H1N1 2009 influenza virus infection during pregnancy in the USA

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Summary

Background **Pandemic H1N1 2009 influenza virus has been identified as the cause of a widespread outbreak of febrile respiratory infection in the USA and worldwide. We summarised cases of infection with pandemic H1N1 virus in pregnant women identified in the USA during the first month of the present outbreak, and deaths associated with this virus during the first 2 months of the outbreak.**

Methods **After initial reports of infection in pregnant women, the US Centers for Disease Control and Prevention (CDC) began systematically collecting additional information about cases and deaths in pregnant women in the USA with pandemic H1N1 virus infection as part of enhanced surveillance. A confirmed case was defined as an acute respiratory illness with laboratory-confirmed pandemic H1N1 virus infection by real-time reverse-transcriptase PCR or viral culture; a probable case was defined as a person with an acute febrile respiratory illness who was positive for influenza A, but negative for H1 and H3. We used population estimates derived from the 2007 census data to calculate rates of admission to hospital and illness.**

Findings **From April 15 to May 18, 2009, 34 confirmed or probable cases of pandemic H1N1 in pregnant women were reported to CDC from 13 states. 11 (32%) women were admitted to hospital. The estimated rate of admission for pandemic H1N1 influenza virus infection in pregnant women during the first month of the outbreak was higher than it was in the general population (0·32 per 100 000 pregnant women, 95% CI 0·13–0·52 *vs* 0·076 per 100 000 population at risk, 95% CI 0·07–0·09). Between April 15 and June 16, 2009, six deaths in pregnant women were reported to the CDC; all were in women who had developed pneumonia and subsequent acute respiratory distress syndrome requiring mechanical ventilation.**

Interpretation **Pregnant women might be at increased risk for complications from pandemic H1N1 virus infection. These data lend support to the present recommendation to promptly treat pregnant women with H1N1 influenza virus infection with anti-influenza drugs.**

Funding **US CDC.**

Introduction

Pandemic H1N1 2009 influenza virus infection has been identified as the cause of a widespread outbreak of febrile respiratory infection in the USA[1] and worldwide.[2] Although the severity of this illness has ranged from mild to severe, little has been reported about how this outbreak has affected pregnant women.[3,4] During both seasonal influenza epidemics[5,6] and previous pandemics,[7–9] pregnant women have increased morbidity and mortality from influenza infection compared with women who are not pregnant. In the present outbreak beginning April, 2009, the second documented death from pandemic H1N1 virus infection in the USA was in a healthy pregnant woman.[3] Because of concerns about the severity of disease during pregnancy, the US Centers for Disease Control and Prevention (CDC) implemented enhanced surveillance for pandemic H1N1 influenza virus infections in pregnant women in the USA. This report summarises the cases of infection with pandemic H1N1 influenza virus in pregnant women that have been reported to the CDC during the first month of the outbreak (April 15–May 18, 2009) and deaths associated with this virus during the first 2 months of the outbreak (April 15–June 16, 2009).

Methods

Setting

On April 15 and 17, 2009, CDC identified a novel influenza A virus of swine origin in two children in two different counties in California. The children did not have any epidemiological links to each other, and neither had recent exposure to pigs. In response, CDC implemented enhanced surveillance for novel influenza A virus infection.

Pandemic H1N1 is diagnosed from respiratory specimens with a real-time reverse-transcriptase PCR testing assay that was developed at the CDC.[1] Initially, CDC tested all specimens that were identified as unsubtypable influenza A by state public health laboratories. On May 6, 2009, CDC began to supply state

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public health laboratories with assays for testing, and by May 18, 2009, 40 states were certified to do their own testing.

Case definition and reporting

CDC developed nationally standardised case definitions for confirmed and probable cases of pandemic H1N1 virus infection that were disseminated via the Internet. A confirmed case was defined as an acute respiratory illness with laboratory-confirmed pandemic H1N1 virus infection by real-time reverse-transcriptase PCR or viral culture. A probable case was defined as a person with an acute febrile respiratory illness who was positive for influenza A, but negative for H1 and H3 by influenza real-time reverse-transcriptase PCR. In one report,[4] about 96% of unsubtypable specimens were later confirmed as pandemic H1N1 virus.

For the **CDC protocol of real-time reverse-transcriptase PCR for influenza A (H1N1)** see http://www.who.int/csr/resources/publications/swineflu/realtimeptpcr/en/index.html

For **CDC interim guidance on case definition to be used for investigations of novel influenza A (H1N1) cases** see http://www.cdc.gov/h1n1flu/casedef.htm

CDC requested that state and local health departments complete a five-page standardised case-report form for every confirmed and probable case of pandemic H1N1 virus infection. As part of this reporting system, CDC began to receive some preliminary reports of infection in pregnant women, and on May 4, CDC developed a one-page standardised addendum to collect additional information about cases in pregnant women with pandemic H1N1 virus infection. Both forms were completed by state and local health departments for any pregnant woman who was a confirmed or probable case. The de-identified information about pregnant women with pandemic H1N1 virus infection was reported by states to CDC, and these reports were compiled at CDC. After the first death in a patient with pandemic H1N1 virus infection occurred on May 4, 2009, CDC initiated active follow-up with state health departments to obtain additional information about people with this virus infection who died.

This study was reviewed by CDC and determined to be a public health response and to not need approval from an institutional review board nor written informed consent. Additionally, the privacy rule of the Health Insurance Portability and Accountability Act did not apply since this activity was an emergency public health response.

Statistical analysis

For more about the **population estimates** see http://www.cdc.gov/nchs/about/major/dvs/popbridge/popbridge.htm

To calculate rate of admission to hospital and illness, population estimates were derived from the 2007 census data. In 2007, the US Census Bureau and the National Center for Health Statistics estimated that there were 301 621 157 people, including 62 097 211 women of reproductive age (15–44 years) in the USA. Similar to previously published methods,[10] we calculated the number of pregnant women as follows: the fertility rate (69·5 per 1000 women of reproductive age) was multiplied by nine-twelfths of the population of women of reproductive age, since pregnancy lasts roughly 9 months. Similarly, the abortion rate (15·0 per 1000 women of reproductive age) was multiplied by a sixth of the population of women of reproductive age since these pregnancies last an average of 2 months. These two numbers were added together to estimate the number of women who are pregnant. We calculated that there were 3 392 060 women currently pregnant in the USA. We compared admission rates in three groups: pregnant women, non-pregnant women of reproductive age (15–44 years), and the general population. Because of changes in the information that states reported to the CDC, admission rates for non-pregnant women of reproductive age could be calculated only until May 12, 2009, rather than the full reporting period ending May 18, 2009.

Admission rates were expressed as the number of cases per 100 000 population at risk. 95% CIs for rates were estimated with exact binomial methods. For proportions with denominators greater than 10 000, we manually calculated 95% CIs with standard methods that assume a normal distribution. We used χ^2 tests, and Fisher's exact test for small numbers, to assess differences in proportions. The proportions of cases with specific manifestations were compared for pregnant women, non-pregnant women of reproductive age (15–44 years of age), and the non-pregnant general population. Risk ratios (RRs) for specific manifestations and admission were calculated with standard methods, and 95% CIs were calculated with the Taylor series method. Most states began reporting aggregate data to the CDC, and we were therefore unable to calculate illness and admission rates for pregnant women after May 18, 2009. We were able, however, to calculate the proportion of all deaths from pandemic H1N1 in pregnant women for 2 months from April 15 to June 16, 2009.

Role of the funding source

The US CDC, the funding source for this study, employs some of the study authors, who had responsibility for study design and analysis and interpretation of the data. The report received approval for publication from other employees of the US Government. Additionally, some study authors are employed by local and state health departments, which report public health information to the US Government. DJJ and MAH had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

From April 15 to May 18, 2009, CDC received reports of 31 pregnant women with confirmed pandemic H1N1 virus infection and of three pregnant women meeting the definition as a probable case. The women were reported from 13 states: Arizona (n=4), California (13), Colorado (3), Delaware (2), Georgia (1), Iowa (1), Kentucky (1), Massachusetts (1), Michigan (3), Oklahoma (1), Pennsylvania (1), Texas (2), and Washington state (1). They ranged in age from 15–42 years

	n (%)
Maternal age (years)	
<18	5 (15%)
18–29	17 (50%)
30–39	11 (32%)
≥40	1 (3%)
Maternal race/ethnic origin	
Non-Hispanic white	9 (26%)
Non-Hispanic black	2 (6%)
Hispanic	15 (44%)
Asian	1 (3%)
American Indian/Alaskan native	1 (3%)
Unknown	6 (18%)
Gravidity	
One	6 (18%)
≥Two	16 (47%)
Unknown	12 (35%)
Parity	
Nulliparous	7 (21%)
One	5 (15%)
≥Two	10 (29%)
Unknown	12 (35%)
Weeks pregnant at time of infection	
0–13	3 (9%)
14–28	19 (56%)
>29	9 (26%)
Unknown	3 (9%)
Prenatal care initiated in first trimester	
Yes	11 (32%)
No	5 (15%)
Unknown	18 (53%)
Family member or close contact with pneumonia or influenza-like illness in 7 days before illness onset	
Yes	11 (32%)
No	15 (44%)
Unknown	8 (24%)
(Continues in next column)	
(Continued from previous column)	
Travel to Mexico in 7 days before illness onset	
Yes	4 (12%)
No	27 (79%)
Unknown	3 (9%)
History of asthma	
Yes, currently receiving prescription drugs	1 (3%)
Yes, no current prescription drugs	6 (18%)
No	18 (53%)
Unknown	9 (26%)
Other drugs for chronic health disorders	
Yes	2 (6%)
No	25 (73%)
Unknown	7 (21%)
Seasonal influenza vaccine in 2008–09 season	
Yes	3 (9%)
No	19 (56%)
Unknown	12 (35%)
Antiviral drugs	
Oseltamivir*	17 (50%)
Started within 2 days of symptom onset	8 (24%)
Acetaminophen for fever treatment	16 (47%)
Admitted to hospital	
Any admission	14 (41%)
≤24 h	3 (9%)
>24 h	11 (32%)
Admitted to intensive care unit	3 (9%)
Intubated/required mechanical ventilation	1 (3%)

*One woman also received amantadine and one woman also received zanamivir.

***Table 1:* Characteristics and reported treatment of 34 pregnant women with pandemic H1N1 influenza virus infections in the USA, from April 15 to May 18, 2009**

(median 26). Nearly half of the women were Hispanic and a fifth were nulliparous (table 1). 22 (65%) women were in the first or second trimester of pregnancy and nine (26%) were in the third trimester. 11 (32%) started prenatal care in the first trimester. 11 (32%) women reported a family member or close contact with pneumonia or influenza-like illness in the 7 days before illness onset, and four (12%) reported recent travel to Mexico. 22 (65%) women had no reported epidemiological link (ie, travel or close contact) with pandemic H1N1 virus. Three women were health-care workers, none of whom reported close contact with a patient with influenza in the past 7 days. Although seven (21%) women reported a history of asthma, only one was taking medication for it. In addition to the woman with asthma, two others reported taking drugs for chronic health disorders: one was using insulin for diabetes in pregnancy and one who was in the first trimester and unaware that she was pregnant was taking labetalol for hypertension and methimazole for hyperthyroidism. Vaccination for seasonal influenza in the 2008–09 season was reported by three (9%) of the 34 pregnant women.

Of the 34 pregnant women with pandemic H1N1 virus infection, symptom onset ranged from April 14 to May 6, 2009. 33 (97%) women with pandemic H1N1 virus infection presented with a febrile illness (table 2). 32 (94%) women had influenza-like illness, which was defined as having a fever plus either cough or sore throat. Other than fever, the most common symptoms were cough, rhinorrhoea, sore throat, headache, shortness of breath, and myalgia, with vomiting and diarrhoea reported less frequently (table 2). Generally, manifestations of pandemic H1N1 influenza virus infection reported by pregnant women were similar to those reported by the non-pregnant general population. However, pregnant women were more likely to report shortness of breath compared with non-pregnant women

	Pregnant women (n=34)	Non-pregnant women of reproductive age (15–44 years) (n=142)	Risk ratio (95% CI)*	Non-pregnant people† (n=730)	Risk ratio (95% CI)‡
Fever	33 (97%)	131 (92%)	1·1 (1·0–1·1)	678 (93%)	1·0 (1·0–1·1)
Above 37·8°C	24	114		567	
Subjective	9	17		111	
Cough	32 (94%)	133 (94%)	1·0 (0·9–1·1)	642 (88%)	1·1 (1·0–1·2)
Rhinorrhoea	20 (59%)	71 (50%)	1·2 (0·8–1·6)	357 (49%)	1·2 (0·9–1·6)
Sore throat§	17 (50%)	97 (68%)	0·7 (0·5–1·0)	437 (60%)	0·8 (0·6–1·2)
Headache	16 (47%)	90 (63%)	0·7 (0·5–1·1)	368 (50%)	0·9 (0·6–1·3)
Shortness of breath¶	14 (41%)	35 (25%)	1·7 (1·0–2·7)	128 (18%)	2·3 (1·5–3·6)
Myalgia‖	12 (35%)	..	..	..	..
Vomiting	6 (18%)	22 (15%)	1·1 (0·5–2·6)	157 (22%)	0·8 (0·4–1·7)
Diarrhoea	4 (12%)	28 (20%)	0·6 (0·2–1·6)	130 (18%)	0·7 (0·3–1·7)
Conjunctivitis	3 (9%)	12 (8%)	1·0 (0·3–3·5)	81 (11%)	0·8 (0·3–2·4)

Data are number (%), unless otherwise indicated. *Pregnant women compared with non-pregnant women of reproductive age. †Includes men, non-pregnant women, and children of all ages. ‡Pregnant women compared with all non-pregnant people. §p=0·05 for pregnant women compared with non-pregnant women of reproductive age. ¶p=0·05 for pregnant women compared with non-pregnant women of reproductive age; p=0·0005 for pregnant women compared with non-pregnant people. ‖Information about myalgias not consistently collected for non-pregnant people because it was only ascertained in an "other, specify" field.

Table 2: **Presenting manifestations in cases with pandemic H1N1 influenza virus infections in the USA, from April 15 to May 18, 2009**

of reproductive age (RR 1·7, 95% CI 1·0–2·7) and the non-pregnant general population (RR 2·3, 1·5–3·6).

17 (50%) women took oseltamivir; eight (24%) began oseltamivir within 2 days of symptom onset (table 1). Two of the 17 women receiving oseltamivir also received a second antiviral drug (zanamivir [n=1] and amantadine [1]). Of the pregnant women with known date of symptom onset, 40% (eight of 20) with symptom onset from April 14 to April 30, 2009, took oseltamivir and 73% (eight of 11) with symptom onset from May 1 to May 6, 2009, took oseltamivir (RR 0·55, 95% CI 0·29–1·05; p=0·08). 16 (47%) women reported use of acetaminophen for fever treatment. Of the 34 cases, three women were admitted for less than 24 h and 11 were admitted for more than 24 h, with lengths of stay ranging from 2 to 15 days. Three women were admitted to the intensive care unit during their admission. A 33-year-old woman at 35 weeks' gestation was admitted in severe respiratory distress, was intubated and mechanically ventilated, and underwent an emergency caesarean delivery. The patient continued to need mechanical ventilation, developed pneumonia and acute respiratory distress syndrome, and died on the 15th hospital day.[3]

Six women had confirmed or suspected pneumonia, including four with pneumonia confirmed by plain chest radiograph. Two women were diagnosed with dehydration. Two women gave birth to their child during their admission to hospital and both were febrile intrapartum. A 42-year-old woman with a twin gestation at 34 weeks' gestation presented with fever and cough, was diagnosed with influenza, and started taking oseltamivir. 6 days later she presented with preterm premature rupture of membranes and underwent caesarean delivery of two healthy babies. A 34-year-old woman at 9 weeks' gestation presented to a local emergency department with complaints of shortness of breath, cough, and fever for the past 5 days. In the emergency department she had vaginal bleeding and a positive serum human chorionic gonadotropin test supporting a diagnosis of a 9-week spontaneous abortion, based on the date of her last menstrual period. She was admitted with a diagnosis of dehydration with electrolyte abnormalities.

Pregnant cases represented 0·62% (34/5469) of the total number of confirmed or probable cases reported nationally of pandemic H1N1 virus infection during the first month of the outbreak. We recorded 34 reported cases of pandemic H1N1 in an estimated 3 392 060 pregnant women in the USA (1·0 reported case per 100 000 pregnant women). A higher proportion of pregnant women were admitted than in the general population (11/34 [32·4%, 95% CI 17·4–50·5] *vs* 229/5469 [4·2%, 3·7–4·8]). Admission rates were also higher in pregnant women than in the general population. The estimated admission rate for pregnant women was 0·32 per 100 000 pregnant women (95% CI 0·13–0·52); the estimated admission rate in the general population was 0·076 per 100 000 population at risk (0·07–0·09). Thus, pregnant women were more than four times more likely to be admitted than was the general population (RR 4·3, 95% CI 2·3–7·8).

To account for the uncertainty in the estimated number of pregnant women in the USA, we did a sensitivity analysis assuming that there were 10% more pregnant women (n=3 731 266) and 10% fewer pregnant women (3 052 854) than was estimated. With use of these estimates, the resulting RRs for admission ranged from 3·9 (95% CI 2·1–7·1) to 4·7 (2·6–8·7). Although we were unable to compare admissions for non-pregnant women of reproductive age during the same reporting period because of changes in the information that states reported to the CDC, we calculated the proportion of admissions and an admission rate for a reporting period until May 12, 2009. In non-pregnant women of reproductive age, 24 of 569 (4·2%, 95% CI 2·7–6·2) were admitted and the estimated admission rate was 0·04 cases per 100 000 (95% CI 0·03–0·06).

Of the 45 deaths from pandemic H1N1 virus infection reported to the CDC from April 15 to June 16, 2009, six (13%) were in pregnant women, including one death from the original case series of 34 pregnant cases. Of the pregnant women who died, one was in the first trimester, one in the second trimester, and four were in the third trimester. All the women were fairly healthy before their influenza illness (table 3). The time from symptom onset to initial presentation for clinical care ranged from 1 to 7 days (median 3·5). Two patients were admitted on the same day that they initially presented for care. The other three presented 3–4 days before

admission, and one woman was assessed three times as an outpatient (on 3 consecutive days) before admission to the hospital. During the course of their illness, all women received treatment with oseltamivir. The length of time from symptom onset to receipt of antiviral medication ranged from 6 to 15 days (median 9), and the length of time from initial presentation to medical care until receipt of antiviral treatment ranged from 2 to 14 days (median 4·5).

All patients developed primary viral pneumonia and subsequent acute respiratory distress syndrome requiring mechanical ventilation. None of the patients had evidence of secondary bacterial pneumonia or haemorrhagic pneumonia. All five patients with viable pregnancies underwent caesarean delivery. In three cases, the patient or her fetus was not stable enough to transport to the labour and delivery unit, and the caesarean delivery was done in the intensive care unit or emergency department. The time from initial presentation to medical care until death ranged from 6 to 19 days (median 12). None of the five infants born to the women who died had any evidence of influenza infection. Four infants were discharged home from the hospital in good health. The infant born at 27 weeks' gestation remains admitted and is doing well, with supplemental oxygen via nasal cannula and feeding via a nasogastric tube.

	Age (years)	Weeks' gestation (at time of delivery)	Underlying medical conditions	Receipt of antiviral drug	Days from symptom onset to receipt of antiviral drugs	Pregnancy outcome
Case number 1	33	35	Mild asthma, psoriasis	Oseltamivir	14	Livebirth by caesarean delivery
Case number 2	24	32	Obesity*	Oseltamivir	10	Livebirth by caesarean delivery
Case number 3	20	27	None	Oseltamivir and rimantadine	6	Livebirth by caesarean delivery
Case number 4	21	11	Factor V Leiden deficiency	Oseltamivir and rimantadine	8	Fetal loss at time of mother's death
Case number 5	22	36	None	Oseltamivir	15	Livebirth by caesarean delivery
Case number 6	30	30	None	Oseltamivir and amantidine	8	Livebirth by caesarean delivery

*In patient's medical record she was reported as morbidly obese. Her body-mass index at 32 weeks of gestation was 49·6 kg/m², but her pre-pregnancy weight was not available.

Table 3: **Deaths in pregnant women due to pandemic H1N1 influenza virus infection in the USA, from April 15 to June 16, 2009**

Discussion

This study summarises the cases of pregnant women with pandemic H1N1 virus infection in the USA and shows that this virus can cause serious illness in healthy pregnant women. Before the present outbreak, published work of influenza virus of swine origin in pregnant women was limited to a single case in 1988: a 32-year-old previously healthy pregnant woman at 36 weeks' gestation was infected with a swine influenza virus, contracted through exposure to pigs, and later died of complications related to primary viral pneumonia.[11,12]

On the basis of our investigation, pregnant women seem to be at increased risk for complications from pandemic H1N1 virus infection, with a higher estimated rate of hospital admission than in the general population. Although the decision to admit a pregnant woman is complex and might include considerations beyond simply the severity of disease, that a high proportion (>10%) of influenza-related deaths in the USA have been in pregnant women is concerning. In the previous influenza pandemics of 1918 and 1957, mortality seemed to be higher in pregnant women than in non-pregnant populations, although appropriate comparison groups were often not available. In a series of 1350 pregnant women reported during the 1918 pandemic,[8] about 50% developed pneumonia and of these women, more than half died (overall case fatality rate 27%), with the highest mortality in the third trimester. During the pandemic of 1957, 50% of deaths due to Asian influenza in Minnesota among women of reproductive age occurred in pregnant women.[7] The groups of women selected for inclusion in reports from the 1918 and 1957 pandemics might have been biased towards more severe cases, and in 1918, the diagnosis of influenza was based on the clinical syndrome alone because human influenza viruses were not identified until 1933. Thus, comparison of severity of disease in pregnant women in previous pandemics compared with the present outbreak, particularly in view of the few documented cases so far, is difficult. However, that all six deaths reported during the present outbreak were in relatively healthy pregnant women is noteworthy.

Pregnant women are also at increased risk for pregnancy complications during seasonal influenza epidemics. In one study,[6] pregnant women were more likely to be admitted for a cardiopulmonary event during influenza season than were those who were post partum (a group considered similar to pregnant women demographically and by health status). The risk varied by weeks of gestation, with odds ratios of 1·06 (95% CI 0·68–1·67) during weeks 1–7, 2·52 (1·74–3·65) during weeks 21–26, and 4·67 (3·42–6·39) during weeks 37–42. A study from Nova Scotia[5] showed that women were more likely to be admitted to the hospital for respiratory illness during influenza season during pregnancy than during the year before pregnancy. In pregnant women with no comorbidities (defined as pre-existing diabetes, pulmonary disease, heart disease, renal disease, and anaemia), rate ratios for hospital admissions by trimester of pregnancy compared with the year before pregnancy were 1·7 (1·0–2·8) for first, 2·1 (1·3–3·3) for second, and 5·1 (3·6–7·3) for third trimesters. The effects of pregnancy were greatest in women with one or more comorbidities, with rate ratios

of 2·9 (1·5–5·4), 3·4 (1·9–6·0), and 7·9 (5·0–12·5), respectively. In our investigation, a fifth of women admitted to hospital had a history of mild asthma, but only one reported using any medications for asthma.

The present circulating pandemic H1N1 virus is sensitive to the neuraminidase inhibitors oseltamivir and zanamivir. In randomised controlled clinical trials,[13] these drugs have reduced the severity of seasonal influenza if started within 48 h of illness onset. Although data suggest that oseltamivir can reduce mortality in admitted patients even when started more than 48 h after illness onset, CDC recommendations for pregnant patients are that antiviral drugs be started as soon as possible after the onset of influenza symptoms. The benefit is expected to be greatest if started within 48 h of onset. However, many pregnant women in our series were not treated with either of these drugs at the time of their presentation with influenza-like illness. Furthermore, none of those who died were treated within 48 h of illness onset.

For **CDC guidance on pregnant women and novel influenza A (H1N1) virus: considerations for clinicians** see http://www.cdc.gov/h1n1flu/clinician_pregnant.htm

We did not record a delay in diagnosis of influenza in pregnant women. However, in many cases, there seem to have been delays in initiation of antiviral therapy. Health-care providers might have been reluctant to treat patients with antiviral drugs because they were pregnant, or before laboratory confirmation of disease, or the pregnant woman might have been reluctant to take an antiviral drug. As with most drugs,[14,15] information about the safety and effectiveness of these anti-influenza drugs during pregnancy is scarce.[16–18] In view of the expected effects of pandemic H1N1 influenza virus on the pregnant woman, the benefits of treatment with these drugs are likely to outweigh potential risks to the fetus.[19,20] Current CDC guidance suggests that antiviral treatment with oseltamivir or zanamivir is recommended for groups at high risk for influenza complications from infection with H1N1 virus, including pregnant women (oseltamivir is preferred). However, some women were diagnosed before the availability of these guidelines. Communication messages aimed at pregnant women and their health-care providers should include information about the benefits and risks of anti-influenza drugs, and about the increased risk of influenza complications in pregnant women. Additionally, improved understanding of the effects of influenza during pregnancy, both seasonal influenza and novel strains, and of anti-influenza drugs used for treatment is crucial; additional data could be obtained through establishment of a national pregnancy registry.

For more on the **CDC interim guidance on antiviral recommendations for patients with novel influenza A (H1N1) virus infection and their close contacts** see http://www.cdc.gov/h1n1flu/recommendations.htm

Since most women in this series are still pregnant, little is known about the effects of the pandemic H1N1 virus on the fetus. Although no infections have been reported in infants born to women with H1N1 virus infection, these infants might have had more subtle effects from maternal pandemic H1N1 virus infection. Furthermore, the effects of seasonal influenza on the fetus are not well understood. Although viraemia seems to be rare in seasonal influenza[21] and placental transmission seems to occur infrequently,[22] highly pathogenic strains of influenza virus, such as avian influenza A (H5N1), might be transmitted across the placenta. This was shown in a pregnant woman infected with H5N1, with viral genomic sequences identified in the placental cytotrophoblasts and in the fetal respiratory tract.[23,24] Additionally, even in the absence of placental transmission, the fetus could be adversely affected by influenza or its effects. For example, fever, which often accompanies influenza, has been associated with an increased risk for neural tube defects when occurring in the first trimester[25] and with other adverse neonatal or developmental outcomes, when occurring later in pregnancy;[26–28] thus, treatment of fever with acetaminophen is recommended.[20] Seasonal influenza has been associated with a small increased risk of birth defects in some studies, although others have not reported this association.[29]

Concerns about influenza's effects on the fetus were raised during previous pandemics. In the pandemic of 1918, high rates of pregnancy loss and preterm delivery were reported,[8,9] and during the pandemic of 1957–58, possible increases in CNS defects and other adverse outcomes were shown.[30–33] Follow-up of outcomes of pregnancy to women infected with H1N1 virus is needed to improve understanding of the possible effects of this novel virus.

Once available, vaccination will be an essential component of the public health response to this influenza, and US guidelines place pregnant women in a high-priority group for receipt of pandemic influenza vaccine.[20] However, in one study,[34] pregnant women had the lowest vaccine coverage level (14·4% in 2004) of all adult population groups recommended to receive influenza vaccination,[34] despite trivalent inactivated vaccine being recommended by the US Advisory Committee on Immunization Practices and the American College of Obstetricians and Gynecologists during any trimester of pregnancy.[13,35] The low level of use of influenza vaccine in pregnant women[34] is disconcerting and has important implications for future pandemic vaccination planning.

In addition to the protection provided to mothers, influenza vaccination also seems to provide benefit to infants; in a randomised study in Bangladesh,[36] inactivated influenza vaccine reduced proven influenza illness by 63% in infants aged 6 months or younger. The reasons for the low level of influenza vaccination coverage in the USA are not well understood, although concerns about vaccine safety are often cited by mothers as barriers to vaccination.[37] Information about safety of influenza vaccine during pregnancy is scarce, but available data show no evidence of adverse effects on women or their infants.[38] Knowledge gaps in women and their health-care providers must be addressed[39] to improve vaccination

coverage for pregnant women during interpandemic periods and during a pandemic.[20]

Our investigation has several limitations. Ascertainment of women infected with pandemic H1N1 influenza virus was dependent on surveillance and laboratory testing methods used by state public health authorities during the outbreak. These methods varied by state and by the timing during the outbreak. For example, because of limitations on laboratory capacity and the likelihood that results of testing would be unlikely to change clinical care, laboratory testing for the virus varied as the outbreak progressed: early in the outbreak, most people with influenza-like illness who presented for medical care were tested, but later in the outbreak, testing was focused on more severe cases (eg, those admitted). Furthermore, data from a survey of obstetricians and gynaecologists in 2004,[40] suggested that pregnant women might be less likely to be tested than were those who were not pregnant. Of the obstetricians and gynaecologists who had seen pregnant women whom they suspected of having influenza, 84% reported that they rarely or never tested pregnant women for influenza. This report also summarises information that was collected by the states and reported to the CDC. In view of the substantial stress on the public health system during this outbreak, states might not have reported all cases and might have been most likely to report severe cases.

Another limitation is that health-care providers might be more likely to admit a pregnant woman than a non-pregnant person with similar findings, which could lead to an exaggerated admission rate in pregnant women. Last, the estimated proportion of all pandemic H1N1 deaths in pregnant women is an unstable estimate, in view of the small number of deaths reported so far. If we increased the reporting period by 1 week, the proportion of pandemic H1N1 influenza deaths in pregnant women would be 8% (seven of 87) instead of 13% (six of 45).

Findings from this study will be crucial to inform public health planning for pregnant women, both for this virus and for other novel pathogens. Crucially, health-care providers have to realise that pregnant women are at increased risk for severe disease and complications from pandemic H1N1 influenza virus infection, and should start treatment with anti-influenza drugs promptly.

Contributors

DJJ was involved with designing the study, wrote the report, and collected and reviewed clinical information about cases from clinicians. MAH was involved with designing the study, assisted with report writing, collected information about cases, and analysed data. SAR was involved with designing the study, interpreted and analysed data, and assisted with report writing. JLW reviewed clinical information about cases and multiple versions of the report. DLS, LF, and SJO were involved with designing and implementing the study, provided oversight of data collection, and assisted with interpretation of data including reviewing multiple versions of the report. KFM reviewed multiple versions of the report, assisted with interpretation of data, and provided oversight of data collection. MSB analysed data and reviewed multiple versions of the report. SL and BS provided laboratory testing of specimens and reviewed multiple versions of the report. JKL, CMC, SRB, VPF, KAR, DJK, PE, HB, HAD, EL, MLH, KAR, CB, and NC work at health departments with cases and helped to collect information about the reported cases. They also reviewed multiple versions of the report.

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Conflicts of interest

We declare that we have no conflicts of interest.

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