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

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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.

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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].

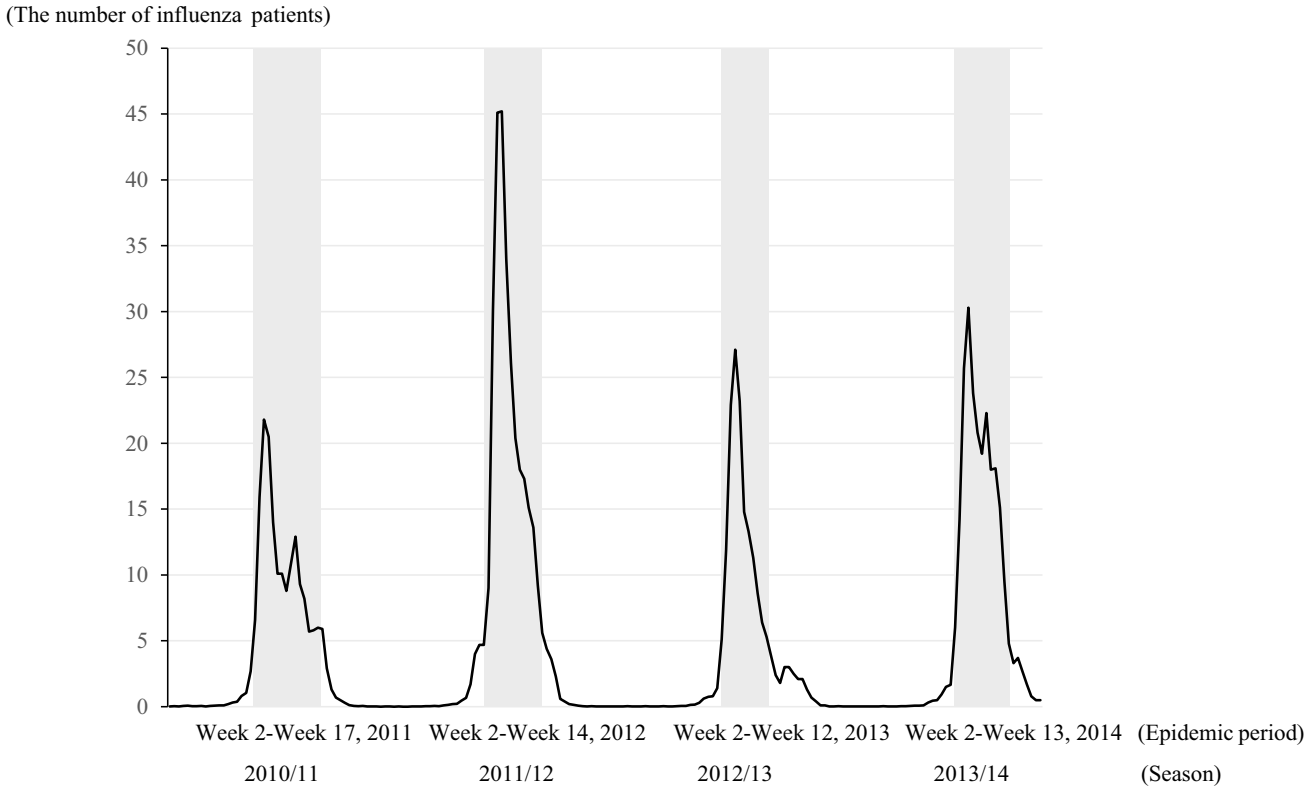

Fig. 1. Weekly number of influenza patients reported by sentinels in Osaka Prefecture during influenza seasons.

2.4. Statistical analysis

The number of woman-days for each influenza season was counted from the beginning of each epidemic period until the date of hospitalization due to respiratory illnesses or the end of the epidemic period, whichever came first. Next, based on the information regarding the date and gestational week of delivery experiences, the number of woman-days was divided into pregnancy and non-pregnancy period for each study subject.

To compare the hospitalization rate between the pregnancy and non-pregnancy periods within the same single study subject, Mantel-Haenzel rate ratio (RR_{MH}) and 95% confidence intervals (CI) were calculated [13,14]. Analyses were conducted using woman-days, but the results were translated to woman-months for ease of interpretation. All tests were two-sided. All analyses were performed using SAS version 9.3 software (SAS Institute, Cary, NC, USA).

3. Results

Among the 20,420 study subjects enrolled, 12,838 subjects responded to both the baseline and the second surveys, and included in the analysis. The characteristics of the subjects are shown in Table 1. Median age was 32 years, and median gestational week at the time of recruitment was 23.0 weeks. One third of the subjects had any underlying illnesses, and the proportion of subjects with influenza-related underlying illnesses was 15%. Only a small number of subjects had pregnancy-induced complications such as hospitalization due to threatened abortion (5%), hypertension (3%), diabetes (3%), intrauterine growth restriction (3%) or multiple pregnancy (2%). Most of the subjects had lived in Osaka Prefecture since three years or more before, suggesting similar recent exposure to the influenza virus.

The weekly number of influenza patients reported from sentinels in Osaka Prefecture since January 2011 are shown in Fig. 1. The magnitude and length of the epidemic period in the 2013/14 season was similar to that in the 2012/13 season. The epidemic in the 2011/12 season was the largest of the 10 most recent seasons, and that in the 2010/11 season was smaller but longer continuing until May 2011.

Table 2 shows the number of hospitalizations and the hospitalization rate in each influenza season according to pregnancy status. In the 2013/14 season, eight subjects were admitted to hospital due to respiratory illnesses during pregnancy. The hospitalization rate was 4.04 per 10,000 woman-months, which was higher than that during the non-pregnancy period in any of the four influenza season examined in this study. During the four seasons, a total of nine subjects were admitted to hospital due to respiratory illness during pregnancy, whereas 17 were hospitalized during non-pregnancy. 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% CI, 1.96–9.41).

When limited to subjects who had lived in Osaka Prefecture since three years or more before, these results were almost unchanged. During the four seasons, the hospitalization rate was 2.59 per 10,000 woman-months during pregnancy and 1.04 per 10,000 woman-months during non-pregnancy. The RR_{MH} for hospitalization rate during pregnancy compared with that during non-pregnancy was 5.17 (95%CI, 2.14–12.5).

4. Discussion

In this study, which utilized a specific epidemiological technique called the “self-control method”, we found that the rate of

Table 1
Baseline characteristics among pregnant women.

Variables		N	n (%) or median (range)
Age at the time of recruitment (years)	Median (range)	12,838	32.0 (15–51)
Gestational age at the time of recruitment (weeks)	Median (range)	12,831	23.0 (4–42)
Body mass index before pregnancy (kg/m^2)	Median (range)	12,646	20.4 (9.1–62.5[a])
Underlying illnesses before pregnancy	Present	12,838	3978 (31)
Influenza-related	Present	12,838	1909 (15)
Obstetrics and gynecology-related	Present	12,838	2329 (18)
Mental disorders	Present	12,838	339 (3)
Allergic disorders	Present	12,838	53 (0.4)
Pregnancy-induced complications			
Hospitalization due to threatened abortion	Present	11,138	588 (5)
Pregnancy-induced hypertension	Present	11,127	375 (3)
Gestational diabetes	Present	11,152	310 (3)
Intrauterine growth restriction	Present	11,135	315 (3)
Multiple pregnancy	Present	11,186	168 (2)
Intrauterine infection	Present	11,128	98 (0.9)
Placenta previa	Present	9453	56 (0.5)
Placental abruption	Present	11,141	43 (0.4)
Smoking habit			
Before pregnancy	Present	12,618	2376 (19)
During pregnancy	Present	11,974	386 (3)
Drinking habit			
Before pregnancy	Present	12,613	4790 (38)
During pregnancy	Present	11,990	82 (0.7)
Duration of residence in Osaka Prefecture (years)	3 years or more	12,131	11,045 (91)

[a] Including 9 subjects whose body weight before pregnancy was less than 35.0 kg and 14 subjects whose body weight before pregnancy was more than 100.0 kg. When excluding these 23 subjects, body mass index before pregnancy ranged from 14.1 to 40.2 kg/m^2.

the hospitalization during pregnancy was 4.3 times higher than that during non-pregnancy. This suggests that pregnant women are at a higher risk than non-pregnant women for hospitalization due to respiratory illnesses during the influenza season. To the best of our knowledge, only one study has applied the self-control method to investigate hospitalization due to respiratory illnesses during the influenza season among pregnant women. That study, which examined data from pregnant women enrolled in the Nova Scotia Atlee Perinatal Database in Canada, reported that the hospitalization rate among pregnant women was 1.7 and 5.1 times higher during the first and third trimesters, respectively, than that of the same subjects' non-pregnancy periods [8]. Other cohort or case-control studies, as well as those using descriptive epidemiology, also found that pregnant women were at 3–22 times higher risk for influenza-related hospitalization [17–19] or ICU hospitalization [15–17] compared with non-pregnant women. Taken together, the self-control method seemed to provide comparable results to those using other study designs, and the results from all of these studies suggest that pregnancy is a risk factor for influenza-related hospitalization.

Regarding possible causal mechanisms, a previous study suggested that during pregnancy, the immune system adapts to tolerate a genetically foreign fetus, and this immunologic adaptation results in an increased risk for influenza-related complications. Another possible interpretation is that physiological changes during pregnancy, including increased heart rate, stroke volume, oxygen consumption, and decreased lung capacity might put women at an increased risk for severe influenza illness [20–22]. Therefore, our results seem reasonable in terms of the mechanisms.

However, in our study, the observed hospitalization rate during pregnancy was 2.54 per 10,000 woman-months, and that during non-pregnancy was 1.08 per 10,000 woman-months; these rates were lower than those reported in other countries [4,8]. For example, the Canadian study reported that the hospitalization rate (per 10,000 woman-months) among women without comorbidities was 2.4 during the first trimester, 3.0 during the second trimester, 7.4 during the third trimester, and 1.4 during non-pregnancy [8]. The discrepancy in the results between our study and the Canadian study might be partly explained by the estimated influenza vaccination coverage among the study subjects. In the Canadian study, only 2.6% of pregnant women and 6.7% of non-pregnant women were immunized [8], whereas vaccination coverage in our study subjects was estimated to be 45% in the 2013/14 season, 38% in the 2012/13 season, and 37% in the 2011/12 season. Therefore, the relatively higher vaccination coverage among our study subjects might have led to lower hospitalization rates, irrespective of pregnancy status.

Our study had several methodological advantages. First, in the self-control method, since hospitalization rates during pregnancy and non-pregnancy were compared in the same study subjects, the effect of confounding factors would be almost negligible. Second, the information on hospitalization rates was highly reliable, because the accuracy of the data on reported hospitalization was guaranteed by contacting the relevant hospital of admission. In fact, we were able to obtain the information from their hospital records in 69% of the reported hospitalizations. The information obtained from their hospital records proved the reported hospitalization to be right through the agreement of data on admission date and disease name led to hospitalization for almost all verified hospitalizations. Third, since we enrolled women from a single prefecture, our study subjects are expected to have shared a similar exposure to the influenza virus.

However, when interpreting the present results, the following limitations should be kept in mind. First, the self-control method could not control the effect of time-dependent factors, although

Table 2
Hospitalization due to respiratory illnesses during influenza season according to pregnancy status.

Influenza season	Pregnancy status	Observation period (woman-months)	No. of hospitalizations	Rate per 10,000 woman-months
2013/14	Pregnant	19,785	8	4.04
	Nonpregnant	18,712	2	1.07
2012/13	Pregnant	4398	0	0
	Nonpregnant	34,109	4	1.17
2011/12	Pregnant	3874	1	2.58
	Nonpregnant	47,464	5	1.05
2010/11	Pregnant	7418	0	0
	Nonpregnant	57,186	6	1.05
2010/11∼2013/14	Pregnant	35,475	9	2.54
	Nonpregnant	157,471	17	1.08

some behaviors or situations might differ between the pregnancy and non-pregnancy periods. For example, pregnant women typically avoid going to crowded places where many people mingle. These health-conscious behaviors during pregnancy, if any, could be expected to result in an underestimation of the association between pregnancy and the risk of hospitalization due to respiratory illnesses. Second, since the present study subjects were pregnant women under clinical follow-up before the 2013/14 season, their pregnancy period occurred during the 2013/14 season. In other words, if they were pregnant for the first time in the 2013/14 season, their data during the previous seasons (i.e., the 2010/11 to 2012/13 seasons) only contributed to those during the non-pregnancy period in the 2010/11 to 2012/13 seasons. Thus, fewer pregnancies were observed in the 2010/11 to 2012/13 seasons, which resulted in fewer hospitalized cases and unstable hospitalization rates during pregnancy in the 2010/11 to 2012/13 seasons. On the other hand, most of the pregnancy period were concentrated in the 2013/14 influenza season, and thus the hospitalization rate during pregnancy was likely affected by the influenza activity in the 2013/14 season. In that situation, if the 2013/14 season was a larger epidemic season than the other seasons examined in this study, we would not be able to interpret whether the higher hospitalization rate observed during pregnancy was explained by the pregnancy status itself or by the larger influenza epidemic in the 2013/14 season. Fortunately, however, the magnitude of influenza epidemic in the 2013/14 season was similar to that in the 2012/13 season, and was smaller than that in the 2011/12 season. In addition, the hospitalization rate during the pregnancy period in the 2013/14 season was higher than that during the non-pregnancy period in any of the past three seasons, including the 2011/12 season, which was the largest epidemic in the past 10 seasons. Thus, it is not conceivable that the magnitude of influenza epidemic was enough to explain the observed risk of hospitalization during pregnancy. Third, although our results suggested that pregnancy was a high risk condition for hospitalization due to respiratory illnesses, the magnitude of this risk may be biased upward if clinicians had a lower threshold for admitting pregnant women as a precaution. However, this upward bias could also have occurred even in the other study designs unless care providers have identical thresholds for admitting pregnant women. Fourth, the outcome of the present study, hospitalization due to respiratory illnesses during an influenza epidemic, might be less specific to influenza compared with laboratory confirmation, and thus some outcome misclassification might be concerned. However, we considered that this misclassification, if any, should not differ between those in the pregnancy and non-pregnancy periods. Such misclassification, if any, could be expected to result in an underestimation of the association between pregnancy and the risk of hospitalization because of the diluting effect, and was therefore considered not to materially affect the validity of the present results. Finally, since the study subjects were pregnant women under clinical follow-up at hospitals in Osaka Prefecture, there may be some concern about the generalizability of the study results. Therefore, additional studies in other areas or influenza seasons would be desirable to confirm the validity of the present results.

Despite these limitation, the results of our study using the self-control method support previous findings that pregnancy is a high risk condition for hospitalization due to respiratory illnesses during the influenza season. Although the self-control method is used less frequently than other epidemiological methods such as cohort or case-control studies, our results suggest that the self-control method is appropriate for evaluating seasonal influenza disease burden among pregnant women.

Conflict of interest

None.

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Appendix A

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