2009 H1N1 Influenza A and Pregnancy Outcomes in Victoria, Australia

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(See the editorial commentary by Elliot, on pages 691–692.)

Background. Pregnant women have been identified as a group at risk of increased morbidity and mortality associated with the pandemic H1N1 influenza A 2009 (H1N1/09) outbreak.

Methods. Six hospitals in the state of Victoria, Australia, contributed retrospective and prospective demographic and clinical data, reason for admission data, and maternal and fetal outcome data for women with laboratory-confirmed H1N1/09 admitted to the hospital from 20 May 2009 through 31 July 2009.

Results. Forty-three cases were reported during the study period, including 8 intensive care unit admissions, 1 maternal death, 2 fetal deaths, and 1 neonatal death. The most common reason for admission was uncomplicated influenza-like illness. Patients hospitalized for uncomplicated influenza-like illness had a length of stay significantly less than those with confirmed pneumonia. Thirty-six percent of women delivered during the hospitalization. Of the women delivering before 37 weeks’ gestation, almost all had pneumonia. Almost half of our case series had no other comorbidity, a large proportion (77%) of women received antivirals, and 56% received antibiotics. The incidence of hospitalization was estimated at 0.46% (95% confidence interval, 0.31%-0.66%) of all 6094 pregnant women in the third trimester during the 3-month study period. The incidence of hospitalization in the second trimester was estimated at 0.21% (95% confidence interval, 0.11%-0.36%).

Conclusions. This case series confirms a high number of complications in pregnant women due to pandemic H1N1/09. Many of these women had comorbidities, although almost 50% of the women in this case series who required hospitalization did not have an additional risk factor other than being pregnant.

In April 2009 an outbreak of H1N1 influenza A 2009 (H1N1/09) began in Mexico and spread rapidly across many countries. A pandemic was declared by the World Health Organization on 11 June 2009. As of 13 September 2009, more than 296,471 laboratory-confirmed cases had been reported worldwide, with 3486 reported deaths [1]. Whether this new strain is more virulent than seasonal influenza in humans is controversial, but recent animal data clearly show heightened virulence compared with seasonal H1N1 strains [2]. Among human cases, pregnant women have been identified as a group at risk of increased morbidity and mortality [3, 4].

During previous pandemics and seasonal influenza outbreaks, evidence has suggested that pregnant women are at increased risk of complications [5, 6] and death [7, 8]. The effect of maternal influenza on the fetus is not as clearly defined. Adverse pregnancy outcomes, such as preterm labor and spontaneous abortions, have been reported during previous pandemics, especially in women with pneumonia [7, 9]. Data are conflicting on the effect of maternal influenza on the rate of congenital defects. Some reports suggested an increased rate of central nervous system defects during the 1957 pandemic [10, 11], whereas other studies reported an association between influenza and congenital anomalies, which was reduced by the use of antipyretic medication, suggesting an indirect teratogenic effect mediated by maternal hyperthermia [12].
The first confirmed case of pandemic H1N1/09 in Australia was reported in Victoria, Australia, on 20 May 2009. Pandemic H1N1/09 rapidly spread, leading to an influx of influenza illness ~2 months before the usual influenza season. As of 6 September 2009, 3032 laboratory-confirmed cases and 24 confirmed deaths had been reported within the state of Victoria. This study aims to describe the spectrum of illness and complications among pregnant women hospitalized with confirmed H1N1/09 from 20 May 2009 through 31 July 2009 in Victoria, Australia.

METHODS

Six public hospitals in Victoria contributed cases of pregnant women admitted with H1N1/09 from the start of the pandemic until 31 July 2009. Five of these 6 hospitals provide maternity services, and 3 of these 5 provide all the tertiary-level maternity/neonatal services for the state. The sixth hospital is geographically colocated with a maternity hospital and provides infectious diseases services and intensive care support for women who require high-level care. The number of registered births in Victoria for 2008 was 71,263. The estimated number of deliveries in 2008 from the 5 hospitals participating in this study combined is 24,377 (34%).

Cases were identified as women in any trimester of pregnancy admitted to the hospital with a history of an influenza-like illness (ILI) and a positive polymerase chain reaction result for swine lineage H1N1 on a respiratory tract specimen. All polymerase chain reaction tests were performed at a centralized reference laboratory.

A standard case record form was used at all sites. Medical histories were retrospectively reviewed or case record information was prospectively collected if the case was identified after ethics approval. Deidentified data were forwarded to a central site for analysis. Statistical analysis was performed with the Stata statistical package (release 9, 2005; StataCorp). Basic frequency and proportions were calculated. Comparison of proportions across groups was performed using Fisher’s exact test. A population at risk was derived, assuming that each trimester is 3 months; thus, the number of women in each trimester is the total number of births divided by 4. This assumes that the rate of pregnancy is constant over the year. Because of the likelihood of incomplete ascertainment, we did not calculate a rate for the first trimester. Confidence intervals for incidence rates were calculated assuming the Poisson distribution.

The study proposal was presented to each institution’s human research and ethics committee. Each independent research and ethics committee determined that the study proposal met the National Health and Medical Research Council requirements for quality assurance and audit projects or the proposal underwent expedited review and was approved.

RESULTS

Forty-three patients were identified during the study period. Of the 43 patients, 2 (5%) presented in the first trimester. The remainder presented during the second trimester (13 [30%] of 43) and third trimester (defined as ≥28 weeks; 28 [65%] of 43). Of these 28, 16 were at term (defined as ≥37 weeks). Fifty-eight percent of women were admitted to the hospital because of an ILI; in some cases more than 1 reason for admission may have applied (Table 1).

The cumulative incidence of hospitalization was estimated at 0.46% (95% confidence interval, 0.31%-0.66%) of all pregnant women in Victoria in the third trimester during the 3-month study period. The incidence of hospitalization in the second trimester was estimated at 0.21% (95% confidence interval, 0.11%-0.36%).

Comorbidity was present in 51% of cases. The most common comorbidity was asthma (9 [21%] of 42) followed by obesity (8 [19%] of 43) and diabetes mellitus (6 [14%] of 42). Of the 6 women with diabetes mellitus, 4 had been diagnosed as having gestational diabetes and 4 required insulin. Only 2 women were smokers.

Table 1. Symptoms at Presentation and Reason for Hospital Admission

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%) of patients (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom at presentation</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>43 (100)</td>
</tr>
<tr>
<td>Fever</td>
<td>38 (84)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>27 (63)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>26 (60)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23 (53)</td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td>21 (49)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>16 (37)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>10 (23)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (12)</td>
</tr>
<tr>
<td>Reason for admission</td>
<td></td>
</tr>
<tr>
<td>Uncomplicated ILI</td>
<td>25 (58)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>12 (28)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>8 (19)</td>
</tr>
<tr>
<td>Labor</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Obstetric complication</td>
<td>10 (23)</td>
</tr>
<tr>
<td>Fetal distress</td>
<td>2</td>
</tr>
<tr>
<td>Preeclampsia</td>
<td>1</td>
</tr>
<tr>
<td>FDIU</td>
<td>2</td>
</tr>
<tr>
<td>Hyperemesis</td>
<td>1</td>
</tr>
<tr>
<td>PPH</td>
<td>1</td>
</tr>
<tr>
<td>Preterm labor or TPL</td>
<td>3</td>
</tr>
</tbody>
</table>

NOTE. More than 1 reason for admission may apply. FDIU, fetal death in utero; PPH, postpartum hemorrhage; TPL, threatened preterm labor.
intensive care unit (ICU) care. Of 6 patients with diabetes, 1 developed pneumonia and 1 developed an obstetric complication. Of 8 obese patients, 1 developed pneumonia and none had an obstetric event, such as preterm labor or premature rupture of membranes, complicating their hospitalization for H1N1.

Three of the 9 patients with asthma required ICU care, compared with 5 of 30 nonasthmatic patients ($P = .36$, by Fisher’s exact test). Four of 9 asthmatic patients developed pneumonia compared with 7 of 30 nonasthmatic patients ($P = .23$). Only 1 of 9 patients with asthma had an obstetric complication.

Influenza vaccination status was unknown for 29 of the 43 patients. Only 1 patient was known to have received influenza vaccination during the current pregnancy, and vaccination was not received by 13 (31%). The frequencies of symptoms at presentation are listed in Table 1.

Sixteen women had a sputum culture performed. Nine of these cultures revealed growth, including upper respiratory tract flora ($n = 5$), oral flora ($n = 2$), Pseudomonas species ($n = 1$), and Streptococcus pneumoniae ($n = 1$). Blood cultures were performed in 21 (49%) of 43 patients, and all cultures were sterile. A chest x-ray examination was performed in 25 (59%) of 42 patients, and the findings indicated consolidation in 14 (56%) of 25 patients, with equal distribution between multifocal consolidation (7 [28%] of 25) and unifocal consolidation (7 [28%] of 25). The proportion of women with pneumonia in their first and second trimesters was 27% compared with 29% with pneumonia in their third trimester.

Antiviral treatment was prescribed for 33 (77%) of 43 patients and was oseltamivir in 29 patients and zanamivir in 4 patients. Of all women receiving antivirals, 12 commenced treatment within 2 days of symptom onset. In the remainder, treatment was commenced ≥3 days after symptom onset (range, 3–14 days). Antibiotics were prescribed for 24 (56%) of the 43 patients, most commonly ceftriaxone and azithromycin (9 of 24). Of the 14 women with consolidation apparent on chest radiograph films, 13 (92%) received antibiotics, most frequently ceftriaxone and a macrolide.

Eight women (19%) were admitted to the ICU. Three required intubation, 2 required extracorporeal membrane oxygenation, and 1 required noninvasive ventilation. Vasopressor support was required in 4 women (10%), and none required renal replacement therapy.

Outcome data were available for 42 of the 43 women because 1 woman was transferred to another hospital for further treatment. One patient died and the remainder were discharged home. The woman who died was admitted 7 days after the onset of symptoms in her second trimester. She was treated in the ICU with antivirals and antibiotics. Her risk factors for severe disease were cardiac disease and asthma. She died on day 9 of her hospitalization. The median length of stay (LOS) for the cohort was 2 days (range, <24 h to 30 days). Ten women (24%) were hospitalized for <24 h, and 8 women were hospitalized for >7 days.

In our case series, 15 (36%) of 42 women delivered during their hospitalization. Of these, 6 women (40%) delivered at <37 weeks and 9 women (60%) delivered at term (defined as after 37 weeks). By 31 July 2009, outcome data were known for 24 neonates. Twenty-one of these were alive, 2 died in utero (at 26 and 31 weeks), and 1 died after delivery. This neonate was delivered at 26 weeks’ gestation and died 26 days after delivery from complications related to prematurity. Seven neonates, including the neonate who died, were tested for H1N1 and all results were negative. No neonates were given antivirals.

**DISCUSSION**

To date, this is the largest case series of hospitalized pregnant women during the H1N1/09 pandemic. This study demonstrates a high number of complications in pregnant women due to pandemic H1N1/09 infection presenting to 6 Melbourne hospitals, including 8 patients admitted to the ICU, 1 maternal death, 2 fetal deaths, and 1 neonatal death. Although our case series only includes admissions to the hospital and is observational and not able to define relative risk in the community, these numbers are unprecedented in our clinical experience. For comparison, the 2 largest obstetric hospitals participating in this study recorded 35 admissions for influenza or pneumonia in 2009, with only 8 admissions for influenza or pneumonia during the same period in 2008.

In this study, the most common reason for admission was uncomplicated ILL. Of these 25 patients admitted for ILL, 24 had a LOS <7 days (median LOS, 2 days; interquartile range, same day discharge to 3 days). Of the 11 patients with pneumonia, 7 patients had a LOS of ≥7 days (median LOS, 9 days; interquartile range, 3–22 days; $P = .001$, by rank sum test). This finding demonstrates the spectrum of clinical disease in those requiring admission to the hospital for mild, uncomplicated short stays to lengthy stays predominantly to manage the respiratory complication of pneumonia. The obstetric complications leading to admission (Table 1) are not all thought to be attributable to maternal influenza infection. Preterm labor has been previously reported to occur in higher rates among pregnant women with influenza [7, 9], but preeclampsia, hyperemesis, and postpartum hemorrhage have not been reported to occur at a higher frequency. The background rate of preterm labor at the hospitals in this study is ~10%.

In our case series, 22 (51%) of 43 patients had at least 1 other comorbidity that has previously been reported as a risk factor for morbidity or mortality associated with influenza infection. These comorbidities include asthma, smoking, diabetes mellitus, or obesity. The prevalence of these risk factors was higher than that reported in the general Australian population: asthma, 23%
in our series and 10% in Australian population cross-sectional surveys; diabetes (including gestational diabetes), 15% in our series and 3% in the Australian population; and obesity, 22% in our series and 16% in the Australian population [13]. The women with additional risk factors did not appear to be overrepresented in those admitted to the ICU with confirmed pneumonia or development of an obstetric complication. The finding that almost one-half of our admitted women had a comorbidity is consistent with previous publications reporting medical comorbidities in pregnancy as a risk factor for hospital admission during the influenza season [6].

It is well recognized that influenza in pregnancy is associated with poor outcomes in both interpandemic influenza and previous pandemic seasons [14]. Neuzil et al. [5] reported an increase in the estimated relative risk of hospital admission for influenza-related serious morbidity according to length of pregnancy. In our study, 65% of admissions were in women in their third trimester. Forty-nine percent of our patients had no recognized comorbidity aside from pregnancy itself, but the mechanism by which pregnancy, particularly late pregnancy, increases disease severity is unknown. Possibilities include both the immunologic [15] and physiologic changes [16] that occur during pregnancy, including a shift from cell-mediated to antibody-mediated immune responses, respiratory compromise due to mechanical effects, and increased cardiorespiratory demands. One observation is an association between low total immunoglobulin subclass levels, particularly IgG2, in both pregnant and nonpregnant patients with H1N1/09 who developed respiratory failure [17].

In contrast to the maternal complications of influenza, the fetal complications of maternal influenza infection are less clearly defined. Whether this pandemic strain of H1N1 is associated with placental transmission and the implications, if any, that this may have on fetal outcome over and above the potential adverse effect of maternal hyperthermia on pregnancy are unclear. In our case series, 40% of women admitted had preterm labor. This high rate of preterm birth has been reported during previous influenza pandemics, especially in women with pneumonia [7, 9]. Of 6 women who delivered at <37 weeks, 5 underwent a chest x-ray examination and all demonstrated pneumonia. For comparison, the usual rate of preterm delivery at the hospitals involved in this study is ~10%. There were 2 cases of fetal death in utero. The first case occurred in a 28-year-old woman at 26 weeks’ gestation. She presented 14 days after her first reported symptom of influenza with pneumonia and respiratory failure. She had no coexisting morbidity and was admitted to the ICU for 3 days. She was treated with antivirals and antibiotics. The second case of fetal death in utero occurred in a 25-year-old woman at 31 weeks’ gestation who had symptoms 6 days before admission. She also had gestational diabetes and was admitted for 1 day. No chest radiograph examination was performed. She received antivirals but no antibiotics. A postmortem examination was not performed for either fetus.

Seventy-seven percent of women received antiviral treatment compared with 50% of pregnant women recently described with H1N1/09 influenza in the United States [3]. This may be partially attributable to a heightened awareness among local practitioners of the risks of pandemic influenza in this population, given its delayed introduction into Australia and that our series includes only hospitalized women. In our series, 64% of women prescribed antivirals had symptoms for ≥48 h. Similarly, the cohort from the United States reported that only 24% of patients began treatment within 48 h of symptom onset [3]. Antiviral treatment should be initiated as early as possible after the onset of symptoms for maximum benefit.

Oseltamivir product information states that it “should not be used during pregnancy unless the potential benefit to the mother justifies the potential risk to the fetus” [18]. However, although the safety and efficacy are not firmly established during pregnancy and there are no randomized controlled trials confirming the efficacy of antivirals during pregnancy, benefits are likely to outweigh the risks; hence, its use has been recommended by groups internationally, such as the Centers for Disease Control and Prevention [4] and the European Medicines Agency [19]. A recent review of 232 cases of maternal exposure to oseltamivir, including 12 cases with a fetal outcome of birth defect, concluded that there did not appear to be any evidence to suggest maternal exposure to oseltamivir was associated with adverse pregnancy or fetal outcomes [19].

The findings in this report confirm a high number of complications in pregnant women with H1N1/09. The observed delay in presentation and administration of antivirals highlights an area to direct future education and research. It would be important to ascertain whether the delay is attributable to patient recognition of symptoms and awareness of the potential preventable adverse outcomes, reluctance of medical practitioners to prescribe antivirals during pregnancy, or patient reluctance to accept these medications because of safety concerns. This information would in turn help inform the content and direction of future education campaigns and public health messages.

Only 1 woman in our case series had documentation of influenza vaccination during pregnancy. Although the seasonal influenza vaccine is unlikely to confer any benefit in the current H1N1/09 pandemic, it is a timely reminder of the current recommendations pertaining to influenza vaccination during pregnancy and the previously recognized poor uptake of immunization [20]. In Australia, national immunization guidelines recommend that influenza vaccination should be offered to women planning a pregnancy and to pregnant women who will be in the second or third trimester during the influenza sea-
son [21]. It is essential to understand the barriers to uptake of vaccination in this population because pregnant women are considered a priority group for the H1N1 vaccine [22]. Although commonly ascribed to maternal reluctance to have immunization or medication during pregnancy, some data suggest that a lack of awareness by treating medical practitioners is a major contributor, with good acceptance by mothers when the risks and benefits are explained [23, 24].

This case series of hospitalized pregnant women with laboratory-confirmed influenza A suggests that pregnant women are at high risk of complications, particularly those with a co-existing medical condition, such as asthma, obesity, or diabetes. This finding underscores the importance of education regarding recommendations for vaccination in pregnancy and the need for rapid testing and earlier use of antivirals in suspected influenza. Most admissions for uncomplicated ILI were of short duration, but those women who developed pneumonia were inpatients for longer. Of those who delivered prematurely, all who received a chest radiograph examination had radiologic evidence of pneumonia.

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References