Three recent case series of novel H1N1 influenza and their contribution to our understanding of the H1N1 infection in pregnancy

The first influenza pandemic of the 21st century is now well upon us and several articles published in prominent journals in the past three months provide us with some information about the characteristics of H1N1 infection in the pregnant population. Although data from previous pandemics have significant limitations, it has repeatedly been shown that pregnant women are particularly prone to severe cases of influenza.^{1,2} The following three reports appear to confirm this pregnancy-associated increase in influenza virulence and suggest the wisdom of early antiviral treatment for pregnant women with influenza-like illness. A summary of their findings can be found in Table 1.

H1N1 2009 influenza virus infection during pregnancy in the USA

Jamieson DJ, Honein MA, Rasmussen SA, *et al.*
Lancet 2009;**374**:451–8

Jamieson *et al.*³ reviewed confirmed or probable cases of H1N1 influenza virus infection in pregnant women that were reported to the US Center for Disease Control and Prevention in the spring of 2009. The authors identified a total of 34 cases of pandemic H1N1 in pregnant women from 13 different states between 15 April to 18 May 2009. These cases represented 0.62% of all cases of H1N1 infection identified in the USA in the same timeframe. They estimated an overall incidence of one case per 100,000 pregnant women in the USA during this period. The majority of these women were previously

healthy. Three (9%) women presented in the first trimester, 19 (56%) in the second and nine (26%) in the third trimester. Their presentation did not appear to differ from that seen in the general population except for a slight increase in the presence of shortness of breath. Despite the similar presentations, 11 (32%) of these 34 women were admitted to hospital. This is more than four times the rate of hospitalization for H1N1 infection than was seen in the general population during the same period (0.32 per 100,000 pregnant women, 95% confidence interval [CI] 0.13–0.52 versus 0.076 per 100,000 population at risk, 95% CI 0.07–0.09) and suggests either more severe disease in pregnant patients or greater caution on the part of the clinicians caring for pregnant patients.

Of greater concern is the authors' finding that of the 45 deaths in the USA attributed to H1N1 between 15 April and 16 June 2009, 13% (6) were in pregnant women – 13 times higher than would be expected based on the prevalence of pregnancy in the general population. All of the mothers who died had developed pneumonia and subsequent acute respiratory distress syndrome requiring mechanical ventilation. Four of these women were in the third trimester. Five had living children by cesarean delivery and one had fetal loss at the time of maternal death at 11 weeks gestation. None of the infants born to infected mothers showed evidence of infection.

Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009

Jain S, Kamimoto L, Bramley AM, *et al.*; the 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team
N Engl J Med 2009; DOI: 10.1056/NEJMoa0906695

Jain *et al.*⁴ describe the characteristics of 272 pregnant and non-pregnant patients admitted to hospital for documented H1N1

Table 1 Summary of findings of recent case series of H1N1 infections in pregnant and non-pregnant patients

Study group	Number and type of patients studied	Country studied	Period studied	Percent of patients over the age of 65	% with no risk factors	Percent of patients who were pregnant and proportion of these in each trimester of pregnancy*	Percent of pregnant patients who died
CDC (Jamieson <i>et al.</i>)	34 pregnant women with known H1N1 infection	USA	15 April to 18 May 2009	N/A	Not reported	100% pregnant 9% in the first trimester 56% in the second trimester 26% in the third trimester	18% (6% of 34 pregnant patients)
CDC (Jain <i>et al.</i>)	272 pregnant and non-pregnant patients admitted to hospital with H1N1	USA	29 April to mid-June 2009	5	27	7% pregnant 11% first trimester 17% second trimester 67% third trimester	16% (3 of 18 pregnant patients) as compared with 6% (16 of 254) of non-pregnant patients
ANZIC study group	722 pregnant and non-pregnant patients admitted to ICU with H1N1	Australia and New Zealand	1 June to 31 August 2009	7.3	31.7	9% pregnant Data on trimester of pregnancy not reported	Pregnancy death rate not reported Total death rate 14.3%

CDC = Center for Disease Control and Prevention; ANZIC = Australian and New Zealand Intensive Care; ICU = intensive care unit

*Percentages do not add up to 100% because not all patients' trimesters were reported

influenza infection in the USA during a similar but longer period in the spring of 2009. Almost half of these patients were under the age of 18 years and more than one-third were between the ages of 18 and 49 years. Most had normal chest X-rays and white blood cell counts on presentation. In addition to the typical features of influenza, 39% of patients had diarrhoea or vomiting, 25% of patients were admitted to the intensive care unit and a total of 7% died. The only variable that was associated with a positive outcome was the receipt of antiviral drugs within two days of the onset of illness.

Of Jain *et al.*'s 272 patients, 18 (7%) were pregnant – a prevalence that is seven times higher than that expected in the general population. Only six of the pregnant patients (33%) had another underlying medical condition (asthma in 4 patients and diabetes in 2 patients). Of the 18 pregnant patients, two (11%) were in the first trimester, three (17%) were in the second trimester and 12 (67%) were in the third trimester. Three of the 18 infected pregnant women died (16%) as compared with 16 of the 254 (6%) non-pregnant patients.

Critical care services and 2009 H1N1 influenza in Australia and New Zealand

The ANZIC Influenza Investigators

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The Australian and New Zealand Intensive Care study group show similar findings from the perspective of the intensivist.⁵ They describe 722 patients admitted to intensive care units in Australia and New Zealand over the period of 1 June to 31 August 2009. This number represents an incidence of intensive care unit (ICU) admission for 2009 H1N1 influenza of 28.1 per million inhabitants and is 15 times the number of ICU admissions due to viral pneumonitis seen in recent years in these countries. In all, 92.7% of the patients were under the age of 65 and 31.7% had no known predisposing factor. The median length of stay for these patients in the ICU was seven days. Of all patients, 14.3% died. The authors report a peak in ICU admissions due to influenza approximately four weeks after the infection becomes widespread in a region and that the increase in ICU patient volume continues for several weeks after this peak.

As was seen in the report by Jamieson *et al.*, pregnant women composed a disproportionate share of the patients admitted to the ICU with H1N1. In all, 9.1% of the patients admitted to the ICU over the study period with H1N1 infection were pregnant. This number is nine times what would be expected based on the prevalence of pregnancy in the general population and again suggests that pregnant women are at increased risk for severe disease after contracting influenza A H1N1.

CONCLUSIONS

What are the implications of these data for practitioners caring for women with influenza-like illness during pregnancy? The data offer additional confirmation that symptomatic influenza and particularly H1N1 infection appears to be both more common in pregnant women and more severe in its manifestations. What remains unclear from these data-sets is how much the disproportionate number of pregnant women with H1N1 infection (severe and otherwise) is due to an increase in pregnancy susceptibility to the virus and how much is due to physician behaviour. Clinicians believing that pregnant women are more at risk of and from influenza than other populations may be more likely to test pregnant patients with influenza-like illness for H1N1 and subsequently admit them to either the hospital or an ICU environment. Data directly comparing the severity of illness in pregnant and non-pregnant patients admitted to hospital or ICU with H1N1 may help clarify the relative contribution of biology and clinician practice. However, while clinical practice may offer some explanation for increased admissions to hospitals or ICUs, it is unlikely to account for the high death rate among pregnant women that has been reported in two of these studies. Therefore, clinicians are well advised to follow the US CDC recommendations to encourage all pregnant women to be vaccinated against both seasonal influenza and H1N1. Clinicians should also follow their recommendations to treat pregnant patients with influenza-like illness early with antiviral agents despite the relative paucity of human pregnancy safety data for these agents.⁶

REFERENCES

- 1 Freeman DW, Barno A. Deaths from Asian influenza associated with pregnancy. *Am J Obstet Gynecol* 1959;78:1172–5
- 2 Dodds L, McNeil SA, Fell DB, *et al.* Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. *CMAJ* 2007;176:463–8
- 3 Jamieson DJ, Honein MA, Rasmussen SA, *et al.* H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* 2009;374:451–8
- 4 Jain S, Kamimoto L, Bramley AM, *et al.* Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. *N Engl J Med* 2009 Oct 8 DOI: 10.1056/NEJMoa0906695
- 5 The ANZIC Influenza Investigators. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *N Engl J Med* 2009 Oct 8 DOI: 10.1056/NEJMoa0908481
- 6 Updated interim recommendations for the use of antiviral medications in the treatment and prevention of influenza for the 2009–2010 season. Centers for Disease Control and Prevention, Atlanta. See <http://www.cdc.gov/h1n1flu/recommendations.htm> (last checked 21 October 2009)

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