Vaccine 35 (2017) 4811–4816

Contents lists available at ScienceDirect

Vaccine

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

Estimating influenza disease burden among pregnant women: Application of self-control method

Satoko Ohfuji [a,*], Masaaki Deguchi [b], Daisuke Tachibana [c], Masayasu Koyama [c], Tetsu Takagi [d], Takayuki Yoshioka [e], Akinori Urae [f], Wakaba Fukushima [a], Yoshio Hirota [a,g,h], for the Osaka Pregnant Women Influenza Study Group [1]

[a] Department of Public Health, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka-city, Osaka 545-8585, Japan
[b] Department of Obstetrics and Gynecology, Kishiwada City Hospital, 1001, Gakuhara-cho, Kishiwada-city, Osaka 596-8501, Japan
[c] Department of Obstetrics and Gynecology, Osaka City University Graduate School of Medicine, 1-4-3, Asahi-machi, Abeno-ku, Osaka-city, Osaka 545-8585, Japan
[d] Takagi Ladies Clinic, 1-13-44, Kamihigashi, Hirano-ku, Osaka-city, Osaka 547-0002, Japan
[e] Osaka Branch, Mediscience Planning Inc., 3-6-1, Hiranomachi, Chuo-ku, Osaka-city, Osaka 541-0052, Japan
[f] Head Office, Mediscience Planning Inc., 1-11-44, Akasaka, Minato-ku, Tokyo 107-0052, Japan
[g] College of Healthcare Management, 960-4, Takayanagi, Setaka-machi, Miyama-shi, Fukuoka 835-0018, Japan
[h] Clinical Epidemiology Research Center, Medical Co. LTA, 3-5-1, Kashii-Teriha, Higashi-ku, Fukuoka 813-0017, Japan

ARTICLE INFO

Article history:
Received 18 May 2016
Received in revised form 2 September 2016
Accepted 4 October 2016

Keywords:
Influenza
Disease burden
Pregnant women
Self-control method

ABSTRACT

To evaluate influenza disease burden among pregnant women, an epidemiological study using the self-control method was conducted. Study subjects were 12,838 pregnant women who visited collaborating maternity hospitals and clinics in Osaka Prefecture, Japan, before the 2013/14 influenza season. As a study outcome, hospitalization due to respiratory illnesses between the 2010/11 and 2013/14 seasons was collected from each study subject through a baseline survey at the time of recruitment and a second survey after the 2013/14 season. The hospitalization rates during pregnancy and non-pregnancy periods was calculated separately. To compare the hospitalization rate during pregnancy with that during non-pregnancy within the same single study subject, Mantel-Haenzel rate ratios (RR_{MH}) were calculated.

During the four seasons examined in this study, nine and 17 subjects were hospitalized due to respiratory illnesses during pregnancy and non-pregnancy periods, respectively. The hospitalization rate was 2.54 per 10,000 woman-months during pregnancy and 1.08 per 10,000 woman-months during non-pregnancy. The RR_{MH} for the hospitalization rate during pregnancy compared with that during non-pregnancy was 4.30 (95% confidence interval, 1.96–9.41).

Our results suggest that during the influenza season, pregnant women have a higher risk than non-pregnant women for hospitalization due to respiratory illnesses. The self-control method appears to be an appropriate epidemiological method for evaluating the disease burden of influenza among pregnant women.

1. Introduction

In November 2012, the World Health Organization recommended that pregnant women should be the highest priority group for influenza vaccination. This recommendation was based on compelling evidence regarding the substantial risk of severe disease in pregnant women, the effectiveness of vaccines against severe disease, and the secondary protection of vaccination for infants under 6 months of age [1]. However, in Japan, during the influenza A(H1N1)pdm09 pandemic, influenza-related hospitalization reported among pregnant women was only 74 cases [2] (cf. the number of annual births was 1,070,035 in 2009) [3], which was lower than that in other countries. Besides, no specific data regarding seasonal influenza disease burden among pregnant women has been reported. Therefore, before the highest priority group for influenza vaccination in Japan can be identified, information on seasonal influenza disease burden among pregnant women must be obtained.

Abbreviations: OR, odds ratio; CI, confidence interval.

* Corresponding author.
E-mail address: satop@med.osaka-cu.ac.jp (S. Ohfuji).

[1] Other members of the study group are listed in the Appendix.

http://dx.doi.org/10.1016/j.vaccine.2017.07.006
0264-410X/

The objective of this study was to investigate whether pregnancy is a high risk condition for hospitalization due to severe influenza. To examine this hypothesis, some might firstly consider the feasibility of conventional epidemiological methods such as cohort or case-control studies. In the countries that have established databases capable of identifying cohorts and hospitalization of pregnant women, cohort and case-control studies can be used to examine our hypothesis. For example, Neuzil et al. conducted a case-control study using a database of women aged 15–44 years enrolled in the Tennessee Medicaid program. They found that compared with postpartum women, those at 14–42 weeks' gestation had increased odds ratios for influenza-related hospitalization [4]. However, under the situation that there is no available database for child-bearing aged women and their hospitalization, it is difficult to conduct such case-control study, and even more cohort study.

As an alternative, a new epidemiological method called the "self-control method" has been proposed. The self-control method is described as a variant of the cohort study; however, as opposed to a different comparison group, it comprises a comparison of the person-time experience between the exposed and the unexposed period within the same study subjects [5]. To date, this study design has primarily been used to investigate the association between vaccines and adverse events [6,7]; however, it has also been widely used to investigate several issues in relation to infectious diseases [8]. To apply the self-control method in an epidemiological study, the study hypothesis needs to satisfy in principle the following three points: (1) exposure status is changing according to the time experience of the subjects; (2) the effect of exposure is transient and only continues for a brief time; and (3) outcomes must be characterized by an abrupt onset [5]. In our study hypothesis, pregnancy status (i.e., exposure) varies from time to time within the subject, and its related effects only continue within a period of about 10 months. In addition, influenza-related hospitalization (i.e., outcome) occurs suddenly. Thus, the self-control method was considered appropriate for investigating our hypothesis.

Here, we present our experience using the self-control method to examine whether pregnancy is a high risk condition for influenza-related hospitalization.

2. Materials and methods

2.1. Study subjects

The Osaka Pregnant Women Influenza Study was conducted at 117 collaborating maternity hospitals and clinics in Osaka Prefecture, Japan. Between September 2013 and January 2014 (i.e., recruitment), pregnant women who had been under clinical follow-up for pregnancy at these hospitals and clinics were invited to participate in this study. Eligible subjects were women at any stage of pregnancy at the time of recruitment. A total of 20,420 subjects agreed to participate and were enrolled. All study subjects verbally provided their informed consent prior to participation.

The study protocol was approved by the Ethics Committees at the Osaka City University Faculty of Medicine and the collaborating hospitals, and was performed in accordance with the Declaration of Helsinki.

2.2. Information collection

To collect information on hospitalization during four influenza seasons from 2010/11 to 2013/14 as a study outcome, a baseline and a second survey were conducted on each study subject using self-administered questionnaires. The baseline survey was carried out at the time of recruitment. The baseline questionnaire was composed of items regarding history of influenza vaccination, physician-diagnosed influenza, and hospitalization (as a study outcome) since January 2011, as well as the following background characteristics: demographic factors such as age and date of birth; gestational week at the time of recruitment, expected delivery date; height and weight before pregnancy; influenza-related underlying illnesses before pregnancy (e.g., asthma, chronic respiratory disease, hypertension, heart disease, renal disease, liver disease, anemia, blood disease, diabetes mellitus, diseases of the thyroid gland, diseases of the nerve or muscle systems, immunodeficiency), underlying illnesses in obstetrics and gynecology (myoma uteri, endometriosis, ovarian disease, infertility, etc.), mental disorders, allergic disorders; smoking and alcohol drinking habits; and duration of residence in Osaka Prefecture. Next, after the 2013/14 influenza season ended in May 2014, a second survey was conducted on the study subjects each time they underwent a regular medical examination for their pregnancy. In the case that they had already delivered during the season and were not under clinical follow-up at the hospitals, a questionnaire was sent by mail to their residence. The questionnaire for the second survey was composed of items regarding influenza vaccination, physician-diagnosed influenza, and hospitalization (as a study outcome) since the time of the baseline survey, and the delivery date. In both surveys, subjects who answered "hospitalized" were also asked to provide the reason for hospitalization and the hospital name.

The self-reported information on hospitalization in these two surveys was confirmed by hospital records at the reported hospitals. Based on the reported hospital name, we sent the questionnaire to physicians in the hospitals, and collected information for confirmation, including date of admission, date of discharge, name of disease that led to hospitalization, and laboratory data at the time of hospitalization.

In addition, a structured questionnaire, completed by the obstetrician-in-charge after delivery, was used to collect information about the clinical course of pregnancy for each study subject. The questionnaire gathered information about: pregnancy-induced complications during pregnancy, pregnancy outcome (i.e., abortion, dead birth, or live birth) and date; and reproductive history (i.e., parity number, delivery date, and gestational week for older children).

2.3. Outcome definitions and epidemic

The study outcome was defined as hospitalization due to respiratory illnesses that occurred during an influenza epidemic. The period of the influenza epidemic was determined using surveillance data from Osaka Prefecture [9–12], and defined as the period in which the weekly number of influenza patients remained at $\geq$5 per sentinel. Based on the epidemic curve (Fig. 1), the epidemic periods were from the second week to the 17th week of 2011 in the 2010/11 season, from the second week to the 14th week of 2012 in the 2011/12 season, from the second week to the 12th week of 2013 in the 2013/14 season, and from the second week to the 13th week of 2014 in the 2013/14 season.

Hospitalization due to respiratory illnesses was extracted from all reported hospitalization during the epidemic period when the following disease names were noted in the hospital records or reported on the self-administered questionnaires: influenza, pneumonia, bronchitis, common cold, infectious disease, asthma, high fever, tonsillitis, otitis media, or sinusitis. The selected disease names were adapted from those used in the previous studies [4,8].