H1N1 Influenza in Pregnancy

Cause for Concern

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CASE 1

A 39-year-old multigravida at 32 weeks of gestation presented to Labor and Delivery triage with a chief complaint of headache for 2 days. Her temperature was 38.6°C, blood pressure 114/61 mm Hg, heart rate 121 beats per minute (bpm), and respiratory rate 22 per minute. Her oxygen saturation was 96% on room air. She reported a sore throat the day prior and, on presentation, a mild cough and fatigue. Past medical history was remarkable for obesity and current tobacco use. On auscultation her chest was clear, and fetal monitoring was reassuring. Laboratory studies were notable for a white blood cell count of 5.8×10^3/microliters, and rapid antigen tests for influenza A and B were negative. Her fever resolved with acetaminophen, so she was discharged to home. Given her negative rapid influenza testing and mild symptoms, her presentation was felt to be consistent with a viral upper respiratory infection. Recommendations at that time regarding treatment of symptomatic patients with negative test results were vague, and she was managed expectantly.

Less than 24 hours later, she presented to triage again with severe worsening of her symptoms, complaining of increased work of breathing and generalized malaise. On initial examination she was febrile to 38.5°C, tachycardic (126 bpm), hypotensive (93/46 mm Hg), and tachypneic (40 per minute), and her oxygen saturation was 74% on room air (Table 1 for additional findings on admission). Initial fetal monitoring was reassuring. She was transferred to the intensive care unit (ICU) where she was intubated within 40 minutes of arriving at the hospital. She required a norepinephrine drip for blood pressure support after intubation. Empiric therapy of ceftriaxone, azithromycin, and oseltamivir (Tamiflu; Roche Pharmaceuticals, Nutley, NJ) was also initiated. Although external fetal monitoring in the ICU was initially reassuring, 15 minutes after intubation a terminal bradycardia to the 80s (bpm) was noted on the fetal heart rate tracing, which was confirmed by ultrasonography. Given this nonreassuring fetal status, she was delivered by emergency cesarean in the ICU. She delivered a female neonate with Apgar scores of 2, 3, and 5 (at 1, 5, and 10 minutes of life, respectively) and a weight of 1,500 g.

After delivery, the patient remained acutely ill and was treated with prostacyclin and prone bed positioning for alveolar recruitment. Oxygenation was extremely challenging, with ventilator settings reaching values of 100% FIO_2 and positive end expiratory pressure of 37. Her course was complicated by acute renal failure and massive fluid retention requiring a bumetanide drip. On hospital day 13, she developed femoral deep vein thromboses, despite enoxaparin prophylaxis, and a transthoracic echocardiogram revealed right ventricular enlargement, with elevated pulmonary artery pressures consistent with pulmonary embolism. She was too unstable for evaluation with computed tomography, so she was treated empirically with intravenous unfractionated heparin as anticoagulant. She continued to demonstrate profound hypoxia, with arterial oxygen tension ranging from 30–56 mm Hg, despite clot lysis with tissue-type plasminogen activator. On hospital day 19, she be-

Table 1. Presentation

| Case | Age (y) | Estimated Gestational Age (wk) | Vital Signs | | | | | Arterial Blood Gas (pH/P_{CO_2}/pO_2/HCO_3/BE) | Chest Radiography |
			Temp (°C)	BP (mmHg)	HR (bpm)	RR	% Sa_{O_2} on Room Air		
1	39	32 1/7	38.5	93/46	126	40	74	7.50/21/52/20.9/−4.2	Bilateral diffuse patchy opacities with consolidation of bilateral lower lung fields
2	32	34 6/7	37.0	105/61	119	26	96	7.45/29/79/20/9/−2.4	Bibasilar opacities, right greater than left
3	34	29 1/7	39.1	120/75	123	30	93	7.48/30/63/22/−1	Mild hazy opacity at left costophrenic angle
4	31	23 1/7	39.5	125/75	116	32	90	7.49/26/59/20/−33	Patchy bibasilar and right middle lobe opacities
5	21	26 3/7	38.6	132/76	123	30	94	7.48/28/60/20/−3	Patchy bibasilar air space opacities
6	28	18 6/7	38.2	106/60	127	16	100	7.46/29/73/20/−1	Bilateral patchy opacities, consolidation of right lung base
7	18	38 4/7	37.6	139/90	120	20	99	None	None

BP, blood pressure; HR, heart rate, RR, respiratory rate; % Sa_{O_2}, arterial oxygen saturation measured with peripheral pulse oximeter; BE, base excess.

came acutely unstable and died. Given her prolonged hypoxia, no resuscitation was attempted at both the request of her family and recommendation of her physicians.

CASE 2

A 32-year-old multigravida at 34 weeks and 6 days of gestational age presented to the Emergency Department with subjective fever, productive cough, and generalized malaise and was sent to obstetrics triage for evaluation. She was afebrile, had normal oxygen saturation and normal arterial blood gas (ABG) values. A direct fluorescence antibody for influenza was sent, and she was discharged with a presumptive diagnosis of influenza before results were made available and was prescribed oseltamivir. When contacted by phone for follow-up by the obstetrics team, she reported that she had also been called by an emergency department physician and told not to take the oseltamivir because greater than 48 hours had elapsed since the onset of her symptoms. The obstetrics team reiterated the importance of starting the treatment immediately, especially in light of the positive test result and continued symptoms, but the patient failed to comply.

Three days later, she presented to Labor and Delivery complaining of fever, productive cough, and pain with inspiration. Evaluation at that time included a temperature of 37.0°C, pulse of 119 bpm, respiratory rate of 26, and oxygen saturation of 96% on room air. Arterial blood gas sampling revealed a Pa_{O_2} of 79

mm Hg. Her white count was 26×10^3/microliter, and her chest X-ray revealed bibasilar opacities. She was started on oseltamivir, initially standard dosing, then increased to double-strength dosing on day 2, and antibiotic treatment for superimposed pneumonia with ceftriaxone, azithromycin, and vancomycin. She clinically improved with this regimen, requiring only oxygen supplementation using nasal cannula. She was discharged to home on hospital day 4.
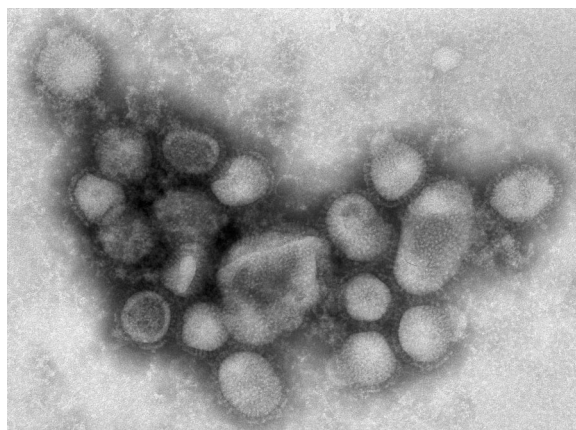

Fig. 1. This negative-stained transmission electron micrograph depicted some of the ultrastructural morphology of the A/CA/4/09 swine flu virus taken in the CDC Influenza Laboratory. Centers for Disease Control and Prevention. Images of the H1N1 influenza virus. Available at: http://www.cdc.gov/h1n1flu/images.htm. Retrieved August 3, 2009. Photo courtesy of CDC/C. S. Goldsmith and A. Balish.

Saleeby. H1N1 Influenza in Pregnancy. Obstet Gynecol 2009.

Table 2. Delivery Data*

Case	EGA	Method of Delivery	Indication	Sex	Apgar Scores[†]	Birth Weight	Cord UA/Cord UV (pH/Pco$_2$/pO2/BE)
1	32 1/7	Cesarean	Terminal bradycardia 80 bpm	Female	2, 3, 5	1,500 g	7.21/58/26/−5.3 7.28/45/49/−5.6
3	31	Cesarean	PPROM, preterm labor, severe repetitive decelerations	Female	8, 9	1,300 g	7.34/60/31/6 7.38/54/31/6
7	38 4/7	Cesarean	Arrest of descent	Male	7, 8	3,575 g	7.18/70/25/−2 7.31/46/22/−3

EGA, estimated gestational age at delivery; UA, umbilical artery; UV, umbilical vein; BE, base excess; bpm, beats per minute; PPROM, preterm premature rupture of membranes.
* For patients delivered during the index admission.
[†] Apgar scores at 1 minute, 5 minutes, and 10 minutes (if applicable).

QUESTIONS FOR THE SPECIALIST

What is the spectrum of H1N1 disease being observed in the general population? Is this different in pregnant women?

The H1N1 (Fig. 1) influenza pandemic is having far-reaching effects, with a wide range of disease presentations. Influenza-like illness is defined as fever and cough or sore throat. Other common symptoms include rhinorrhea, headache, shortness of breath, and myalgia, with some patients also reporting vomiting and diarrhea.[1] Most cases reported by the Centers for Disease Control and Prevention (CDC) are described as mild, with only 11% of patients requiring hospitalization between April 15 and July 24 of this

year.[2] Our institution has initiated evaluation and treatment algorithms for both over-the-phone and clinic settings for this large group of women (Box 1). Although many patients will fall into this category, especially if presumptively treated, moderately ill patients with influenza may rapidly worsen.[3]

Influenza A infections in pregnancy have been associated with adverse maternal and neonatal outcomes, including preterm labor, preterm birth, pneumonia, adult respiratory distress syndrome, and most seriously, overwhelming maternal illness and death. The rate of hospital admission for H1N1 in pregnant women is much higher than for nonpregnant women.[1] We have detailed above two different presentations

Table 3. Management

Case	Testing (DFA or Rapid/PCR)	Clinical Course	Treatment*	Complications
1	Neg/Pos	ICU monitoring, intubated on admission, ARDSnet[†]	Oseltamivir 150 mg bid × 10 d, ceftriaxone/ azithromycin, cefepime/vancomycin, norepinephrine, prostacyclin, rotaprone positioning, heparin drip, tissue-type plasminogen activator	Acute renal failure, pulmonary embolus, death
2	Pos/NA[†]	Supplemental o$_2$ by nasal cannula	Oseltamivir 150 mg bid × 5 d, ceftriaxone, azithromycin, vancomycin, clindamycin	Superimposed bacterial pneumonia
3	Neg/Pos	ICU monitoring, intubated HD #2; modified ARDSnet[†]; extubated HD #13	Oseltamivir 150 mg bid × 10 d, amantadine, cefepime and vancomycin	Acute renal failure
4	Neg/Pos	ICU monitoring, Supplemental O$_2$ by nonrebreather face mask	Oseltamivir 150 mg bid × 10 d	None
5	Pos/NA[‡]	ICU monitoring, Supplemental O$_2$ by nonrebreather face mask	Oseltamivir 150 mg bid × 10 d, amantadine and azithromycin	None
6	Pos/NA[‡]	Stepdown unit, supplemental O$_2$ by nonrebreather face mask	Oseltamivir 75 mg bid × 5 d	Superimposed bacterial pneumonia
7	Pos/NA[‡]	Supplemental O$_2$ by nasal cannula	Oseltamivir 75 mg bid × 5 d, ceftriaxone and azithromycin	None

DFA, direct fluorescence antibody; PCR, polymerase chain reaction; Neg, negative; Pos, positive; ICU, intensive care unit; bid, twice daily; HD, hospital day; NA, not applicable.
* Oseltamivir route was per oral. All other drug therapy given intravenously.
[†] ARDSNet refers to specific ventilation protocols determined by the Acute Respiratory Distress Syndrome Network. In general, these settings are used in patients with ARDS (PaO$_2$/FiO$_2$ less than 300), and the protocol recommends PaO$_2$ goal of 55–80 mm Hg and a minimum positive end expiratory pressure of 5 mm Hg. Protocol modified in pregnancy to achieve goal PaO$_2$ of greater than 70 mm Hg.
[‡] San Francisco Department of Public Health stopped typing direct fluorescence antibody-positive specimens with polymerase chain reaction because 99% were H1N1 in July 2009.

but also have described five additional cases, not previously described in the literature, of confirmed H1N1 in pregnancy at our institutions, University of California, San Francisco, and San Francisco General Hospital, all seen between June 15 and July 30, 2009 (Tables 1, 2, and 3). Reviewing these cases underscores the variable presentations and wide range of acuity that can be seen with this illness. Estimated gestational age at presentation ranged from 18 6/7 weeks to 38 4/7 weeks on admission. Patients were noted to follow either a rapidly progressive disease course and become critically ill within 24–48 hours of admission, or to exhibit a milder disease process with a stable course. This report adds to a growing body of data that supports the notion that pregnant women may be both more susceptible to and exhibit more severe symptoms with H1N1 influenza than is seen in nonpregnant patients.[1,4]

How should pregnant women presenting with viral symptoms be evaluated?

Evaluation with serial monitoring of vital signs, including pulse oximetry, and physical examination is

imperative for any pregnant woman presenting with viral symptoms consistent with influenza. Clinical assessment should guide judgment regarding the use of chest radiography and ABG measurement. A low threshold for obtaining these tests is reasonable, however, given quite abnormal ABG findings in our cases of women with normal oxygen saturations on room air. We err in favor of obtaining chest radiography and ABG in patients with findings on chest auscultation or with sustained pulse oximetry of less than 96% on room air (Box 1). Any patient with an abnormal ABG finding should be admitted to the hospital.

Given the highly infectious nature of H1N1, we recommend trying to evaluate symptomatic patients isolated from other pregnant patients. Safe telephone triage is highly dependent on the patient population, their access to health care, and their ability to reliably follow up. Telephone triage should be used quite cautiously with a low-threshold for in-person evaluation, preferably in a general medicine clinic or urgent care or emergency department with obstetrics consult. Any patient with obstetric complaints should be evaluated on Labor and Delivery; a mask should be worn by the patient and immediate respiratory droplet precautions should be taken.

What are the diagnostic dilemmas?

One factor complicating rapid diagnosis and treatment of the patient in Case 1 was the negative initial rapid influenza antigen testing. Unfortunately, although rapid antigen and DFA results are often available within 1–2 hours, the sensitivity of rapid antigen testing has been reported as low as 30%, with specificity as low as 58% in some studies.[5–7] The direct fluorescence antibody test, however, can have a sensitivity equivalent to viral culture (98%) when an adequate sample is collected.

The rapid influenza antigen test, direct fluorescence antibody assay, and viral culture are dependent on the quantity of respiratory epithelial cells in the sample. In contrast, polymerase chain reaction (PCR) testing for Influenza A RNA is as sensitive as viral culture and is less dependent on the quantity of respiratory epithelial cells in the sample. Unfortunately, PCR test results are often not available in a timely fashion (often taking 1 week for results) and may not be accessible to practitioners. All of the above tests, with the exception of PCR, detect Influenza A generally and do not identify specific Influenza A subtypes. Moreover, these tests should be used diagnostically, with their limitations in mind, and not as a marker for disease progression. There is no evidence that repeat testing to indicate the presence

or absence of continued viral shedding is indicated if the patient is clinically improving.

Given these test characteristics and the potential for aggressive and severe disease, we recommend an increased index of suspicion for H1N1 influenza in women with influenza-like illness in pregnancy, even with negative rapid antigen or direct fluorescence antibody testing. During the coming influenza season, when the incidence of H1N1 is anticipated to be high, patients with influenza-like illness in pregnancy should be diagnosed and treated presumptively on the basis of symptoms alone.

What are the risk factors for severe disease?

Risk factors in our patients, which also have been noted in nonpregnant patients, included obesity, low socioeconomic status, active or past tobacco use, third-trimester gestation, and underlying cardiac disease (Case 3).[1,3,8,9] In contrast to previous influenza epidemics, children, young adults, and obese patients have been widely reported to bear a disproportionate burden of disease caused by H1N1 influenza. Pregnant women, however, have been known to be at increased risk with previous influenza epidemics, as is being seen in this pandemic of H1N1 disease.

What are potential maternal and fetal complications from influenza?

In our patients, we observed adult respiratory distress syndrome, superimposed bacterial pneumonia, renal failure, pulmonary embolus, and maternal death. The increased minute ventilation, reduced tidal volumes, and decreased functional residual capacity of normal pregnancy physiology leave less reserve capacity for significant stress on pulmonary function. Although the immune system perturbations in pregnancy that may account for increased severity of disease are poorly understood, recent research posits that cytotoxic T-cells and dendritic cell changes may help explain the observed alterations in the maternal systemic immune response.[10]

In our experience, significant volume overload contributed to worsened respiratory status. Interestingly, the gestational age of both intubated patients, both in their third trimester, is consistent with observations from a large epidemiologic study from 1998 evaluating the rate of influenza-related complications over 17 influenza seasons in women enrolled in the Tennessee Medicaid system. The authors demonstrated a high risk for hospitalization for influenza-related reasons in low-risk pregnant women during the last trimester of pregnancy.[9] The decreased colloidal oncotic pressure in the third trimester of normal

Saleeby et al   *H1N1 Influenza in Pregnancy*

gravid subjects when compared with normal non-gravid subjects supports the increased propensity for severe respiratory complications during this time.[11] Decreased oncotic pressure predisposes gravid women to develop pulmonary edema, This is consistent with our clinical experience of volume overload complicating clinical management of our critically ill patients in the third trimester.

Careful attention to fluid status and aggressive diuresis significantly improved the respiratory status of both mechanically ventilated patients. Acute renal failure was seen, but resolution followed appropriate fluid management. Venous thromboembolic events have also been noted in other case reports[3] and deserve special attention in the pregnant and postpartum critically ill patient as physiologic hypercoagulability compounded by immobilization predisposes these patients to this complication.

At this time there have been no reported cases of placental transmission of the virus. Fetal complications are related to the perturbations in maternal physiology and the accompanied fetal stress response. These can include preterm premature rupture of membranes, preterm labor, and preterm birth (Table 2). Acute pyrexia and hypoxia can be associated with fetal tachycardia, minimal variability, and late decelerations of the fetal heart rate. In acutely ill patients, early administration of steroids for fetal lung maturity is recommended, because the potential for preterm birth is high. For patients with mild disease, antipyretics and close follow-up to ensure response to treatment are recommended.

Is there any evidence for alternate dosing of oseltamivir?

Oseltamivir, a neuraminidase inhibitor, prohibits progeny virions from being released from infected cells. The standard adult dose for treatment of influenza A is 75 mg twice daily for 5 days. In nonpregnant patients, oseltamivir decreases the duration of febrile illness and the incidence of secondary lower respiratory tract infections.

Based on the observation in animal models exposed to pandemic influenza strains that novel infection was associated with prolonged viral shedding and increased virulence, it has been suggested that higher doses of oseltamivir for longer duration may be indicated both to reduce severity of disease and to prevent the development of resistance.[12] Furthermore, oseltamivir resistance was observed from postmortem samples in two patients with influenza A (H5N1). Both patients had standard oseltamivir treatment regimens initiated within 48 hours of symptom onset. These reports suggest incomplete suppression of viral replication at standard doses of oseltamivir, leading to opportunity for viral mutation and uncontrollable clinical disease.[13]

Additional considerations for the dosing of oseltamivir in pregnancy include the increased glomerular filtration rate normally seen in pregnancy. Few data exist regarding the effect of normal physiology of pregnancy on plasma concentrations of this drug. However, because this drug is cleared by the kidney, it is plausible that lower circulating concentrations of the drug may be seen in pregnant women.

In acutely ill patients requiring assisted ventilation, these data have helped guide our practice to increase oseltamivir dosing to 150 mg twice daily, orally, for a total of 10 days (Table 3). This increased dosing regimen is only being used for patients presenting with or developing severe disease. For patients with mild influenza symptoms who can be managed at home, or are hospitalized but not requiring assisted ventilation, we are still using the standard adult oseltamivir dose of 75 mg twice daily for 5 days.

What is the ideal time frame for treatment?

The paucity of data regarding the safety profile of oseltamivir in pregnancy and lactation makes overtreatment of pregnant and nursing women unappealing. However, in light of the severity of disease and serious morbidity and mortality complicating severe cases, we follow the Center for Disease Control and Prevention's recommendations and feel that the benefits outweigh the theoretical harms of treatment in this population.

Ideally, treatment should be initiated within the first 48 hours of influenza symptoms for maximal benefit. Neither negative rapid test results nor mild initial presentations should delay treatment. All pregnant women with suspected influenza should be prescribed treatment with oseltamivir. In addition, based on our experience, we feel that treatment should not be withheld in gravid patients who present with febrile illness consistent with influenza outside of the 48-hour window, because treatment even at a later stage may prevent more serious complications such as bacterial pneumonia.[8]

What are the current recommendations for influenza vaccination in pregnancy? Are vaccinations available for H1N1 influenza?

The most recent practice bulletin of the American College of Obstetricians and Gynecologists supports the routine vaccination of pregnant women during flu season.[14] Although no vaccination yet exists for the

prevention of the H1N1 strain of influenza, trials are underway to study candidate vaccines and their efficacy in pregnant patients. The Centers for Disease Control and Prevention have listed pregnant women as a priority group for vaccination, along with children and health care workers. Public health authorities are working to ready a vaccine for distribution and administration in October 2009. Currently, it is unclear whether the vaccine will be ready by this target date and if so, in what quantity. Practitioners should remain attuned to situation updates from CDC and implement vaccination programs for their patients as vaccine becomes available this fall and winter.

REFERENCES

1. Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet 2009 Jul 28. [Epub ahead of print].
2. Centers for Disease Control and Prevention. H1N1 flu. Available at: http://www.cdc.gov/h1n1flu/surveillanceqa.htm. Retrieved August 10, 2009.
3. Centers for Disease Control and Prevention (CDC). Intensive-care patients with severe novel influenza A (H1N1) virus infection–Michigan, June 2009. MMWR Morb Mortal Wkly Rep 2009;58:749–52.
4. Centers for Disease Control and Prevention (CDC). Novel influenza A (H1N1) virus infections in three pregnant women–United States, April–May 2009 [published erratum appears in MMWR Morb Mortal Wkly Rep 2009;58:541]. MMWR Morb Mortal Wkly Rep 2009;58:497–500.
5. Ruest A, Michaud S, Deslandes S, Frost EH. Comparison of the Directigen flu A+B test, the QuickVue influenza test, and clinical case definition to viral culture and reverse transcription-PCR for rapid diagnosis of influenza virus infection. J Clin Microbiol 2003;41:3487–93.
6. Uyeki TM, Prasad R, Vukotich C, Stebbins S, Rinaldo CR, Ferng YH, et al. Low sensitivity of rapid diagnostic test for influenza. Clin Infect Dis 2009;48:e89–92.
7. Quach C, Newby D, Daoust G, Rubin E, McDonald J. QuickVue influenza test for rapid detection of influenza A and B viruses in a pediatric population. Clin Diagn Lab Immunol 2002;9:925–6.
8. Glezen WP, Greenberg SB, Atmar RL, Piedra PA, Couch RB. Impact of respiratory virus infections on persons with chronic underlying conditions. JAMA 2000;283:499–505.
9. Neuzil KM, Reed GW, Mitchel EF, Simonsen L, Griffin MR. Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol 1998;148:1094–102.
10. Gonzalez JM, Ofori E, Burd I, Chai J, Scholler N, Elovitz MA. Maternal mortality from systemic illness: unraveling the contribution of the immune response. Am J Obstet Gynecol 2009;200:430.e1–8.
11. Clark S, Cotton D, Lee W, Bishop C, Hill T, Southwick J, et al. Central hemodynamic assessment of normal term pregnancy. Am J Obstet Gynecol 1989;161:1439–42.
12. Ward P, Small I, Smith J, Suter P, Dutkowski R. Oseltamivir (Tamiflu) and its potential for use in the event of an influenza pandemic. J Antimicrob Chemother 2005;55 suppl:i5–21.
13. De Jong MD, Tran TT, Truong HK, Vo MH, Smith GJ, Nguyen VC, et al. Oseltamivir resistance during treatment of influenza A (H5N1) infection. N Engl J Med 2005;353:2667–72.
14. ACOG Committee on Obstetric Practice. ACOG committee opinion number 305, November 2004. Influenza vaccination and treatment during pregnancy. Obstet Gynecol 2004;104:1125–6.