MASTER CLASS

Pandemic H1N1 Flu and Pregnancy

BY E. ALBERT REECE, M.D., PH.D., M.B.A.

Our nation is facing an influenza pandemic this fall and winter, adding to the difficulties of dealing with a struggling economy, two foreign wars, and attempts to reform our health care.

Indeed, on June 11, 2009, the World Health Organization announced that a pandemic of influenza A(H1N1) was underway. The U.S. count includes thousands of hospitalizations and more than 350 deaths to date.

Although most people who have become ill with this new virus have recovered without requiring medical treatment, there is great concern regarding the effects of this novel flu virus on vulnerable populations.

Seasonal influenza typically poses the greatest risk to the very young and the very old, but this influenza pandemic poses the greatest risk to young people and to pregnant women, in particular. High rates of severe illnesses and even deaths have been reported among pregnant women during this current outbreak. Thus, this pandemic has to be taken very seriously in obstetrics, and we need to employ all preventive measures possible. If we can do this effectively, we can head off the most significant and severe adverse consequences in our pregnant patients.

In an effort to provide the greatest education for the obstetrical community, and to create the greatest preparedness for managing the H1N1 pandemic, we have chosen to do a comprehensive Master Class on this subject. We have invited Mark Phillippe, M.D., M.H.C.M., to tell us how previous influenza pandemics have affected pregnant women and to discuss what impact the current pandemic is already having. We also have asked him to provide in detail his preparedness plan for practicing obstetricians.

Dr. Phillippe is John Van Sicklen Maeck Professor and Chairman of the department of obstetrics, gynecology, and reproductive sciences at the University of Vermont, Burlington. He is a nationally recognized maternal-fetal medicine expert, and has a research interest in influenza and how and why it impacts maternal mortality and the risk of pregnancy loss. ■

DR. REECE, *who specializes in maternal-fetal medicine, is vice president for medical affairs at the University of Maryland, Baltimore, as well as the John Z. and Akiko K. Bowers Distinguished Professor and dean of its school of medicine. He is chair of the Association of American Medical Colleges National Colleges of Deans for 2008-2009. He is a member of the* OB.GYN. NEWS *editorial advisory board and the medical editor of this column.*

Ob.Gyns. on the Front Line in the H1N1 Flu Pandemic

As obstetricians we stand at the front line of preventing and treating pandemic influenza A(H1N1). Our pregnant patients who become infected with the H1N1 virus will potentially be more likely than the general population to develop severe disease, to be hospitalized, and to die from complications of the infection. They also will be at high risk of having preterm birth and fetal loss.

All this means that we must take an aggressive approach to therapy, treating women at the time they present with symptoms and being honest with them about their risks. Moreover, we must plan and execute infection control protocols and other nonpharmacologic interventions that traditionally have not been part of our armamentarium.

BY MARK PHILLIPPE, M.D., M.H.C.M.

To be prepared, it is important that we understand influenza—why and how seasonal and pandemic influenza occur, how pregnant women have fared in previous pandemics, and what their outcomes have been thus far in the current pandemic. Most of us know little about influenza, but as we now practice on the front line with patients who are highly vulnerable, we must know more.

Understanding Pandemic Influenza

Influenza viruses are RNA viruses composed of eight separate negative-strand RNA segments that code for 11 viral proteins. These viruses regularly mutate while replicating themselves, altering their genome and shuffling their genes enough each year that our immune systems do not recognize them.

These ongoing genetic alterations are what drive annual epidemics of seasonal flu and are what make the influenza virus so different from the varicella-zoster virus (chickenpox) and other familiar viruses that are not RNA viruses. While infection with the varicella-zoster virus, or vaccination against it, gives most of us immunity for life, we are all susceptible to annual occurrences of seasonal influenza, regardless of how healthy we are.

There are three influenza virus types: influenza A, B, and C. Only types A and B cause infection in humans. Influenza A, which has been associated with most major pandemics and causes about two-thirds of seasonal influenza, is subtyped according to two surface proteins/antigens: hemagglutinin (H) and neuraminidase (N). Viruses with three different hemagglutinin subtypes H1, H2, and H3, as well as neuraminidase subtypes N1 and N2, have been previously associated with infections in humans.

The major natural reservoir for influenza A virus subtypes is the intestinal track of birds, particularly ducks, geese, and other water fowl. A significant number of different flu virus variations are normal flora in the intestinal tract of these birds.

While most viral infections that humans occasionally acquire from the birds are self-limited, some infections can be dangerous. If one is unlucky enough to be simultaneously infected with an avian influenza virus and a human influenza virus, the genes in each of these two viruses can randomly reassort, or rearrange themselves, to form a new virus.

This phenomenon, called reassortment, is one of two possible phenomena that lead to "antigen shift," which results in immunologically unique viruses that produce pandemic influenza strains.

The other phenomenon that produces intermittent pandemic strains is called adaptation. In this scenario, an avian virus mutates enough over time—particularly with respect to its hemagglutinin molecule—that it becomes able to infect humans and to be easily transmissible from person to person.

The 1918 "Spanish" influenza pandemic produced by an H1N1 influenza virus—the most lethal pandemic in recorded history that was responsible for an estimated 50-100 million deaths worldwide—is believed to have resulted from genomic adaptation. An avian virus mutated enough that it spread from birds to humans and was then transmissible from person to person by common methods of viral spread. An attenuated version of this H1N1 virus then recurred annually for almost the next 30 years.

The 1957 "Asian flu" pandemic, on the other hand, emerged as a result of reassortment. A person infected with the then seasonally recurring H1N1 human virus was simultaneously infected with an H2N2 avian virus, and the genes reassorted to produce a new immunologically unique H2N2 virus. Fortunately, this virus did not contain many of the virulence factors that influenza viruses need to be highly lethal, so the 1957 pandemic was far milder than the 1918 pandemic.

A similar reassortment process led to the "Hong Kong flu" pandemic in 1968. It is believed that a person infected with the then seasonal H2N2 virus became infected with an H3 avian virus as well, generating a new H3N2 virus. Again, this virus was not as lethal as the 1918 virus, and after the pandemic subsided, an attenuated version became the annual seasonal influenza strain.

It is important to appreciate the fact that pandemic influenza can occur in waves, with alternating periods of high infectivity and weeks or months of fewer infections.

Interestingly, the H1N1 virus suddenly reappeared in the 1970s. Since then, seasonal influenza has been produced by a combination of the H3N2 virus and the H1N1 virus. Thus, annual influenza vaccines target both the seasonal H1N1 virus and the virus derived from the 1969 pandemic, along with the influenza B virus.

Epidemiological data going back over a hundred years show that influenza pandemics occur about every 30 years. Although the reasons for this recurring time interval are not understood, the data are strong enough that, especially since the late 1990s, experts have anticipated the development of the next pandemic.

The H5N1 avian influenza that emerged in Hong Kong in 1997 fortunately has not mutated enough to be easily transmissible among humans. Experts have been concerned, however, that this virus will undergo either adaptation or reassortment and lead to a severe pandemic. Thus far, human infections with the H5N1 avian influenza virus have been associated with an overall mortality of approximately 60%. Of the 433 cases reported to the World Health Organization through June of this year, 262 people had died.

A novel H1N1 influenza A virus containing genes from human, avian, and swine viruses was first identified in pigs in the United States in 1998. Although less significant than birds, pigs play an important role in the spread of influenza because they are susceptible to influenza virus from both birds and humans. Between 2005 and 2009, 11 cases of human infection with this triple-reassortment virus were described in the United States. In March and April of this year, further reassortment of this novel influenza A(H1N1) virus—one with uniquely different hemagglutinin and neuraminidase surface proteins—was identified in patients in Mexico. Transmissibility of the new H1N1 flu virus is high. Since initial cases of the novel H1N1 influenza virus were identified in Mexico, and then in Southern California, the virus has spread rapidly. In June, the WHO declared a pandemic. As of early September, tens of thousands of cases had been reported in the United States, and hundreds of thousands of cases had been reported worldwide.

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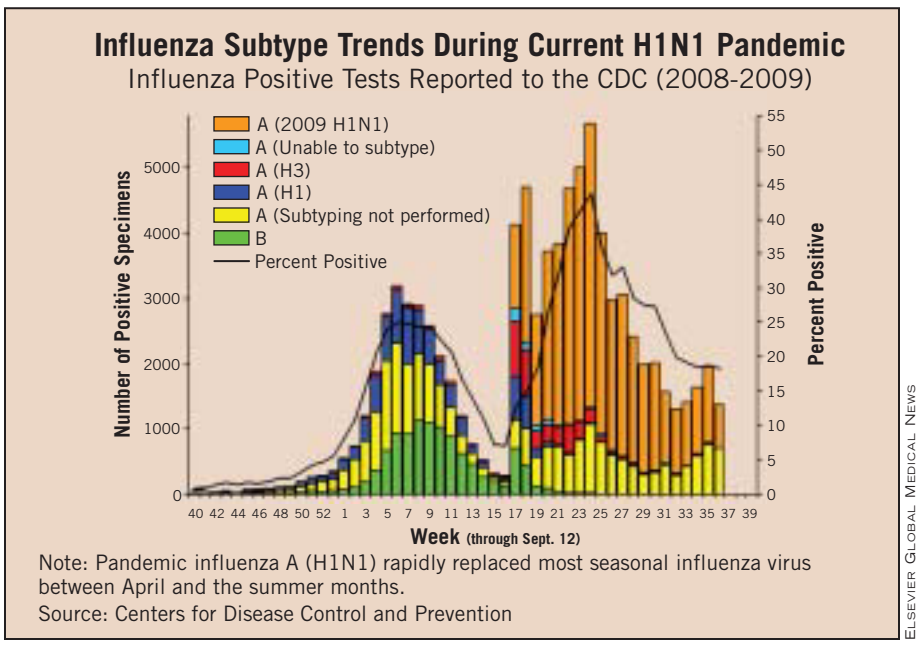

Note: Pandemic influenza A (H1N1) rapidly replaced most seasonal influenza virus between April and the summer months.
Source: Centers for Disease Control and Prevention

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waves, with alternating periods of high infectivity and weeks or months of fewer infections; this pattern was particularly apparent in the 1918 pandemic.

In the 1918 pandemic, the second wave (lasting 8-10 weeks) occurred in the fall and was associated with a much higher mortality (up to 2%) than the first wave that had occurred in the spring. A third wave occurring in the spring of 1919 was similar to the first wave in terms of its high morbidity and relatively lower mortality.

Pandemics and Pregnancy

For reasons that are unclear, pregnant women have been observed to have higher morbidity and mortality compared with nonpregnant patients during influenza infections—seasonal or pandemic.

Observational reports of the 1918 pandemic paint a grim picture. One report published in the Journal of the American Medical Association in 1918, for instance, showed that 52 of 101 pregnant women who were admitted to Cook County Hospital in Chicago during a 2-month period with severe influenza succumbed to the illness. This mortality of 51% in pregnant patients was significantly higher than the observed 33% mortality rate in nonpregnant patients admitted to the hospital (719 of 2,154 nonpregnant patients who were admitted during the same time period died).

Additionally, among the 49 pregnant survivors in this sample, 43% either aborted or delivered prematurely (J. Am. Med. Assoc. 1918:71;1898-99). These are remarkable numbers.

Milder pandemics have had lower mortality overall, but reports have clearly shown that disproportionate numbers of pregnant women—particularly in the third trimester—have succumbed during influenza pandemics compared with the general population. An observational report from the milder 1968 pandemic, for instance, shows that pregnant women still were disproportionately represented among those dying during the pandemic.

Thus far in the current pandemic, the Centers for Disease Control and Prevention has reported similar trends—that pregnant women who contract the virus are significantly more likely to require hospitalization and are disproportionately represented among those who have died from it.

Of 34 cases of confirmed or probable H1N1 influenza in pregnant women that were reported to the CDC during the first month of the pandemic (mid-April to mid-May), 11 (32%) were admitted to the hospital. Dr. Denise Jamieson and her coinvestigators at the CDC noted that this hospitalization rate was four times higher than the hospitalization rate in the nonpregnant population due to influenza infection (Lancet 2009 Aug. 8; doi:10.1016/S0140-6736[09]61304-0).

This report by Dr. Jamieson also noted that the mortality is disproportionately elevated among pregnant women, especially in the third trimester. Four of six relatively healthy pregnant women who died during the first 2 months of the pandemic (mid-April to mid-June) were in the third trimester.

Each of the six women who succumbed developed acute viral pneumonia and subsequent acute respiratory distress syndrome requiring mechanical ventilation. (There were 45 total deaths reported during this period.)

Overall, just as it was in the 1918 pandemic, the highest mortality in the current pandemic appears to be occurring in the healthiest segments of the population—those in their late teens to late 40s—rather than in the very young and elderly (in addition to the chronically ill) as is typical for seasonal influenza. There is some evidence that suggests this increased mortality among the young, healthy population is due to a phenomenon called "cytokine storm," or cytokine dysregulation. The body launches such a robust, overly exuberant immune response that it becomes self-destructive.

How this relates to pregnant women is unclear, as is their overall higher risk for more severe disease, complications, and death. There is speculation that their higher morbidity and mortality risk with influenza relates to immunologic changes in pregnancy, alterations in their respiratory physiology, and/or the overall greater metabolic demands of pregnancy. At this point, however, the testing of these hypotheses with the necessary animal studies has not been done.

In Practice Today

Therapeutic recommendations are driven by this history of pandemic influenza and the outcomes for pregnant women, as well as experience thus far with the current H1N1 influenza pandemic. Because pregnant women tend to have such a rapid onset and progression of disease, it is important to treat women at the time they present with symptoms, rather than waiting until these patients get worse or until culture results have been obtained.

The CDC has recommended that symptomatic pregnant women be treated with oseltamivir (Tamiflu), an antiviral neuraminidase inhibitor, as soon as possible after the onset of symptoms, and that pregnant women with significant exposure receive a prophylactic course of oseltamivir or zanamivir (Relenza). The benefit is expected to be greatest when treatment is initiated within 48 hours.

(In the CDC's Lancet-published report on H1N1 in pregnancy, the earliest initiation of oseltamivir in the pregnant women who died was 6 days after symptom onset.)

The vast majority of patients who have influenza—at least 80%—will present with a fever. Cough, sore throat, and muscle aches are other common symptoms. Occasionally, patients will have nausea or vomiting. During an active influenza pandemic, if a pregnant patient presents with signs and symptoms consistent with an influenzalike illness, we should err on the side of caution and begin empiric treatment.

In cases in which the diagnosis is unclear—in a patient with new nausea and vomiting but no fever or other symptoms suggestive of influenza, for instance—it is critical that we caution patients to call right away if they develop respiratory symptoms and/or a fever.

Because of concerns regarding the potential side effects of the antiviral medications, pregnant women can be expected to be hesitant about initiating treatment. However, given the increased risks of significant morbidity and mortality associated with untreated influenza infection, the risk-benefit ratio strongly favors the early initiation of effective antiviral medication.

Pregnant women are in the CDC's high-risk category for early vaccination, and certainly this is the best way to prevent their risk of significant morbidity and mortality. It is important that we educate our support staff to encourage patients to receive the vaccine; studies have shown that flu vaccination rates were low when nurses and front office staff were not committed to and invested in the idea.

There is only a small chance that individuals will acquire the seasonal influenza strain, but because pregnant women face increased risks with seasonal influenza as well, the CDC has recommended that they should still receive the seasonal influenza vaccine.

Vaccination also will protect pregnant women against the potential dangers of sequential influenza infections; being compromised with an infection of seasonal flu would potentially further increase a pregnant woman's risk of becoming severely ill with a subsequent pandemic H1N1 infection.

Public health measures call for "social distancing" as a nonpharmacologic method of influenza prevention—that is, these measures recommend limiting the number of people one is surrounded by or exposed to. Such measures have special meaning for us as obstetricians. It is imperative that we see infected and noninfected patients at separate time periods and/or in separate locations, and that we limit the numbers of pregnant women coming into our offices for prenatal care in the midst of a pandemic.

The use of masks and other standard infection control procedures also is imperative, and will help decrease viral transmission. But we must do more. We don't want one infected patient sitting in our waiting room with 10 other noninfected patients. Given what we know about the transmissibility of the virus, at least three or four of them would become infected in such a scenario.

In the middle of an active influenza pandemic, the benefit of having an otherwise healthy woman at midgestation keep her routinely scheduled prenatal visit as opposed to deferring her visit and staying at home (possibly calling in to talk with a triage nurse) will need to be considered.

The alternatives are not perfect, but we certainly do not want to expose healthy pregnant women to a potentially lethal infection in our waiting room or even in the bus or elevator of our office building.

Our other challenge will involve hospital care. As obstetricians we will need to facilitate and lead the development of labor and delivery triage systems aimed at separating infected and noninfected laboring patients. ■

DR. PHILLIPPE *said he has no disclosures relevant to this article. To respond to this column, e-mail him at obnews@elsevier.com.*

Key Points

► The newly emerged pandemic influenza A(H1N1) virus is expected to present significant challenges to the entire health care system.
► The challenges will be especially great for pregnant women and those who provide medical care for them.
► Previous influenza pandemics have been notable for increased morbidity and mortality among pregnant women, especially during the third trimester.
► In the past, all that could be offered to pregnant women was supportive care. We now have antiviral medications and will soon have a vaccine for the pandemic H1N1 virus.
► We need to educate ourselves and our patients about how to use these therapeutic interventions effectively.

Source: Dr. Phillippe