Novel Influenza A(H1N1) Virus Among Gravid Admissions

Andrew C. Miller, MD; Farnaz Safi, MD; Sadia Hussain, BS; Ramanand A. Subramanian, PhD; Elamin M. Elamin, MD, MSc; Richard Sinert, DO

Background: Pandemic novel influenza A(H1N1) is a substantial threat and cause of morbidity and mortality in the pregnant population.

Methods: We conducted an observational analysis of 18 gravid patients with H1N1 in 2 academic medical centers. Cases were identified based on direct antigen testing (DAT) of nasopharyngeal swabs followed by real-time reverse-transcriptase polymerase chain reaction analysis (rRT-PCR) or viral culture. Patient demographics, symptoms, hospital course, laboratory and radiographic results, pregnancy outcome, and placental pathologic information were recorded. Results were then compared with published reports of the H1N1 outbreak and reports of flu pandemics of 1918 and 1957.

Results: Eighteen pregnant patients were admitted with H1N1 during the study period. All patients were treated with oseltamivir phosphate beginning on the day of admission. Mean (SD) age was 27 (6.6) years (age range, 18-40 years); median length of hospital stay was 4 days. Intensive care unit admission rate was 17% (n=3). Demographically, 2 patients were health care workers (11%); 15 were black (83%); 2, Hispanic (11%); and 1, white (6%). None reported recent travel. Half of the patients presented with gastrointestinal or abdominal complaints; 13 patients met sepsis criteria (72%). The most common comorbidities were asthma, sickle cell disease, and diabetes. Fourteen patients tested positive for H1N1 on DAT (initial or repeated) (78%); in the other 4 cases, H1N1 was identified by viral culture or rRT-PCR (22%). Seven patients delivered during hospitalization (39%), 6 prematurely and 4 via emergency cesarean delivery. There were 2 fetal deaths (11%). No maternal mortality was recorded.

Conclusions: Admitted pregnant patients with H1N1 are at risk for obstetrical complications including fetal distress, premature delivery, emergency cesarean delivery, and fetal death. A high number of patients presented with gastrointestinal and abdominal complaints. Early antiviral treatment may improve maternal outcomes.

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Author Affiliations: Departments of Internal Medicine (Dr Miller), Emergency Medicine (Drs Miller, Subramanian, and Sinert), and Obstetrics and Gynecology (Dr Safi), State University of New York Downstate Medical Center and Kings County Hospital Center, Brooklyn; State University of New York Downstate College of Medicine, Brooklyn (Ms Hussain); and Pulmonary, Critical Care, and Sleep Medicine Section, James A. Haley Veterans Hospital, Tampa, Florida (Dr Elamin).

NOVEL INFLUENZA A(H1N1) virus is a pandemic respiratory infection commanding much attention by the international medical community. Little data have been reported regarding the impact of H1N1 on pregnant patients or the gestational fetus, and published reports have been conflicting.[1] However, during prior seasonal influenza epidemics and pandemics, pregnant women have been reported to have increased hospitalization rates, increased morbidity and mortality, but no increase in congenital birth defects.[2-10] Moreover, recent reports suggest that gravid patients may be at increased risk for H1N1-related complications.[1,11,12] Because obstetrical patients make up a vulnerable population, it is crucial to characterize in them the severity and course of H1N1. Herein we describe a case series of 18 pregnant patients admitted for H1N1 infection during the second and third months of the initial outbreak. We compare these with other recently reported H1N1 cases from the first month of the outbreak and with cases from prior epidemics and pandemics.

See also pages 861 and 913

METHODS

Data were obtained from retrospective medical chart analysis of 18 patients admitted to 2 urban academic medical centers with a diagnosis of H1N1 from May 18 to June 24, 2009. The protocol was approved by the institutional review boards at the State University of New York Downstate Medical Center and Kings County Hospital Center. Patient identification remained anonymous, and informed consent was waived based on 2 factors: (1) the study was observational; (2) it was part of an emergency public health response.

According to the Centers for Disease Control and Prevention (CDC) definitions,[13] a con-

firmed case of H1N1 requires an acute respiratory illness and positive H1N1 findings by real-time reverse-transcriptase polymerase chain reaction analysis (rRT-PCR) or viral culture. A probable case is defined as a case of acute febrile respiratory illness with positive rRT-PCR findings for influenza A but negative rRT-PCR findings for H1 and H3. Probable H1N1 cases were included in the study because approximately 96% of nonsubtypeable specimens taken during this first wave of the pandemic were later confirmed to show H1N1 viral infection.[13]

Per New York City Department of Health and Mental Hygiene (NYCDOHMH) recommendations[14] and hospital policy, only patients presenting with an influenzalike illness (ILI) who were being admitted to the hospital or were critically ill were tested for influenza. Inclusion criteria were (1) age 18 years or older; (2) ILI requiring hospital admission; and (3) microbiologic confirmation of influenza A by direct antigen testing (DAT) (BD Directigen Flu A test kit; Becton, Dickinson and Company, Franklin Lakes, New Jersey) with confirmation of H1N1 by viral culture or rRT-PCR. Patients were excluded if they were younger than 18 years, if they refused to take the influenza test, or if they had an ILI that did not require admission or discharge from the emergency department (ED). (Per NYCDOHMH recommendations[14] and hospital policy, patients with ILIs that did not require admission or discharge from the emergency department were not tested for H1N1.)

All tests and procedures were ordered by attending physicians or by resident physicians under the supervision of an attending physician or chief resident. Admission requirements were determined by the ED attending physician. Special consults (eg, critical care, obstetrics) were obtained in the ED when appropriate. Intensive care unit (ICU) admission criteria and treatment decisions were not standardized and were determined by the ICU attending physician. Nasopharyngeal swab specimens were collected at admission, and respiratory secretions were obtained from intubated patients. Direct antigen testing and viral cultures were performed in house, whereas rRT-PCR was performed by the CDC or NYCDOHMH.[15] A confirmed case was defined as an acute respiratory illness and confirmation of H1N1 infection by rRT-PCR or viral culture. In both hospitals, infection control measures were strictly enforced, including respiratory isolation of infected patients, use of personal protective equipment for health care workers, and strict hand hygiene. All patients received oseltamivir phosphate, 75 mg, twice daily for 5 days beginning on the day of admission. No patients received amantadine or rimantadine. Patients also received supportive therapy with oxygen, intravenous hydration, and acetaminophen when appropriate. Corticosteroids and bronchodilators were administered as indicated on a case-by-case basis. Antibiotics were not routinely administered except when indicated for comorbid conditions. Comorbid conditions were treated as indicated.

The following patient demographic characteristics were recorded: age; length of hospital stay; known influenza contacts; and comorbidities such as pregnancy, asthma, diabetes, renal disease, sickle cell disease, or human immunodeficiency virus. Also recorded were each patient's presenting symptoms and triage vital signs including blood pressure, heart rate, oxygen saturation, and body temperature. Laboratory assessments included a complete blood cell count (CBC) with differential analysis, serum electrolyte panel, blood gas analysis, and blood cultures. Chest radiograms were interpreted for the presence of infiltrate or effusion. Also recorded were rates of ICU admission, delivery during hospitalization, emergency cesarean section, and premature delivery. Reported fetal outcomes included fetal distress, fetal death, cord blood gas (CBG) measurements, and placental pathologic findings, when available. Fetal distress was defined as repetitive decelerations on fetal heart monitoring, fetal bradycardia, fetal tachycardia consistent with chorioamnionitis remote from delivery, malpresentation in active labor, eclampsia, or other emergency condition necessitating emergency delivery.

Table 1. Patient Demographic Characteristics

Characteristic	Pregnant Patients[a] (n=18)
Age, median, y[b]	26
Length of hospital stay, median[c]	4
Health care provider	2 (11)
Asthma	5 (28)
Diabetes	1 (6)
Renal insufficiency	0
HIV positive	1 (6)
Sickle cell	2 (11)
Influenza antigen positive	14 (78)
Antigen negative but culture or PCR positive	4 (22)
Admitted to ICU	3 (17)
Patients delivered during hospitalization	7 (39)
Fetal distress during hospitalization, No. (all/delivered %)	5 (28/71)
Emergency cesarean delivery, No. (all/delivered %)	4 (22/57)
Premature delivery, No. (all/delivered %)	6 (33/86)
Fetal death	2 (11)
Maternal mortality	0

Abbreviations: HIV, human immunodeficiency virus; ICU, intensive care unit; IQR, interquartile range; PCR, polymerase chain reaction analysis.
[a] Unless otherwise indicated, data are reported as number (percentage) of subjects.
[b] Quartiles at 25%, 50%, and 75%, 21.75, 26.00, and 31.00, respectively.
[c] Quartiles at 25%, 50%, and 75%, 3.0, 4.0, and 6.5, respectively.

To objectively assess illness severity, commonly used illness severity markers were recorded for each patient, including shock index, systemic inflammatory response syndrome score, serum lactate measurement, anion gap analysis, and CURB-65 score (confusion, urea level, respiratory rate, blood pressure, and age ≥65 years).[16-20] The anion gap was calculated according to the equation $Na^+ - (Cl^- + CO_2^-)$. The CURB-65 score was calculated according to the criteria published by Lim et al.[19] A recent study[20] has reported a significant correlation between the CURB-65 score and the need for hospital admission, requirements for mechanical ventilation, and risk of 30-day mortality.

Statistical calculations were performed using SPSS for Windows, version 15.0 (SPSS Inc, Chicago, Illinois). Medians and interquartile ranges (IQRs) were reported for nonnormally distributed continuous variables. Means and standard deviations (SDs) were reported for normally distributed continuous variables. Counts and percentages were reported for nominal data.

RESULTS

Patient demographic characteristics are summarized in **Table 1**. The mean (SD) age was 27 (6.6) years (range 18-40 years); median length of hospital stay, 4 days; and ICU admission rate, 17% (n=3) (Table 1). Two patients were health care workers (1 nursing student and 1 home health aid); 15 were black (83%); 2, Hispanic (11%); and 1, white (6%). None reported recent travel. The most common comorbidities were asthma, sickle cell disease, and diabetes. Fourteen patients tested positive for H1N1 on DAT (initial or repeated) (78%); in the other 4 cases, H1N1 was identified by viral culture or rRT-PCR (22%).

Table 2. Clinical Features of Pregnant Patients With Novel Influenza A(H1N1) Virus at Initial Presentation

Characteristic	Pregnant Patients, No. (%) (n=18)
Symptom	
Cough	12 (67)
Sputum production	3 (17)
Documented fever	10 (56)
Shortness of breath	10 (56)
Wheeze	3 (17)
Chest pain	1 (6)
Sore throat	1 (6)
Myalgia	10 (56)
Nausea	4 (22)
Vomiting	2 (11)
Abdominal pain	4 (22)
Diarrhea	2 (11)
Headache	1 (6)
Imaging findings (n=15)	
Chest radiogram normal	13 (87)
Infiltrate on chest radiogram	2 (13)
Effusion on chest radiogram	0

Seven patients delivered during hospitalization (39%), 6 prematurely and 4 via emergency cesarean delivery. One patient who underwent emergency cesarean delivery for fetal distress was admitted to the ICU. There were 2 fetal deaths (11%). No maternal mortality was recorded.

A wide range of symptoms was reported by patients on initial presentation (**Table 2**). Twelve patients reported cough (67%); 10 each, shortness of breath (56%), fever (56%), and myalgia (56%); and 3 each, wheezing (17%) and cough productive of sputum (17%) (Table 2). Nine patients presented with primarily gastrointestinal complaints (50%), including abdominal pain (22%, n=4), nausea (22%, n=4), vomiting (11%, n=2), and diarrhea (11%, n=2). One patient each reported chest pain (6%), sore throat (6%), and headache (6%).

Thirteen patients met sepsis criteria (72%) (systemic inflammatory response syndrome score ≥2 in presence of documented infection). The shock index was substantially elevated in these patients (median, 1.06 [normal range, 0.5-0.7]), reflecting left ventricular dysfunction, but anion gap and CURB-65 scores were not.

Hematologic and serum analysis data are summarized in **Table 3** as median (IQR) values. Average and median leukocyte counts were not substantially elevated, but elevated serum neutrophil percentages were noted. Findings of serum chemical analyses were normal, and no substantial elevation of creatinine levels was found. No patients had true-positive findings on blood culture. One patient who experienced spontaneous abortion had a single finding on culture of contaminated blood (*Corynebacterium*), but findings were negative on repeated testing. This patient received no antibiotics other than the antiviral agent oseltamivir.

Admission chest radiograms were interpreted for the presence of infiltrate or effusion. Fifteen of the 18 cases included admission chest radiography (Table 2). Of those, 13 were normal (87%); 2 showed an infiltrate (13%); and none had an identifiable pleural effusion.

Table 3. Laboratory Test Findings

Laboratory Test	Value, median	Quartiles, %		
		25	50	75
Hemoglobin, g/dL	10.9	10.1	10.9	11.8
WBC count, $\times10^3$/μL	7.9	6.2	7.9	10.3
Neutrophils, $\times10^3$/μL	6.9	5.0	6.9	8.4
Neutrophils, %	78.2	73.8	78.2	84.7
Lymphocytes, $\times10^3$/μL	0.9	0.4	0.9	1.1
Lymphocytes, %	8.3	3.8	8.3	15.1
Platelets, $\times10^3$/μL	257	228	257	275
Sodium, mEq/L	134	133	134	137
Urea, mg/dL	16.81	14.01	16.81	19.61
Creatinine, mg/dL	0.50	0.4	0.5	0.6
Cord blood pH, median (n=6)	7.30	7.27	7.30	7.35
Cord blood Pao_2, median, mm Hg (n=6)	20.1	15.9	20.1	30.3
Cord blood HCO_3, median, mEq/L (n=4)	21	19.4	21.0	22.1
Cord blood base excess, median, mmol/L (n=6)	–1.65	–6.5	–1.7	–1.0
Positive blood cultures, No. (%) (n=7)	1 (14)[a]	NA	NA	NA

Abbreviations: HCO_3, bicarbonate; NA, not applicable; Pao_2, partial pressure of oxygen in arterial blood; WBC, white blood cell.

SI conversion factors: To convert hemoglobin to grams per liter, multiply by 10; WBCs, neutrophils, and lymphocytes to number of cells $\times10^9$/L, multiply by 0.001; sodium to millimoles per liter, multiply by 1; urea to millimoles per liter, multiply by 0.357; creatinine to micromoles per liter, multiply by 88.4.

[a] One patient's culture grew a single-bottle contaminant (*Corynebacterium*), but a repeated culture from that patient was negative.

Overall, 7 patients delivered during their inpatient course (39%), 6 prematurely (86%) (gestational age, <37 wk). Of the 6 cases of premature delivery, 5 involved fetal distress (83%); 4, emergency cesarean delivery (67%). No congenital birth defects were identified. The overall spontaneous abortion and fetal death rate was 11% (n=2). Both fetal deaths resulting from spontaneous abortion occurred at gestational age younger than 23 weeks (**Table 4**), including 1 case of ICU admission that involved a first trimester miscarriage. There was no observed maternal mortality. Three patients required ICU admission (17%).

Patients who delivered had CBG measurements recorded to assess for signs of fetal hypoxia (Table 3). Results of cord blood analysis were as follows: median pH, 7.3; partial pressure of oxygen in arterial blood, 20.1 mm Hg; bicarbonate level, 21 mmol/L; and base excess, –1.65 mmol/L, all within the normal range.[21] The IQRs for these measurements are listed in Table 3.

COMMENT

Pregnancy has historically been a risk factor for increased hospital admission rates, morbidity, and mortality for pandemic and seasonal influenza outbreaks.[2,3] The increased risk is believed to be related to the multitude of physiologic changes known to occur during pregnancy, including increased heart rate, stroke volume, oxygen consumption, and respiratory rate as well as decreased

Table 4. Report of Pregnant H1N1 Patients

Patient No./ Age, y	GA, wk, d[a]	Comorbid Conditions	DAT	Inpatient Delivery	Patient Hospital Course and Pregnancy Outcome
1/25	4, 0	Asthma	Positive	Yes	Admitted to medical ICU; met sepsis criteria, hospitalized 3 d; no known exposure; had inpatient miscarriage
2/23	39, 4	SSD	Negative	Yes	Had 4 children with ILI at home; met sepsis criteria; had infiltrate on chest radiogram; premature emergency cesarean delivery on day 1 for fetal distress; transferred to ICU immediately after delivery; hospitalized 15 d; rRT-PCR positive; fetal DAT negative; mother isolated from infant; infant remained in good health; placental pathology studies normal; CBG, 7.29/15.7/54/22.4/–0.4[b]
3/40	36, 2	None	Negative	Yes	Nursing student; met sepsis criteria; hospitalized 10 d; premature emergency cesarean delivery for fetal distress; viral culture positive; bowel injury during surgery; infant DAT negative; infant remained in good health; placental pathology studies normal; CBG, 7.36/58/33.6/18.9/–6[b]
4/23	36, 2	None	Positive	No	Had 5-year-old child with ILI; met sepsis criteria; hospitalized 4 d; no fetal distress
5/37	30, 4	SSD, prior stroke, GDM	Positive	No	No known exposure; met sepsis criteria; hospitalized 4 d; no fetal distress
6/22	31, 0	Asthma	Negative	No	Employed as home health attendant; met sepsis criteria; viral culture positive; hospitalized 4 d; no fetal distress
7/21	25, 2	Asthma	Positive	No	No known exposure; met sepsis criteria; hospitalized 6 d; no fetal distress
8/23	24, 2	None	Positive	No	No known exposure; met sepsis criteria; hospitalized 8 d; no fetal distress
9/31	19, 5	HIV, Asthma	Positive	No	No known exposure; did not meet sepsis criteria; hospitalized 3 d
10/30	5, 0	None	Positive	No	No known exposure; met sepsis criteria; hospitalized 3 d; no in-hospital complication
11/31	15, 3	None	Negative	No	No known exposure; met sepsis criteria; hospitalized 4 d; no fetal distress
12/38	22, 4	None	Positive	Yes	No known exposure; met sepsis criteria; hospitalized for 6 d; emergency premature cesarean delivery for fetal distress; baby died on day 2 from sepsis caused by coagulase-negative *Staphylococcus* species and *Enterobacter* species; CBG, 7.35/21/45/21/–1.2[b]; placental pathology studies showed focal hypoplastic tertiary villi, fetal vasculopathy, focal necrosis, cell atypia, Hofbauer cell hyperplasia and necrosis, calcified villi
13/29	41, 0	None	Positive	Yes	No known exposure; did not meet sepsis criteria; had cesarean delivery for arrest of dilation; delivered healthy baby; placental pathology studies normal; CBG, 7.28/19.1/53/20.9/–1.6[b]
14/27	6, 0	Asthma	Positive	No	2-year-old at home with ILI; hospitalized for 1 d; met sepsis criteria; no in-hospital complication
15/19	First trimester[c]	None	Positive	No	20-month-old at home with ILI; did not meet sepsis criteria; hospitalized 13 d
16/18	35, 6	Asthma	Positive	Yes	Admitted to the pediatric ICU; did not meet sepsis criteria; had infiltrate on chest radiogram; underwent emergency cesarean delivery for fetal distress; delivered healthy baby without signs of infection; CBG[b]: 7.23/21/47/X/–7.9[b]; uncomplicated postoperative course
17/28	First trimester[c]	None	Positive	No	No known exposure; hospitalized 5 d; met sepsis criteria; no in-hospital complication; CBG, 7.3/16/53/X/–1.7[b]
18/21	36, 3	None	Positive	Yes	White; no known exposure; did not meet sepsis criteria; hospitalized 3 d; developed premature labor and delivered healthy baby via vaginal delivery; no fetal distress; placental pathology studies showed hypoplasia, diffuse chorangiosis consistent with hypoxia, and retroplacental hematoma reflective of disturbance in the maternal placental blood flow during her stressed state

Abbreviations: CBG, cord blood gas; DAT, direct antigen test; GA, gestational age; GDM, gestational diabetes mellitus; HCO_3, bicarbonate; HIV, human immunodeficiency virus; ICU, intensive care unit; ILI, influenzalike illness; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood; rRT-PCR, real-time reverse-transcriptase polymerase chain reaction; SSD, sickle cell disease; X, missing data point.

[a] At initial presentation.

[b] Expressed as pH/Pao_2, mm Hg/$Paco_2$, mm Hg/HCO_3, mmol/L/base excess, mmol/L.

[c] Known to be in first trimester, but exact GA unclear.

lung capacity, tidal volume, and functional residual capacity.[22] In addition, healthy gravid subjects experience decreased oncotic pressure in their third trimester compared with that of healthy nongravid subjects. This decreased oncotic pressure predisposes gravid women to develop pulmonary edema and increases their propensity for developing severe respiratory complications,[11] all of which work in concert to limit the patient's tolerance to hypoxic stress.

Moreover, during pregnancy there is a shift away from cell-mediated immunity toward humoral immunity, which may render pregnant women more susceptible to, or affected by, viral pathogens.[22] This may in part explain why morbidity from both seasonal and past influenza epidemics has been higher among pregnant women than among nonpregnant and postpartum women.[2,3,23-25]

Historically, gravid patients during the influenza pandemics of 1918 and 1957 had high mortality rates. During the 1918 pandemic, reported maternal mortality rates ranged from 27% (of 1350 patients)[24] to 45% (of 86 patients).[26] In addition, 20% of pregnancy-related deaths in Minnesota during the 1957 pandemic were attributed to influenza, but it is unclear what percentage of influenza-infected gravid patients died during this period.[25] Elevated

maternal mortality rates, however, have not been observed during every flu season. During epidemic influenza outbreaks from 1957 to 1966, no excess maternal mortality was observed in the United States.[27]

As pertains to the H1N1 pandemic of 2009, Jamieson et al[1] report a series of 34 suspected or confirmed H1N1 cases from 13 states during the first month of the outbreak, which differs substantially from the present study in that our series is from a small, densely populated geographic area. Furthermore, 44% of the patients in the report by Jamieson et al[1] were Hispanic, and 6% black compared with 11% Hispanic and 83% black in our series. Moreover, Jamieson et al describe a greater number of first- and second-trimester patients than we do. The preponderance of third-trimester patients in our series is more consistent with prior seasonal influenza studies.[2,3]

It is unclear whether the maternal mortality rate was substantially lower in our patient sample than in other series.[1,11,12] Of the 45 deaths from H1N1 reported to the CDC from April 15 to June 16, 2009, 6 were gravid patients (13%), but it is unclear what percentage of gravid H1N1 patients died. The number includes 1 patient from the Jamieson et al[1] cohort of 34 patients with probable H1N1. No maternal mortalities were observed in the present series of 18 patients. Potential mortality rate differences may in part relate to the differences in patient demographics and treatment received. Of 6 decedent gravid patients, only 2 were admitted the same day that they initially presented for care.[1] Three presented 3 to 4 days prior to admission, and 1 presented as an outpatient on 3 consecutive days before hospital admission. Moreover, substantial antiviral treatment delays existed in these prior series that did not exist in our study.

Among gravid decedents in other studies,[1,11,12] the time from symptom onset to receipt of antiviral medication ranged from 6 to 15 days (median time, 9 days), and the time from initial presentation to receipt of antiviral medication ranged from 2 to 14 days (median time, 4.5 days). Specifically, no decedent received antiviral medications within 48 hours of presentation. This differs substantially from our series, in which treatment with antiviral medications was initiated the day of presentation, often before the results of viral testing were available.

In another series of 3 gravid patients with H1N1 (2 third-trimester patients and 1 second-trimester patient),[12] 1 mother and no infants died. In the case of the single decedent, oseltamivir treatment was not initiated until day 14, 7 days after the patient had already developed acute respiratory distress syndrome and was intubated. The baby was delivered via emergency cesarean delivery on day 5. The Apgar scores were 4 and 6 at 1 and 5 minutes, respectively. The infant was healthy and was discharged home. The delay in antiviral treatment in prior series may have contributed to the increased maternal mortality. It is unclear what role age, ethnicity, gestational age, or other variables might have played in maternal-fetal outcomes.

This notion of potential harm related to delayed antiviral medication administration is further supported by the small series of 7 gravid patients with H1N1 reported by Saleeby et al,[11] which describes 3 deliveries, 1 maternal death, and no fetal deaths. However, in this series, as in that reported by Jamieson et al,[1] the patient population differed significantly from ours. A greater proportion of patients were admitted to the ICU (4 of 7) or intubated (2 of 7) than in our series (3 of 18 and 0 of 18, respectively). Saleeby et al[11] do not specify from how many hospitals, institutions, or states their population was drawn. Also, the ethnic distribution and travel histories are not reported. In addition, although each patient was treated with oseltamivir, the time between presentation and treatment initiation is not specified in 5 of the 7 cases. Moreover, their dosing regimens were not standardized. Five patients received twice-daily doses of oseltamivir phosphate at 150 mg, while 2 received 75-mg doses. Two patients were concurrently treated with amantadine, and 5 of the 7 were treated with additional antibiotics (3 of the 7 were treated with ≥2 additional antibiotics).

Similar to the case of the decedent described by Jamieson et al,[1] antiviral treatment initiation was delayed in the case of the decedent described by Saleeby et al.[11] The patient presented with 2 days of symptoms and negative findings on DAT. She was administered acetaminophen and discharged with expectant management. She returned the following day with worsening symptoms and developed progressive respiratory failure necessitating mechanical ventilation. Her prolonged hospital course was complicated by renal failure and deep venous thrombosis. She died on hospital day 19 from a pulmonary embolus. It is unclear if early antiviral treatment would have altered her disease course.

A substantial number of patients who delivered during their H1N1-associated admission delivered prematurely (6 of 7 [86%]), with most requiring emergency cesarean delivery for fetal distress, possibly due to disruption of uterine placental flow as a result of maternal respiratory distress. However, as evidenced by CBG measurements, the fetal distress was acute, likely due to expedited delivery. Fetal acidosis as measured on CBG generally stems from prolonged or severe hypoxia. Thus, timely delivery may result in CBG measurements that are not profoundly abnormal. Of note, 1 placenta had a retroplacental hematoma (ie, abruption), which might reflect disturbance in the maternal placental blood flow during her stressed state. This is important because, although her CBG findings were not acidotic, a disturbance in placental flow existed. Failure to deliver a fetus in such circumstances potentially risks adverse outcomes, including intrauterine fetal death.

Little data are available regarding fetal outcomes and mortality rates among H1N1-infected mothers. Of the 18 patients in this series, 1 had a spontaneous abortion, and 1 died postnatally from complications of extreme prematurity and sepsis. It is unclear whether this rate is higher than that of other published series.[1,11] Of 4 gravid patients with H1N1 described by Jamieson et al,[1] 2 gave birth during admission, and both of these were febrile during delivery. One delivered healthy twins, and the other had a spontaneous abortion. Jamieson et al[1] also discuss fetal outcomes in the cases of 6 gravid H1N1 mortalities over a different time frame, only 1 of which was included in their data set of 34 patients. They did not count the spontaneous abortion as a deceased fetus. Of the 6 gravid H1N1 mortalities, 1 fetus died concurrently with

the mother, and 5 were live births by cesarean delivery. The authors do not specify which fetal outcome corresponded to the 1 gravid H1N1 mortality from their original data set of 34 patients.

By comparison, the report by Saleeby et al[11] includes data for 3 fetuses born to 7 gravid patients with H1N1. Whether any of these infants survived to discharge is not reported. For example, in 1 case of emergency delivery performed owing to terminal bradycardia, the infant had poor Apgar scores, very low birth weight (1500 g), and an acidotic CBG finding. The mother died from pulmonary embolism, but the fetal outcome was not reported.

Of note from our series was the absence of vertical transmission. No surviving neonates tested positive for influenza antigen. The reason behind the absence of neonatal transmission remains unclear.

The present study is limited by its small sample size. In addition, not all patients with influenzalike symptoms were tested. Only those patients being admitted to the hospital or with severe illness were tested. Furthermore, influenza DATs have low sensitivity. Since confirmatory viral cultures or rRT-PCRs were not performed on all negative samples, there were undoubtedly influenza A–positive patients who were not identified by the screening process and thus not included in the case series. Moreover, there were a number of patients whose initial DAT findings were negative, but whose retested results were positive on the second or third analysis. Finally, because we have not routinely tested admitted patients for influenza prior to this epidemic, no case-control series exists for comparison of H1N1 to seasonal influenza within our institution.

In conclusion, H1N1 poses a serious health threat to pregnant patients. In addition to respiratory complaints, many pregnant patients with H1N1 presented with gastrointestinal complaints. Direct antigen testing is not sufficiently sensitive to diagnose influenza in pregnant patients presenting with an ILI. If a high index of suspicion exists, patients should be empirically treated with antiviral agents. Confirmatory testing with viral culture or rRT-PCR may be undertaken. Fetal distress necessitating emergency delivery or caesarean delivery may result in significant morbidity. The absence of maternal mortality in the present series (vs its presence in prior studies) may be related to early antiviral treatment.

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Correspondence: Andrew C. Miller, MD, 450 Clarkson Ave, Box 1228, Brooklyn, NY 11203 (taqwa1@gmail.com).
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