H1N1 novel influenza A in pregnant and immunocompromised patients

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Objective: To describe the increased risk of severe disease and the appropriate management of patients at high risk such as pregnant women and immunosuppressed patients who acquire novel influenza A (H1N1).

Design: Review of the literature regarding influenza A in these patient groups, and review of published and unpublished data with regard to novel influenza A (H1N1).

Main Results: Pregnant women are at increased risk for severe pneumonia and respiratory failure from influenza infection, particularly during pandemics, including the current pandemic. Fetal morbidity is significant, usually resulting from maternal fever and severe hypoxemia. Early antiviral therapy using oseltamivir may be beneficial, and intensive care unit support should target adequate oxygenation at all times. Immunosuppressed patients are at increased risk for influenza, as well as at risk for more severe or prolonged infection. Patients after hematopoietic stem cell transplantation, after lung transplantation, and those receiving chemotherapy for leukemia are at highest risk, whereas the risk for human immunodeficiency virus-infected individuals appears relatively low. Treatment with antiviral therapy may be beneficial, even after the usual cut-off of 48 hrs after symptom onset.

Conclusions: Optimal management of these patients is preventive by influenza vaccination, but the neuraminidase inhibitor antiviral agents provide effective treatment. (Crit Care Med 2010; 38[Suppl.]:S000–S000)

Key Words: influenza A; pandemic; H1N1; mechanical ventilation; pregnancy; fetal outcome; immunosuppression; transplant; chemotherapy; human immunodeficiency virus

PATIENTS AND METHODS

The Pregnant Patient: Increased Susceptibility

A number of changes occur in a pregnant woman’s immune system to allow tolerance to paternally derived fetal antigens. Some suppression of cell-mediated immunity occurs, and maternal lymphocytes demonstrate a diminished proliferative response to soluble antigens and to allogeneic lymphocytes (4). Decreased numbers of T-helper cells have been documented, either because of an absolute decrease in numbers or because of a reduction in the CD4-to-CD8 ratio (4). These effects are balanced by an intact or possibly enhanced humoral immune response (5). The effect of these alterations on maternal immunity is a predisposition to more severe manifestations of certain infections, including influenza. Preliminary data from the 2009 influenza A (H1N1) pandemic from Australia noted that pregnant women with more severe disease had an immunoglobulin G subclass 2 deficiency (6). The significance of this finding remains unclear.

The Centers for Disease Control and Prevention therefore recommend trivalent inactivated influenza vaccine in otherwise healthy women during the second and third trimesters of pregnancy, although some reports suggest the risk-to-benefit ratio warrants vaccinations at all stages of pregnancy for women with certain comorbidities, and during pandemics (8).

Influenza Outcome in Pregnancy

Viral pneumonia is a serious concern in pregnancy, with reported increased mortality rates compared with the general population, particularly during pandemics. In general, younger patients tend to be at increased risk for severe disease during pandemics, whereas older patients are at risk in the decade after the pandemic. Pregnant women without comorbidities are at increased risk for seasonal influenza-related pulmonary hospitalization, with risk increasing with later gestation and with associated comorbidity (10). Interpandemic maternal mortality related to influenza is low (9). In previous influenza pandemics, the maternal mortality rate has been higher than that of the general population. During the influenza pandemic of 1918 to 1919, the maternal rate of mortality was as high as 27%; in the epidemic of 1957 to 1958, 50% of fatalities among women of childbearing age occurred in pregnant women (11). The recent swine-origin influenza A (H1N1) pandemic has been associated with a high incidence of severe disease in pregnant women, with significant maternal mortality (12). In this study, the rate of admission of pregnant women was four-times higher than in the general population with H1N1 infection. Six maternal deaths occurred among the 34 pregnant cases of H1N1 identified: one in the first tri-
mester, one in the second trimester, and four in the third trimester (12). No significant adverse perinatal outcome has been noted associated with respiratory hospitalization for seasonal influenza (13). Although influenza virus does cross the placenta, viremia is rare. A direct teratogenic effect has not been demonstrated, although there are reports of neural tube defects and cleft lip and palate (14). Indirect effects of influenza, particularly fever, may increase the risk of congenital abnormalities (14). The recent swine-origin influenza A (H1N1) pandemic has been associated with a high incidence of perinatal morbidity and mortality (12, 15). Six pregnant women in Winnipeg, Canada, required mechanical ventilation for influenza A (H1N1) (Oluyomi T, unpublished data). Two maternal deaths occurred, with three fetal losses and one fetus with severe hypoxic encephalopathy. Much of the fetal morbidity was attributed to fetal hypoxia in mothers with severe ARDS and marked hypoxemia.

DISCUSSION

Management of Respiratory Failure Caused by H1N1 in Pregnancy: Antiviral Therapy

Amantadine has been used in pregnancy as treatment and as prophylaxis, but the current pandemic strain is resistant. Oseltamivir has been used quite extensively in pregnancy with good results (16), and zanamivir, administered by inhalation, is increasingly a treatment option. These drugs are of most benefit when administered within 48 hrs of symptom onset and may reduce the incidence of pneumonia in patients with seasonal influenza (17). In a report of six maternal deaths with H1N1 pandemic influenza, none of these patients had received antivirals within 48 hrs of onset of symptoms (12).

Ribavirin, used in some combination therapy options for H1N1, is not recommended in pregnancy. No data exist regarding the use of intravenous neuraminidase inhibitors, such as zanamivir and peramivir.

Intubation

Pregnant women have a diminished functional residual capacity and increased oxygen consumption that result in rapid oxygen desaturation in response to apnea or hypoventilation (18). Upper airway mucosal edema and friability occur in pregnancy and can impede visualization and increase risk of bleeding. Failed intubation is eight-times more common in the obstetric population than in other anesthetic intubations (19). Nasal intubation should be avoided and a smaller endotracheal tube may be required. Preoxygenation with 100% oxygen is essential, but respiratory alkalosis should be avoided because this adversely affects uterine blood flow (20). The pregnant patient should always be considered to have a full stomach because of delayed gastric emptying and the elevated intraabdominal pressure of pregnancy.

Mechanical Ventilation

Little data are available to guide mechanical ventilation of pregnant patients in the ICU. Hyperventilation should be avoided because the respiratory alkalosis causes uterine vasoconstriction (20). The usual ventilatory approach of lung protective ventilation with pressure and volume limitation, sometimes with permissive hypercapnia, has not been assessed in pregnancy. It should be remembered that chest wall compliance is reduced in the near-term patient, and the usual pressure limits (e.g., plateau pressure of 35 cmH2O) may not be appropriate. Slightly higher ventilatory pressures may be acceptable to achieve appropriate tidal volumes in pregnant women near term, because transpulmonary pressures may not be elevated. Oxygenation should be optimized to ensure adequate fetal oxygen delivery, keeping arterial oxygen saturation >92%. Late pregnancy is normally associated with a mild respiratory alkalosis to facilitate fetal excretion of carbon dioxide, resulting in PaCO2 levels of approximately 30 Torr (4 kPa), but it is unclear if it is necessary to keep arterial CO2 levels at these low levels. A case report (21) suggests that maternal hypercapnia up to 60 Torr (8 kPa), in the presence of adequate oxygenation, does not appear to be detrimental to the fetus. Although maternal respiratory acidosis may produce fetal acidemia, with associated fetal heart rate changes, these changes do not have the same implications as fetal acidosis occurring as a result of fetal hypoxia. However, the right shift of the hemoglobin oxygen dissociation curve caused by this acidosis may reduce the beneficial oxygen carrying characteristics of fetal hemoglobin. If marked respiratory acidosis results from permissive hypercapnia, then treatment with bicarbonate should improve maternal and fetal acidemia. Few data exist on the use of non-conventional modes of ventilation and oxygenation, which have not been used extensively in pregnant women until the current 2009 pandemic.

Other Management Issues

Radiologic investigations are necessary for the assessment and management of the pregnant patient with respiratory failure. Although there is potential for risk to the fetus from radiation, the perception of this risk is often higher than the real risk (22). Shielding the abdomen with lead and using a well-collimated radiograph beam can reduce fetal exposure. The adverse effects of radiation exposure of the fetus include oncogenicity (increased incidence of childhood cancer) and teratogenicity. Nevertheless, most common radiologic investigations performed on the mother, including chest X-rays and computed tomography chest scan, can be performed with fetal radiation exposure within safe limits (22), although investigations such as abdominopelvic computed tomography will cause significant fetal radiation exposure. Every effort should be made to minimize uterine exposure, particularly in the first trimester.

The optimal drugs for prolonged sedation, analgesia, or neuromuscular blockade to facilitate ventilation in pregnancy are not known, based on currently available data. Benzodiazepines cross the placenta and their use in early pregnancy may be associated with some increased risk of congenital abnormalities, as well as preterm birth (23). Midazolam and lorazepam cross the placenta to a lesser degree than diazepam, although whether this is clinically significant is unclear. Propofol has been used as an induction agent for cesarean section, but data on its prolonged use in pregnancy are limited. A single report (24) of two cases in pregnancy describes the development of mild acidemia during propofol infusion. Congenital malformations have not been demonstrated with use of narcotic analgesics such as morphine and fentanyl. Most nondepolarizing neuromuscular blocking agents cross the placenta, including pancuronium, vecuronium, and atracurium, but transfer is unlikely to have clinical effects on the fetus in the short term. If sedative or paralytic agents are used in the pregnant woman at the time of delivery, then it is essential that this information be communicated to the

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neonatologist, and the need for ventilatory support for the fetus should be anticipated.

Pregnancy increases the risks of venous thrombosis attributable to hypercoagulability and venous stasis. In the critically ill patient, antithrombotic measures, including physical interventions and heparin prophylaxis, should be utilized.

**Delivery of the Fetus**

Pregnancy has a number of effects on maternal respiratory physiology, and these changes, as well as anecdotal reports, may suggest that delivery of the pregnant patient with respiratory failure will result in improvement in the mother's condition (25). However, two case series (26, 27) addressing this issue have not found a consistent benefit to the mother. Some improvement in oxygenation was noted, but this was not accompanied by a change in PEEP requirements or improvement in compliance (26). If the fetus is at a viable gestation (determined largely by the neonatal resources available) and is at risk because of intractable maternal hypoxia, then there may be a benefit to the fetus in delivery. Any decision to administer steroids to promote fetal lung maturity should be made on an individual basis, in consultation with obstetrics and neonatology. Although cesarean section allows more rapid delivery in the critically ill patient, the increased physiologic stress of operative delivery may be associated with higher mortality in these patients (28). Therefore, delivery should not be performed with the sole purpose of improving maternal oxygenation or ventilation. However, it is important that preparations are made for urgent delivery and neonatal resuscitation in the event of sudden maternal or fetal deterioration or spontaneous labor. Obstetric indications should always determine the mode of delivery.

**The Immunocompromised Patient: Immune Response to Influenza**

The immune response to the influenza virus is complex and multifaceted (29). Defense against acquisition of infection involves the mucous layer and integrity of the mucosal surface, nonspecifically activated phagocytes, and antibody to the virus. Surface-neutralizing antibodies of the IgA subtype are important in the upper respiratory tract, whereas IgG antibodies play a major role in the lower respiratory tract (29). The level of antibodies against hemagglutinin and neuraminidase correlates with resistance to illness and limitation of viral replication in the respiratory tract (30).

Once infection occurs, immune mechanisms are activated to eliminate the virus. Interferon levels are elevated early in infection and play a role in decreasing viral production and promoting elimination of the infection. The cell-mediated immune response is important in viral clearance and promoting recovery (29). The major cellular immune response is CD8 T-lymphocyte–mediated cytoxicity. Reductions in T-cell number or function will produce an increased magnitude and duration of infection.

**Who Is at Risk?**

Patients who are immunocompromised may be at risk for serious influenza-associated complications, as well as prolonged viral shedding, and at increased risk for resistance to antiviral agents (31). Some data in regard to risk factors are available for seasonal and pandemic influenza before the current influenza A H1N1 pandemic, but recent data are limited. An initial report of 18 patients from Mexico with H1N1 pneumonia (32) did not report on immunosuppressed patients, and a subsequent report of 58 patients requiring ICU care describes two patients as having underlying immunosuppressive disease (33). An early report of 30 hospitalized patients with novel influenza A (H1N1) from California describes 20% as having an underlying immunosuppressive condition (34). A larger study from Canada of 168 critically ill patients with pandemic influenza A (H1N1) reports 20% of patients having an underlying immunosuppressive disorder, the majority being corticosteroid treatment (15). A short report on two patients after hematopoietic stem cell transplantation acquiring novel influenza A (H1N1) describes prolonged viral shedding associated with the development of oseltamivir resistance (35).

**Hematopoietic Stem Cell Transplant Recipients**

Patients undergoing hematopoietic stem cell transplantation are profoundly immunocompromised after their intensive regimens before transplantation, and delayed engraftment and graft-versus-host disease can cause more prolonged immune dysfunction. The frequency of influenza among these patients is relatively low (0.2%–2.8%) (36), but high rates of infection have been noted during influenza epidemics (23%–29%) (36). Clinical presentation in these patients may lack the typical features of myalgia and high fever seen in immunocompetent individuals (37). A large European report of 1863 hematopoietic stem cell transplantation patients followed-up through three influenza seasons documented influenza A viral infection in 2.1% (38). Lymphocytopenia was identified as the major risk factor for development of lower respiratory tract infection, and mortality attributable to influenza A was 15.4%. A single-center review of 12 influenza seasons documented an infection rate of 1.3% (39). Among these patients, pneumonia developed in 29%, associated with the presence of lymphopenia and an earlier posttransplantation period. Mortality in patients with pneumonia was 28%, and oseltamivir treatment was noted to prevent the development of pneumonia. Viral shedding was prolonged, particularly in patients administered higher-dose corticosteroids (>1 mg/kg per day) (39).

**Solid Organ Transplants**

Influenza after solid organ transplantation appears to be more common among lung transplant recipients (40) but also causes significant morbidity among renal, liver, and heart transplantation patients. The increased frequency in lung transplantation patients is likely related to local effects, such as ciliary dysfunction and epithelial injury, impaired lymphatic drainage, or decreased secretory antibodies, with the lung being the primary site of influenza infection (36). Influenza infection has also been associated with allograft rejection in lung and kidney recipients (40–42). The risk of influenza in patients with solid organ transplantation may be related to the immunosuppressive regimen, which can also influence the degree of serological response to influenza vaccination (43). However, adequate antibody responses have been documented in patients with a variety of immunosuppressive regimens (44, 45).
Mortality rate of 0.4% (31 deaths in 7606
A pandemic period in August to Sep-
in their HIV population during their win-
not reported a significant effect of H1N1
South Africa, a country with a prevalence
A (H1N1) in HIV-infected individuals.

The effects of chemotherapy on the immu-
system are quite variable and depend
Management

Other Immunosuppressive
Conditions

Several other patient groups are po-
tentially at risk for increased incidence
severity of influenza because of immu-
nosuppression. Common causes in-
clude malignant disease in patients un-
dergoing chemotherapy and receiving
corticosteroid treatment for inflamma-
tory conditions.

The effects of chemotherapy on the
system are quite variable and depend
and complications are not different to
the non-HIV population, although the
duration of illness may be prolonged (46,
47). The prolonged illness may be associ-
ated with prolonged viral shedding (48).
Increased severity of illness is suggested
by a report of a marked increase in the
rate of death from pneumonia among the
25- to 44-yr-old age group in cities with
a high incidence of acquired immune de-
siency syndrome when comparing influ-
zena seasons in the pre-HIV period with
that of the late 1980s (49). The effects of
influenza in the HIV-infected patients are
significantly impacted by treatment with
highly active anti-retroviral therapy. A
retrospective cohort study compared car-
diopulmonary hospitalization rates and
mortality during the influenza seasons
from 1995 to 1999, during the time of
introduction of highly active anti-retrovi-
ral therapy (50). A 53% decline in hospi-
talizations and 77% decline in mortality
were attributed to introduction of highly
active anti-retroviral therapy. A cluster of
seven patients with influenza and HIV
infection, five of whom were adminis-
tered highly active anti-retroviral ther-
apy, was reported from the 1997 to 1998
influenza season (51). A spectrum from
uncomplicated influenza through severe
primary viral pneumonia and secondary
bacterial infection was noted. None of
these patients required mechanical ven-
tilation and all survived.

Little data are available regarding the
effect of the current pandemic influenza
A (H1N1) in HIV-infected individuals.
South Africa, a country with a prevalence
of HIV infection of 15% to 20% (52) has
not reported a significant effect of H1N1
in their HIV population during their win-
ter pandemic period in August to Sep-
tember 2009. In fact, their reported H1N1
mortality rate of 0.4% (31 deaths in 7606
cases) is lower than that in many coun-
tries with a low prevalence of HIV, despite
the difficulties in identifying the denom-
inator of infected cases (53).

Alterations to Usual
Management

The most important approach to influ-
zena management in the immunosup-
pressed patient is prevention by vaccina-
tion and infection control precautions.

Despite abnormalities in immune func-
tion, vaccination has been shown to be
effective in hematopoietic stem cell
transplantation patients (60, 61), in HIV
patients (62), and in those receiving
chemotherapy (63) or corticosteroid therapy
(57, 58). However, steroid use may
prolong viral shedding after severe influ-
zena infection (59). A recent report of 168
critically ill patients with pandemic influ-
zena A (H1N1) describes 15% as using
corticosteroid therapy (15).

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