Influenza A/HINIv in pregnancy: an investigation of the characteristics and management of affected women and the relationship to pregnancy outcomes for mother and infant

L Yates,[1] M Pierce,[2] S Stephens,[1] AC Mill,[3] P Spark,[2] JJ Kurinczuk,[2] M Valappil,[4] P Brocklehurst,[2] SHL Thomas[1,5]* and M Knight[2]

[1]United Kingdom Teratology Information Service, Newcastle upon Tyne Hospitals NHS Foundation Trust, Wolfson Unit, Newcastle upon Tyne, UK
[2]National Perinatal Epidemiology Unit, University of Oxford, UK
[3]School of Biology, Institute of Research on the Environment and Sustainability, Newcastle University, Newcastle upon Tyne, UK
[4]Health Protection Agency Newcastle Laboratory, Institute of Pathology, Newcastle General Hospital, Newcastle upon Tyne, UK
[5]Wolfson Unit of Clinical Pharmacology, Institute of Cellular Medicine and Medical Toxicology Centre, Newcastle University, Newcastle upon Tyne, UK

*Corresponding author

Executive summary

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Executive summary

Background

April 2009 saw the emergence of a novel influenza A virus of swine origin (swine flu), subsequently subtyped (and referred to in this document) as AH1N1v. This spread rapidly, achieving pandemic status in June 2009. Pregnant women were identified as being at high risk of severe influenza-related complications, requiring early assessment and treatment of flu-like symptoms, and as a priority group for vaccination against AH1N1v. There was, however, limited information available about the maternal and fetal risks of AH1N1v infection or of antiviral drug or AH1N1v vaccine use in pregnancy. This study was therefore designed to assess rates of and risk factors for adverse outcomes following AH1N1v infection in pregnancy and to assess the adverse effects of the antiviral drugs and vaccines used in prevention and management.

Objectives

The objectives of this research were to:

1. estimate the incidence of AH1N1v influenza in pregnancy during the 'second wave'
2. determine the effect of AH1N1v infection and/or treatment with neuraminidase antiviral drugs in pregnant women and/or AH1N1v vaccination (timing of use, dose and agent) on pregnancy outcome, including specific adverse or beneficial effects of antiviral treatment or AH1N1v vaccination on eventual maternal and fetal outcome
3. ascertain the influence of demographic or pregnancy characteristics and additional aspects of pregnancy management on outcomes for mother and infant
4. produce guidance on the management of AH1N1v infection in pregnancy: initially following systematic review and updated subsequently by monthly review of emerging data from this study such that outcomes for women and infants could be optimised during the current pandemic.

Methods

Prospective national cohort studies were conducted using different sources to identify women in three specific groups:

1. pregnant women suspected of being infected with AH1N1v or treated with antiviral medication and managed in the community
2. pregnant women vaccinated against AH1N1v
3. pregnant women admitted to hospital with confirmed AH1N1v.

Information about pregnancy management and outcomes was collected directly from health professionals caring for infected women in secondary care settings, and from health professionals as well as women themselves, with consent, where infection was managed in primary care.

Women were identified through the following sources:

1. The UK Teratology Information Service (UKTIS) collected data from general practices within and outside the Primary Care Research Networks (PCRNs), as well as from self-notifications from affected women. Some practices acted as 'sentinel' sites, providing data on all presentations, antiviral prescriptions and vaccinations.
2. The UK Obstetric Surveillance System (UKOSS) collected data through its network of collaborating clinicians in all consultant-led maternity units in the UK.

Characteristics of women with influenza-like illness (ILI) in primary care were compared with those of women without symptoms accepting or declining immunisation. Characteristics of women admitted to hospital with confirmed AH1N1v infection in pregnancy were compared with a historical cohort of over 1200 women giving birth in the UK, identified from the same hospitals as the cohort women and uninfected with AH1N1v.

The incidences of suspected AH1N1v infection, use of antiviral drugs and AH1N1v vaccination were estimated from presentation data provided by sentinel general practices. Characteristics of women with ILI were compared with asymptomatic women who were offered vaccination. Use and timing of antiviral agents and uptake of AH1N1v vaccines were also determined.

The incidence of hospitalisation with confirmed AH1N1v influenza in pregnancy was estimated with 95% confidence intervals (CIs) using the most recently available birth data (2007) as a proxy for September 2009 to January 2010. Outcomes examined in hospitalised women included maternal death, admission to an intensive care unit, perinatal mortality and preterm birth. In addition, risk factors for hospital and intensive care unit admission were examined in a full regression model, which was developed by including both potential explanatory and confounding factors in a core model if there was a pre-existing hypothesis or evidence to suggest that they were causally related to admission with AH1N1v influenza in pregnancy.

Results

The weekly incidence of ILI amongst pregnant women in 24 sentinel practices averaged 51/100,000 over the period of study. In the 23 practices providing these data, antiviral drugs were offered to 4.8% (95% CI 4.0% to 5.9%) and vaccination to 64.8% (95% CI 64.7% to 68.9%) of registered pregnant women.

A total of 90 pregnant women with ILI presenting in primary care were reported to the research team: 55 were prescribed antiviral drugs and in 42 (76%) cases this was within 2 days of symptom onset. After comparison with 1329 uninfected pregnant women who were offered vaccination, the only maternal factor identified as increasing odds of ILI presentation was pre-existing asthma [adjusted odds ratio (aOR) 2.0, 95% CI 1.0 to 3.9]. In this small data set there was no significant effect of other comorbid conditions or of age, racial group, body mass index (BMI), index of multiple deprivation (IMD) or smoking status. The data suggest that vaccination occurred in 56% of pregnant women who were offered it, although information on whether or not vaccination was offered was not always provided.

Overall, 241 pregnant women were admitted to hospital with laboratory-confirmed AH1N1v infection. Eighty-three per cent of women who were hospitalised with AH1N1v influenza were treated with antiviral agents, but only 6% received antiviral treatment before hospital admission.

Women hospitalised with AH1N1v influenza in pregnancy were more likely to be overweight (aOR 1.7, 95% CI 1.2 to 2.4) or obese (aOR 2.0, 95% CI 1.3 to 3.0) than the comparison cohort. They were also more likely to have asthma requiring inhaled or oral steroids (aOR 2.3, 95% CI 1.4 to 3.9), to be multiparous (aOR 1.6, 95% CI 1.1 to 2.2), to have a multiple pregnancy (aOR 5.2, 95% CI 1.9 to 13.8) and to be from a black or other minority ethnic group (aOR 1.6, 95% CI 1.1 to 2.3). Younger smokers had a raised odds of admission with confirmed AH1N1v influenza (aOR 4.2, 95% CI 2.0 to 8.9) when compared with older non-smokers.

Treatment within 2 days of symptom onset was associated with an 84% reduction in the odds of admission to an intensive therapy unit (ITU) (OR 0.16, 95% CI 0.08 to 0.34); women admitted to ITU were more likely to be obese (aOR 3.4, 95% CI 1.2 to 9.2) than women who were not admitted to an ITU.

Sixty-three per cent of hospitalised women had completed their pregnancies at the time of reporting. Women admitted to hospital with AH1N1v infection were more likely to deliver preterm; a conservative estimate accounting for the high proportion of women who are undelivered suggests a three times increased risk compared with an uninfected population cohort (OR 3.1, 95% CI 2.1 to 4.5).

Conclusions

Earlier treatment with antiviral agents is associated with improved outcomes for pregnant women. Further actions are needed in future pandemics to ensure that antiviral agents and vaccines are provided promptly to pregnant women, particularly in the primary care setting.

Maternal obesity during pregnancy is associated with both admission to hospital with confirmed infection and critical illness from AH1N1v infection. This highlights the importance of ongoing work to support obesity prevention at a community level.

Maternal smoking, particularly in younger mothers, is also associated with admission with

AH1N1v infection in pregnancy. Smoking in pregnancy is associated with a number of risks to both mother and fetus and thus prevention programmes continue to be important.

Women with asthma and other comorbidities are more likely to present in primary care or be admitted to hospital with AH1N1v infection in pregnancy. Clinicians should be aware of this association and work to ensure that women with coexisting illnesses in pregnancy are treated appropriately.

Data on outcomes of pregnancy in women admitted to hospital with confirmed AH1N1v influenza are, as yet, incomplete. However, there appears to be a significantly increased risk of preterm delivery, which may impact on service provision in a future pandemic.

Further research is needed on longer-term outcomes for infants exposed to AH1N1v influenza, antiviral drugs or vaccines during pregnancy. This includes studies of the effects of these factors on:

1. fetal development and congenital malformations
2. postnatal development
3. potentially associated conditions, such as childhood leukaemia.

Publication

Yates L, Pierce M, Stephens S, Mill A, Spark P, Kurinczuk J, *et al.* Influenza A/H1N1v in pregnancy: an investigation of the characteristics and managementof affected women and the relationship to pregnancy outcomes for mother and infant. *Health Technol Assess* 2010;**14**(34): 109–182.

The National Institute for Health Research

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This themed issue of the *Health Technology Assessment* journal series contains a collection of research commissioned by the NIHR as part of the Department of Health's (DH) response to the H1N1 swine flu pandemic. The NIHR through the NIHR Evaluation Trials and Studies Coordinating Centre (NETSCC) commissioned a number of research projects looking into the treatment and management of H1N1 influenza.

NETSCC managed the pandemic flu research over a very short timescale in two ways. Firstly, it responded to urgent national research priority areas identified by the Scientific Advisory Group in Emergencies (SAGE). Secondly, a call for research proposals to inform policy and patient care in the current influenza pandemic was issued in June 2009. All research proposals went through a process of academic peer review by clinicians and methodologists as well as being reviewed by a specially convened NIHR Flu Commissioning Board.

The final reports from these projects have been peer reviewed by a number of independent expert referees before publication in this journal series.

Criteria for inclusion in the HTA journal series

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reports in this themed issue were funded through the Cochrane Collaboration; the Health Services Research programme (HSR); the Health Technology Assessment programme (HTA); the Policy Research Programme (PRP); and the Service Delivery and Organisation Programme (SDO).

The Cochrane Collaboration is an international not-for-profit and independent organisation, dedicated to making up-to-date, accurate information about the effects of health care readily available worldwide. It produces and disseminates systematic reviews of health-care interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions. Cochrane reviews and the Cochrane Central Register of Controlled Trials are published and updated in *The Cochrane Library* (www.cochranelibrary.com).

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The PRP provides the evidence base for policy development on public health and social care issues. It funds research in three main ways: 5-year programmes of research in 16 research units, a primary-care research centre, a public health research consortium, and a surveillance unit; programmes of interlinked studies on key policy initiatives; and single projects and literature reviews.

The SDO programme commissions research evidence that improves practice in relation to the organisation and delivery of health care. It also builds research capability and capacity amongst those who manage, organise and deliver services – improving their understanding of the research literature and how to use research evidence.

The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report. The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the Department of Health.

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