Vaccine 35 (2017) 521–528

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Pregnancy as a risk factor for severe outcomes from influenza virus infection: A systematic review and meta-analysis of observational studies

Dominik Mertz [a,b,c,d], Johanna Geraci [e], Judi Winkup [b], Bradford D. Gessner [f], Justin R. Ortiz [g], Mark Loeb [b,c,d,*]

[a] Department of Medicine, McMaster University, Hamilton, ON, Canada
[b] Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada
[c] Department of Pathology and Molecular Medicine, McMaster University, Hamilton, ON, Canada
[d] Michael G. DeGroote Institute for Infectious Diseases Research, McMaster University, Hamilton, ON, Canada
[e] Department of Family Medicine (Midwifery), McMaster University, Hamilton, ON, Canada
[f] Agence de Médecine Preventive, Paris, France
[g] Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland

ARTICLE INFO

Article history:
Received 13 July 2016
Received in revised form 24 November 2016
Accepted 8 December 2016
Available online 23 December 2016

Keywords:
Influenza
Pregnancy
Risk
Systematic review
Vaccination

ABSTRACT

Background: Pregnancy is considered to be an important risk factor for severe complications following influenza virus infection. As a consequence, WHO recommendations prioritize pregnant women over other risk groups for influenza vaccination. However, the risk associated with pregnancy has not been systematically quantified.
Purpose: Systematic review and meta-analysis of observational studies that reported on pregnancy as a risk factor for severe outcomes from influenza virus infection.
Data source: MEDLINE, EMBASE, CINAHL, and CENTRAL up to April 2014.
Data selection: Studies reporting on outcomes in pregnant women with influenza in comparison to non-pregnant patients with influenza. Outcomes included community-acquired pneumonia, hospitalization, admission to intensive care units (ICU), ventilatory support, and death.
Data extraction: Two reviewers conducted independent screening and data extraction. A random effects model was used to obtain risk estimates. Ecological studies were summarized descriptively.
Data synthesis: A total of 142 non-ecological and 10 ecological studies were included. The majority of studies (n = 136, 95.8%) were conducted during the 2009 influenza A (pH1N1) pandemic. There was a higher risk for hospitalization in pregnant versus non-pregnant patients infected with influenza (odds ratio [OR] 2.44, 95% CI 1.22–4.87), but no significant difference in mortality (OR 1.04, 95% CI 0.81–1.33) or other outcomes. Ecologic studies confirmed the association between hospitalization risk and pregnancy and 4 of 7 studies reported higher mortality rates in pregnant women.
Limitations: No studies were identified in which follow-up began prior to contact with the healthcare system and lack of adjustment for confounding factors.
Conclusions: We found that influenza during pregnancy resulted in a higher risk of hospital admission than influenza infection in non-pregnant individuals, but that the risk of mortality following influenza was similar in both pregnant and non-pregnant individuals.

Abbreviations: CI, confidence interval; CENTRAL, Cochrane Central Register of Controlled Trials; ICU, intensive care units; NOS, Newcastle Ottawa Scale; OR, odds ratio; RR, risk ratio; WHO, World Health Organization.

* Corresponding author at: Departments of Pathology and Molecular Medicine & Clinical Epidemiology and Biostatistics, McMaster University, MDCL 3203, 1200 Main St W, Hamilton, ON L8N 3Z5, Canada.
E-mail address: loebm@mcmaster.ca (M. Loeb).

http://dx.doi.org/10.1016/j.vaccine.2016.12.012
0264-410X/

Contents

1. Introduction

It is estimated that three to five million cases of severe influenza illness occur annually worldwide, resulting in 250,000–500,000 deaths [1]. Identifying groups at risk for severe influenza disease is essential to prevention and control efforts.

World Health Organization (WHO) influenza vaccine policy recommendations aim to protect high-risk groups from severe disease. In a 2012 update, WHO recommended for the first time that one risk group, pregnant women, be prioritized over others [2]. This was based on numerous factors, including reports of higher influenza disease risk in pregnant women, the possibility to protect young infants via placental antibody transfer, vaccine safety and effectiveness, and programmatic opportunities [2].

The influenza disease risk posed to pregnant women has never been comprehensively addressed in a systematic review. We conducted a systematic review to quantify the association between pregnancy and severe influenza disease and to summarize the evidence for pregnancy as a risk factor for severe influenza disease.

2. Materials and methods

All the methods outlined below were specified *a priori*.

2.1. Data sources and searches

We searched MEDLINE (since 1966; Supplementary Table 1), EMBASE (since 1980), CINAHL (since 1982), and the Cochrane Central Register of Controlled Trials (CENTRAL). We also searched reference lists of identified articles and review articles. We included relevant studies selected in our previous systematic review on risk factors for severe outcomes from influenza (search up to March 25, 2011 [3]), and updated the search using the same search strategy through April 25, 2014 (Fig. 1).

2.2. Study selection

Studies reporting on pregnancy as a risk factor for the following severe outcomes following influenza: community-acquired pneumonia, death from all causes or related to influenza, hospitalization from all causes or related to influenza, admission to an intensive care unit (ICU) related to influenza, and/or need for mechanical ventilatory support. Study designs included observational studies with a comparator arm of non-pregnant patients with evidence of influenza virus infection. Ecologic studies, also included, were defined as studies that collected data at a group rather than at an individual level, or in which numerators or denominators were imputed or estimated. Non-English language articles were excluded in the search update, based on the limited value demonstrated in the first search [3].

Evidence for influenza virus infection was based on laboratory-confirmed influenza virus infection defined by at least one of the following: serology, viral culture, nucleic acid amplification testing, or antigen detection. Representation of non-laboratory defined evidence, such as influenza-like illness during known influenza circulation, although eligible for the review, was negligible (n = 3 studies, 2.1%). Studies on avian influenza A virus infection in humans were excluded.

2.3. Data extraction and quality assessment

Two reviewers independently screened titles, abstracts and full text articles, extracted data using a standardized and pilot-tested database, and assessed risk of bias. Any disagreement between reviewers was resolved by consensus or arbitration by a third reviewer.

We used the Newcastle Ottawa Scale (NOS) to assess risk of bias for individual-level studies [4]. With this scale, a maximum of 9 points was allocated in four domains: a maximum of 4 points for selection of study groups, 2 points for comparability of groups, and up to 3 points for ascertainment of exposure and outcomes. In order to evaluate publication bias, funnel-plots were made if ten or more studies had been included. The overall quality of evidence was assessed using the recently published GRADE framework for evidence about prognosis [5].

2.4. Data synthesis and analysis

We performed a meta-analyses using a random effects model in Review Manager 5.0 (Cochrane Collaboration) [6] to obtain a summary estimate of the average effect with its 95% confidence interval (CI). Given the small number of non-cohort observational studies, we pooled all design types. Ecologic studies were only synthesized qualitatively.