general population, several studies demonstrated that pregnant women were at increased risk of hospitalization, admission to an intensive care unit, death, and other severe outcomes related to 2009 H1N1. Data from the first month after emergence of 2009 H1N1 in the United States showed that pregnant women were >4 times more likely to be hospitalized than the general population.<sup>21</sup> Although pregnant women comprise 1% of the population in the United States, they accounted for approximately 5% of all 2009 H1N1-related deaths in the United States.<sup>22</sup> In pooled data from a systematic review, pregnant women accounted for 6.3% of hospitalizations, 5.9% of intensive care unit admissions, and 5.7% of deaths that were associated with 2009 H1N1.<sup>23</sup> The highest risk for severe complications appeared to be in the second and especially the third trimesters

of pregnancy, although intensive care unit admissions and deaths occurred in all 3 trimesters.<sup>22,24,25</sup>

Observational data suggest that pregnant women who received antiviral treatment that was initiated within 2 days of onset of 2009 H1N1-associated symptoms were less likely to die or to be admitted to an intensive care unit.<sup>22</sup> As reviewed by Mosby et al,<sup>23</sup> 5 observational studies showed that neuraminidase inhibitor treatment of pregnant women with 2009 H1N1 when started within 48 hours of symptom onset was associated with a lower risk of severe disease. Some clinical benefit was observed when antiviral treatment was started 3–4 days after symptom onset compared with the initiation of treatment >4 days after symptom onset.<sup>23</sup>

Data that were collected during the 2009 H1N1 pandemic also demonstrated an increased risk for influenza-associated complications among postpartum women.<sup>26</sup> Based on 15 case reports of women up to 6 months after delivery in California, severe illness was often reported: 9 postpartum women with 2009 H1N1 were admitted to the intensive care unit; 3 of these died. The risk appeared to be highest during the first postpartum week, although an appropriate comparison group was not included.

Although treatment with antiviral medications appears to decrease the risk of severe influenza outcomes among pregnant women, limited data are available on the effects of antiviral medications on the embryo or fetus when used during pregnancy.<sup>4,27</sup> Available information on antiviral medications during pregnancy is reassuring; however, adequate well-controlled studies of pregnant women are not available, and these medications are considered to be pregnancy category C by the United States Food and Drug Administration.<sup>27</sup> Therefore, pregnant women might be reluctant to take antiviral medications, and health care providers might be reluctant to prescribe such treatment for influenza during pregnancy. Delayed or lack of antiviral treatment of pregnant women with 2009 H1N1 was observed, particularly early in the pandemic, despite clear public health recommendations for treatment. Treat-

ment delay often was associated with adverse outcomes in pregnant women.<sup>22,24</sup>

### Effects of influenza during pregnancy on the newborn infant

Limited information is available on risks to the embryo or fetus that are associated with seasonal or pandemic influenza virus infection. Viremia appears to occur very infrequently during influenza illness<sup>28</sup>; therefore, transplacental (vertical) transmission of influenza virus from mother to the embryo or fetus is expected to be rare.<sup>29-32</sup> As previously noted, transplacental virus transmission has been well-documented in a pregnant woman who was infected with HPAI H5N1 virus, which has been shown to cause extrapulmonary infection, which includes viremia.<sup>15,33,34</sup> This report described a fatal case of H5N1 virus infection in a pregnant woman; on pathologic evaluation, H5N1 viral genomic sequences and antigens were detected in placental tissue and fetal lung cells.<sup>16</sup> Transplacental transmission of 2009 H1N1 virus was suspected in some cases, but definitive evidence was not available.<sup>35-39</sup> Therefore, the limited evidence to date suggests that vertical transmission of influenza viruses can occur but is likely to be very rare.

Even in the absence of transplacental transmission of influenza virus, the embryo or fetus might be affected adversely by influenza in the mother during pregnancy, especially when the mother is severely ill. Data from the 1918 H1N1 influenza pandemic demonstrated an increased risk for pregnancy loss that is associated with influenza illness.<sup>18</sup> In Harris's series, approximately one-quarter of pregnancies with uncomplicated influenza ended in pregnancy loss; among those mothers whose influenza that was complicated by pneumonia, more than one-half of pregnancies ended in pregnancy loss. A recent analysis of birth rates during the time period surrounding the 1918 H1N1 pandemic showed a decline in the birth rate in the spring of 1919; the authors concluded that this decline could be consistent with influenza causing first-trimester pregnancy losses in approximately 1 in 10 women during the peak of the pandemic.<sup>40</sup> An analysis of data from Japan during the

1918-1920 H1N1 influenza pandemic demonstrated a significantly increased risk for stillbirths (risk ratios ranged from 1.1-1.3).<sup>41</sup> Studies from the 1957 H2N2 influenza pandemic showed a possible increase in the risk for pregnancy loss and preterm delivery among women who had influenza during pregnancy.<sup>42</sup>

Seasonal influenza in pregnant women also may increase the risk for adverse infant outcomes. Based on data from a 13-year population-based cohort study in Nova Scotia, infants born to women who were hospitalized for respiratory illness during influenza season (a proxy for influenza illness) at any time during pregnancy were more likely to be born small for gestational age (adjusted relative risk, 1.66; 95% CI, 1.11-2.49) and to have lower mean birthweight ( $P < .009$ ) than infants born to women who were not hospitalized.<sup>43</sup> In contrast, in a study that used data from the Tennessee Medicaid program, infants born to pregnant women with a respiratory hospitalization during influenza season did not differ with regard to prevalence of preterm birth or low birthweight from infants born to women without a respiratory hospitalization, matched on gestational age and the presence of maternal comorbidity.<sup>44</sup>

Data from the H1N1 pandemic indicate that influenza during pregnancy increases the risk for adverse pregnancy outcomes. A study of 256 women who were hospitalized in the United Kingdom with 2009 H1N1 virus infection during pregnancy reported a significantly increased perinatal mortality rate (39 per 1000 total births [95% CI, 19-71] among women with prenatal influenza), compared with a rate of 7 per 1000 (95% CI, 3-13) among the comparison group without 2009 H1N1. This was primarily due to an increase in the rate of stillbirths (27 vs 6 per 1000 total births;  $P = .001$ ). In this study, preterm birth was also more likely with 2009 H1N1 (adjusted odds ratio, 4.0; 95% CI, 2.7-5.9). Risk factors for preterm delivery were third-trimester infection, admission to an intensive care unit, and secondary pneumonia that accompanied 2009 H1N1.<sup>45</sup> Yates et al<sup>46</sup> also identified an increased risk for preterm delivery, based on an examination of 241 preg-

nant women who were hospitalized with laboratory-confirmed 2009 H1N1 (odds ratio, 3.1; 95% CI, 2.4-4.5). In addition, several case series of pregnant women with 2009 H1N1 demonstrated an increased frequency of preterm delivery, particularly among women with severe illness.<sup>23</sup>

A recent follow-up study of severely ill women (defined as women who were admitted to an intensive care unit or who died) with 2009 H1N1 during pregnancy in the United States reported to the Centers for Disease Control showed an increased risk of adverse infant outcomes. Among infants born to women who delivered while hospitalized for 2009 H1N1 illness, 63.6% (95% CI, 51.8-74.3) were born preterm (compared with 12.3% of all US births), 69.4% (95% CI, 57.5-79.8) were admitted to a neonatal intensive care unit (compared with 6.1% of all US births), and 29.2% (95% CI, 19.1-41.1) had 5-minute Apgar scores that were  $\leq 6$  (compared with 1.6% of all US births). Among infants born to mothers who delivered after their hospital discharge for 2009 H1N1, 25% (95% CI, 14.0-39.0) were small for gestational age (compared with 10% of all US births), and 22% (95% CI, 11.5-36.0) were admitted to a neonatal intensive care unit (compared with 6.1% of all US births).<sup>47</sup>

In a prospective study in Rhode Island, infants born to 16 women with 2009 H1N1 during pregnancy had a lower mean birthweight than those born to 25 women with influenza-like illness (defined as fever and cough and/or sore throat in the absence of other known causes of illness) who tested negative for 2009 H1N1.<sup>48</sup> However, in that study, no differences in gestational age, Apgar scores, or cord blood gas pH values were noted.

Other adverse outcomes among children have also been postulated after seasonal or pandemic influenza during pregnancy, but data are limited. For example, some studies suggested that the risk of congenital anomalies was increased among infants born to pregnant women with pandemic H2N2 influenza in 1957.<sup>42,49-51</sup> Seasonal influenza during pregnancy has been associated with congenital anomalies (in particular, cleft

lip with or without cleft palate and neural tube and congenital heart defects) in limited studies.<sup>52,53</sup> Associations between maternal influenza (seasonal or pandemic influenza) and other adverse outcomes that included childhood leukemia, schizophrenia, and Parkinson disease have also been suggested.<sup>54-56</sup>

Fever that often accompanies influenza virus infection has been shown to increase the risk for several adverse infant outcomes and might be responsible for some of the observed associations between maternal influenza and adverse outcomes.<sup>57</sup> For example, a 2-fold risk was suggested by a metaanalysis of the association between maternal hyperthermia and neural tube defects.<sup>58</sup> An association between maternal fever and other congenital anomalies (eg, congenital heart defects and orofacial clefts) has also been observed.<sup>59-62</sup>

Several studies have reported that maternal influenza vaccination reduces adverse outcomes in infants born to pregnant women with influenza. Zaman et al<sup>1</sup> conducted a clinical trial in Bangladesh in which pregnant women were assigned randomly to receive either inactivated influenza or pneumococcal vaccines to assess their effectiveness during pregnancy. Infants born to pregnant women who received influenza vaccine during a time period when influenza virus was circulating were compared with infants born to women who received pneumococcal vaccine during the same time period. Infants born to women who received influenza vaccine had significantly higher birthweights (3178 vs 2978 g;  $P = .02$ ) and were less likely to be born small for gestational age (25.9% vs 44.8%;  $P = .03$ ) than infants born to women who received pneumococcal vaccine, which suggests that prevention of influenza through prenatal vaccination results in improved intrauterine growth.<sup>63</sup> A cohort analysis that used surveillance data from the Georgia Pregnancy Risk Assessment Monitoring System showed that infants born to mothers who received influenza vaccine during pregnancy were less likely to be born preterm (adjusted odds ratio, 0.60; 95% CI, 0.38–0.94) and less likely to be small for gestational age (adjusted odds ratio, 0.31; 95% CI, 0.13–0.75), compared with infants born to

women who did not receive the influenza vaccine.<sup>64</sup>

### Effects of influenza on infants <6 months old

Many studies have shown that young children are at increased risk for influenza-associated complications,<sup>65-70</sup> but only a few of these studies have focused specifically on infants <6 months old. Using data from the Tennessee Medicaid program for the years 1973-1993, Neuzil et al<sup>71</sup> showed a high rate of excess hospitalization for cardiopulmonary conditions when influenza viruses were circulating compared with noninfluenza periods. The average rate of influenza-associated excess hospitalizations was highest in infants <6 months old (104 per 10,000 children per year), compared with 50 per 10,000 in infants 6-12 months old, 19 for children 1-3 years old, 9 for children 3-5 years old, and 4 for children 5-15 years old. Other studies of laboratory-confirmed influenza provide stronger evidence that young infants are at high risk for severe complications from influenza. A study of children during 2 influenza seasons (2002-2003 and 2003-2004) showed that infants <6 months old had the highest rates of hospitalization for laboratory-confirmed influenza among children who were 0-59 months old. The average annual rate of hospitalization because of influenza was 4.5 per 1000 children (95% CI, 3.4–5.5) for infants <6 months old, compared with 0.9 per 1000 (95% CI, 0.7–1.2) for children 6-23 months old and 0.3 per 1000 (95% CI, 0.2–0.5) for children 24-59 months old.<sup>72</sup> In a population-based study from 2003-2008, the highest hospitalization rates among children with laboratory-confirmed influenza were in infants <6 months old and ranged from 9–30 per 10,000 children.<sup>73</sup> In a study of laboratory-confirmed influenza-associated deaths among children during a severe seasonal influenza epidemic in 2003-2004, the highest mortality rate was observed among children <6 months old (0.88 per 100,000 children; 95% CI, 0.52–1.39).<sup>74</sup>

Several studies suggested that children who were infected with 2009 H1N1 influenza virus were at increased risk of complications.<sup>75-78</sup> However, only a few

studies included data for infants <6 months old. In a study from Argentina, infants <6 months old with laboratory-confirmed 2009 H1N1 were at increased risk for hospitalization and death.<sup>79</sup> In that study, infants <6 months old with 2009 H1N1 had the highest rate of hospitalizations and the second highest rate of death (infants who were 6-12 months old had the highest rate of death). In a study of children who were hospitalized with 2009 H1N1 in California, the highest hospitalization rate was in infants <6 months old.<sup>80</sup> In a case series from California of 82 infants who were admitted to an intensive care unit with 2009 H1N1, 27 infants (35%) were born preterm (<37 weeks' gestation), and 46 infants (60%) had at least 1 reported chronic medical condition (eg, chronic lung disease associated with preterm birth, congenital heart defects, and cerebral palsy).<sup>81</sup> In a study of 2009 H1N1 patients that used data from a national hospital discharge database from Japan, infants were 2 times more likely to be hospitalized than children 12-24 months old.<sup>82</sup>

Although infants <6 months old are at increased risk of complications that are associated with influenza, their options for antiviral treatment and chemoprophylaxis options are limited. The neuraminidase inhibitors oral oseltamivir and inhaled zanamivir are not approved by the US Food and Drug Administration for use in children <1 year old, although oseltamivir was made available under an Emergency Use Authorization during the 2009 H1N1 pandemic for this age group<sup>78</sup> and continues to be recommended for use in this age group by the Advisory Committee on Immunization Practices.<sup>83</sup> In addition, influenza vaccines are not approved for use in children <6 months old. Thus, influenza vaccination during pregnancy and influenza vaccination of household contacts and caregivers of infants <6 months old can help prevent influenza in these vulnerable infants who are too young to receive influenza vaccination.<sup>84</sup>

### Comment

In summary, pregnant women and infants <6 months old are at increased risk for ad-

verse consequences that are related to influenza, based on data from seasonal and pandemic influenza. Infants born to women who experienced 2009 H1N1 influenza virus infection during pregnancy, especially women who had severe illness, were more likely to have adverse infant outcomes (eg, low birthweight and preterm birth). In addition, influenza vaccination during pregnancy has been shown to decrease the frequency of influenza or its complications in infants up to 6 months old. Thus, influenza vaccination during pregnancy is a key strategy to prevent influenza and influenza-related complications in pregnant women and their infants. ■

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