OBSTETRICS

Severity of influenza and noninfluenza acute respiratory illness among pregnant women, 2010–2012

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OBJECTIVE: The objective of the study was to identify characteristics of influenza illness contrasted with noninfluenza acute respiratory illness (ARI) in pregnant women.

STUDY DESIGN: ARI among pregnant women was identified through daily surveillance during 2 influenza seasons (2010-2012). Within 8 days of illness onset, nasopharyngeal swabs were collected, and an interview was conducted for symptoms and other characteristics. A follow-up telephone interview was conducted 1-2 weeks later, and medical records were extracted. Severity of illness was evaluated by self-assessment of 12 illness symptoms, subjective ratings of overall impairment, highest reported temperature, illness duration, and medical utilization.

RESULTS: Of 292 pregnant women with ARI, 100 tested positive for influenza viruses. Women with influenza illnesses reported higher symptom severity than those with noninfluenza ARI (median score, 18 vs 16 of 36; $P < .05$) and were more likely to report severe subjective feverishness (18% vs 5%; $P < .001$), myalgia (28% vs 14%; $P < .005$), cough (46% vs 30%; $P < .01$), and chills (25% vs 13%; $P < .01$). More influenza illnesses were associated with fever greater than 38.9°C (20% vs 5%; $P < .001$) and higher subjective impairment (mean score, 5.9 vs 4.8; $P < .001$). Differences in overall symptom severity, fever, cough, chills, early health care–seeking behavior, and impairment remained significant in multivariate models after adjusting for study site, season, age, vaccination status, and number of days since illness onset.

CONCLUSION: Influenza had a greater negative impact on pregnant women than noninfluenza ARIs, as indicated by symptom severity and greater likelihood of elevated temperature. These results highlight the importance of preventing and treating influenza illnesses in pregnant women.

Key words: acute respiratory illness, illness severity, influenza, influenza vaccine, pregnancy

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Pregnant women are at greater risk of hospitalization and serious complications from influenza virus illness than nonpregnant women.[1] Women in their third trimester[2,3] and those with comorbid conditions[4,5] are especially vulnerable to hospitalization. Little is known about the clinical characteristics and severity of laboratory-confirmed influenza illness among nonhospitalized pregnant women or how influenza illness differs from noninfluenza acute respiratory illness (ARI) in pregnant women.

In a previous study, we examined the relationship between vaccination status and influenza positivity.[6] This study examined symptom severity and

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duration of laboratory-confirmed influenza illness among pregnant women compared with noninfluenza ARI during 2 influenza seasons. Although the number of confirmed influenza cases was limited, we conducted exploratory analyses to assess whether influenza illness severity was higher among the women with comorbid conditions or in their third trimester and whether vaccination with a seasonal influenza vaccine was associated with less severe illness among those women with vaccine failure.

Materials and Methods

Recruitment and eligibility

The study methodology[7] and recruitment of the study participants have been described in detail previously.[6] Eligible participants were Kaiser Permanente members who made at least 1 prenatal visit in the Portland, OR (Kaiser Permanente Northwest), or San Francisco, CA, metropolitan areas (Kaiser Permanente Northern California) during the study period, had an expected delivery date after Nov. 15, 2010, and were at least 16 years of age for Kaiser Permanente Northwest or at least 18 years of age for Kaiser Permanente Northern California. The study instruments, procedures, and written consent documents were approved by the institutional review boards at both sites.

Surveillance

The influenza season was defined by the regional/state health department and the Centers for Disease Control and Prevention influenza surveillance data. Thresholds for the beginning and end of the season were defined a priori at each site. During both study seasons, we identified potential ARIs using daily surveillance of electronic medical records (EMRs) for medically attended acute respiratory illness using *International Classification of Diseases*, ninth revision (ICD-9) codes 460-466, 480-488, and 490-491.

The women were contacted by telephone, screened for eligibility, and asked to provide written consent for study participation. Inclusion criteria included enrollment in the health plan for the study season and completion of the enrollment interview.

During the first season, weekly Internet- or telephone-based surveillance monitored the occurrence of nonmedically attended ARI among a prospective cohort of participants at both sites.[7] First-season participants were encouraged to contact staff directly if they became ill; those who did not complete a weekly surveillance report received a reminder e-mail or telephone call to assess current ARI status. For both seasons, nasopharyngeal swab specimens were collected at the homes of women with self-reported cough and fever, feverishness, or chills within 8 days of illness onset.

Participant characteristics

Sociodemographic characteristics were assessed during an enrollment interview. Health status prior to illness was assessed with 3 measures. First, overall self-rated health was assessed using a standard question on current health (poor, fair, good, very good, or excellent) on the enrollment interview.[8] Second, we identified high-risk comorbidities associated with an increased risk of influenza complications by the presence, during 2 or more visits over 1 year prior to conception, of the following conditions: cancer, diabetes mellitus, neurological disorders, chronic pulmonary disease, chronic cardiac disease, immunosuppressive disorders, and chronic renal disease.[9] Third, pregnancy complications, from conception to start of surveillance, were identified from EMRs, using ICD-9 codes related to adverse pregnancy outcomes. All ICD-9 codes are available upon request. Obesity was defined by body mass index, calculated using self-reported prepregnancy weight and height.

Illness characteristics

Illness characteristics were assessed during an illness episode interview at specimen collection and again at a follow-up telephone contact approximately 8 days later. In the first season, participants who were still ill were called again approximately 14 days after the original illness interview.

We assessed 5 indicators of illness severity. First, participants rated the presence and severity of 12 symptoms, using a 4 point scale (0, absent; 1, mild; 2, moderate; and 3, severe). Ten participants who initially reported a cough at the screening interview described a cough as absent during their illness interview; in these instances, responses were recoded as 1 (mild). All symptom ratings were summed to form a 12 symptom severity score, ranging from 1 (a single mild symptom) to 36 (all symptoms severe), as described previously.[10]

Second, participants assessed the overall subjective severity of illness from 0 (normal health) to 9 (worst possible health) and the extent of illness impairment from 0 (able to perform usual activities) to 9 (unable to do so), as described previously.[11]

Third, we examined febrile severity using the subjective severity of feverishness (mild, moderate, or severe) and the highest temperature recorded using any of the following: EMR vital signs (if the illness was medically attended), self-reported highest temperature at either the illness interview or 8−14 day follow-up interview(s), or measured temperature by visiting study staff. Severe fever was defined as 38.9°C, which represents the threshold for assessing teratogenic exposure in the fetus.

Fourth, we calculated illness duration by subtracting the illness onset date (determined from screening or illness episode interview) from the date of symptom resolution as indicated in follow-up interviews. Seventy-eight women (53 noninfluenza and 25 influenza) who either were unable to recall a recovery date or had not yet recovered when the follow-up interview occurred were excluded from our analysis of illness duration.

Fifth, we examined medical utilization and self-care as indicated by the following: (1) any or more than 1 medical visit, (2) any illness-associated hospitalization, (3) seeking health care within 2 days of onset, and (4) use of antibiotic, over-the-counter (OTC), or antiviral medications associated with the ARI as reflected in an EMR-confirmed prescription or self-reported use of a medication during the illness.

Vaccination status

Influenza vaccination status was documented by EMRs if available or by self-report if the participant was vaccinated outside the health plan; 14 (5%) were based on self-report. Participants who received seasonal influenza vaccine 14 days or more before illness onset were considered vaccinated.

Laboratory methods

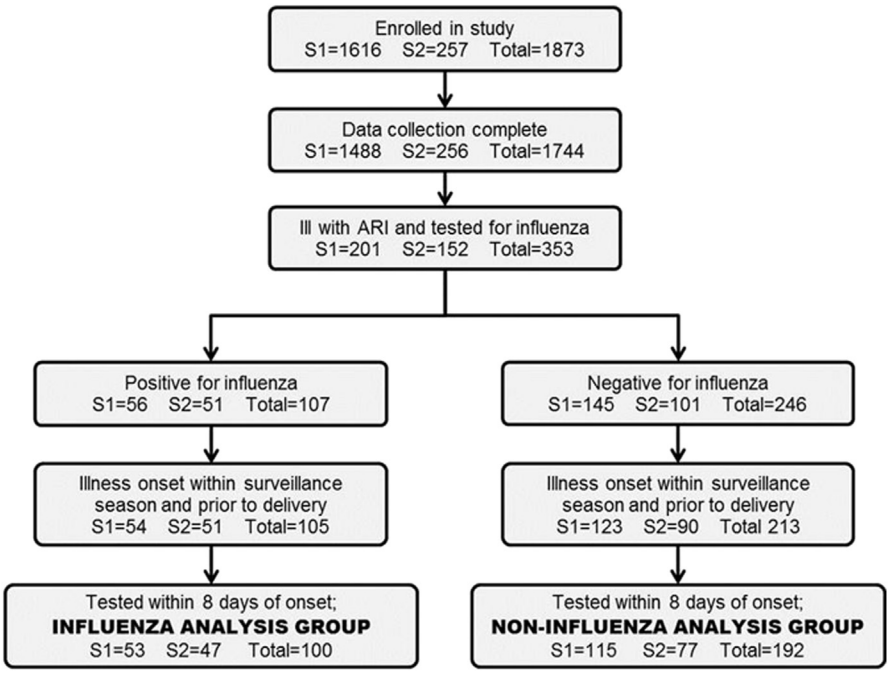
Respiratory specimens were collected using nasopharyngeal swabs and stored with transport medium in cryovials at −70°C before overnight shipping on dry ice to the Marshfield Clinic Research Foundation laboratory (Marshfield, WI). Real-time reverse transcription polymerase chain reaction (RT-PCR) was performed using primer, probes, reagents, and proficiency panel provided by the Centers for Disease Control and Prevention Influenza Division (more information at http://www.cdc.gov/flu/clsis). We excluded participants whose specimens were collected more than 8 days after illness onset from our analysis.

Statistical methods

Six participants (2%) reported having had more than 1 ARI episode during the study period. For women testing positive for an influenza virus, we used the illness episode associated with the positive result. For influenza-negative participants, we used their first illness episode.

We compared participant characteristics using the 2-tailed χ^2 or Fisher exact test for categorical outcomes and the Student t test for continuous variables. Statistically significant ($P < .05$) bivariate associations between influenza and severity indicators were followed by multivariate analyses (logistic regression) to determine whether the observed association persisted after adjusting for site, season, age, days since illness onset, and vaccination status; results were expressed as adjusted odds ratios with accompanying 95% confidence intervals. Analyses were conducted using IBM SPSS (IBM, Armonk, NY) and SAS 9.3 (SAS Institute, Cary, NC) software.

FIGURE 1
Flow chart showing enrollment and exclusions for each study season



ARI, acute respiratory illness; *S1*, season 1 (2010-2011); *S2*, season 2 (2011-2012).

Sokolow. Influenza severity in pregnant women. Am J Obstet Gynecol 2015.

RESULTS

Participant and illness characteristics

Of 1873 participants enrolled in the study, 353 pregnant women with 1 or more ARIs (107 influenza and 246 noninfluenza) were identified over 2 consecutive seasons. Seven influenza illnesses and 54 noninfluenza ARIs were excluded because illness onsets were outside the surveillance season or after delivery or because specimens were collected more than 8 days after illness onset.

After limiting the analyses to a single illness episode per participant, we included 292 illnesses: 100 influenza-positive and 192 noninfluenza ARIs (Figure 1). All of these illnesses were medically attended, with the exception of 27 ARIs (8 influenza and 19 noninfluenza illnesses) identified as part of cohort surveillance during the first season. All 3 influenza viruses circulated in both seasons, although the median onset date of influenza illnesses was 3 weeks later in the second season (Feb. 22, 2011, vs March 14, 2012; Appendix; Supplemental Figure).

Influenza positivity differed by days since illness onset when the specimen was collected ($P < .05$); this difference was due to the relatively high influenza positivity on day 1 since illness onset (65%) compared with a varying range of positivity noted on days 2-8 (26-44%). Combining both seasons, 45 women had RT-PCR–confirmed A(H1N1)pdm09 virus infections, 33 had A(H3N2), 1 had an unsubtyped A virus, and 21 had influenza B virus infections.

Participant characteristics are presented in Table 1. About half of participants (54%) were white non-Hispanics, and 24% were Hispanics. At the time of illness onset, the mean age was 30.7 years, and most women were in their second (44%) or third (41%) trimester.

Women with influenza illnesses were similar to those with noninfluenza ARIs on most sociodemographic and health indicators, with 2 exceptions: women with influenza were less likely to have a preexisting comorbidity (17% vs 30%;

TABLE 1
Sociodemographic characteristics of pregnant women with influenza vs noninfluenza ARIs

Characteristics	Noninfluenza ARI (n = 192)		Influenza (n = 100)		*P* value	Total (n = 292)	
Study site							
Kaiser Permanente Northern California	111	(58)	69	(69)	NS	180	(62)
Kaiser Permanente Northwest	81	(42)	31	(31)		112	(38)
Study season							
2010-2011	115	(60)	53	(53)	NS	168	(58)
2011-2012	77	(40)	47	(47)		124	(42)
Age, y, at illness onset							
Mean ± SD	30.9	±5.8	30.5	±5.8	NS	30.7	±5.8
Race/ethnicity							
Hispanic	45	(23)	25	(25)	NS	70	(24)
White, non-Hispanic	110	(57)	48	(48)		158	(54)
Asian, non-Hispanic	14	(7)	13	(13)		27	(9)
Other, non-Hispanic	23	(12)	14	(14)		37	(13)
Trimester at illness onset date							
First (7-13 wks)	31	(16)	13	(13)	NS	44	(15)
Second (14-26 wks)	85	(44)	44	(44)		129	(44)
Third (27-42 wks)	76	(40)	43	(43)		119	(41)
Recent health history, mean days ± SD							
For how many days during past 30 days was…							
Your physical health not good?	7.1	±9.7	2.0	±4.9	< .001	5.2	±8.6
Your mental health not good?	4.8	±8.8	3.0	±5.4	NS	4.1	±7.7
Self-rated health status, at time of enrollment							
Very good or excellent	116	(61)	68	(68)	NS	184	(63)
Good	60	(31)	27	(27)		87	(30)
Fair or poor	16	(8)	5	(5)		21	(7)
High-risk comorbidities[a]							
At least 1	57	(30)	17	(17)	< .05	74	(25)
>1	23	(12)	2	(2)	< .005	25	(9)
History of asthma[b]	27	(14)	2	(2)	< .005	29	(10)
Obese (BMI >30 kg/m^2)[c]	59	(31)	15	(15)	< .05	74	(25)
High-risk pregnancy[d]	41	(21)	24	(24)	NS	65	(22)
Influenza vaccination status							
Current season[e]	112	(58)	42	(42)	< .01	154	(53)
Current season and at least 1 comorbidity	40	(21)	9	(9)	< .01	49	(17)

Data are counts (column percentage), unless otherwise indicated. *P* values are from Pearson χ^2, Fisher exact test, or Student *t* test.

ACIP, Advisory Committee on Immunization Practices; *ARI*, acute respiratory illness; *BMI*, body mass index; *ICD-9, International Classification of Diseases, ninth revision*; *NS*, not statistically significant.

[a] High-risk comorbidities, identified during 1 year prior to conception, for which influenza vaccination is recommended by the ACIP, including cancer, diabetes mellitus, neurological disorders, chronic pulmonary disease, chronic cardiac disease, immunosuppressive disorders, chronic renal disease (codes available upon request); [b] Any asthma ICD-9 code (493) in the electronic medical record within the prior year to conception; [c] BMI was calculated using self-reported prepregnancy weight and height; [d] Pregnancy complication was indicated by a medical visit associated with a subset of ICD-9 codes related to adverse pregnancy outcomes from conception through the end of the vaccine campaign for the study year (codes available upon request); [e] Current season vaccinated defined as receipt of vaccine at least 14 days prior to illness onset.

Sokolow. Influenza severity in pregnant women. Am J Obstet Gynecol 2015.

$P < .05$), including asthma (2% vs 14%; $P < .005$) or obesity before pregnancy (15% vs 31%; $P < .05$), and women with influenza reported fewer days of poor physical health in the prior 30 days (2.0 vs 7.1 days; $P < .001$). The lower influenza positivity associated with high-risk conditions and poor health remained statistically significant after adjusting for the higher influenza vaccination rate for those in poor health (values of $P < .05$).

Comparisons of influenza and noninfluenza ARI severity

Small but significant differences in symptom severity and illness impairment were observed between influenza and noninfluenza ARI. Specifically, the median summed subjective severity of 12 symptoms was 18 for influenza ARI vs 16 (of 36) for noninfluenza ARI ($P < .05$; Table 2). Women with influenza rated their illnesses as causing greater impairment to their activities than women with noninfluenza ARI (5.9 vs 4.8 on a 9 point scale; $P < .001$).

In terms of specific symptoms, women with influenza were more likely to report severe subjective feverishness (18% vs 5%; $P < .001$), myalgia (28% vs 14%, $P < .005$), cough (46% vs 30%, $P < .01$), and chills (25% vs 13%; $P < .01$; Table 3). On average, women with influenza described their cough, nasal congestion, and fatigue as severe; however, only cough was statistically more severe for those with influenza (Figure 2); myalgia, fever, and chills were more severe among those with influenza, but the mean severity rating for each of these symptoms was moderate.

More women with influenza had an elevated (≥37.8°C) or highly elevated (≥38.9°C) recorded temperature (63% and 20%, respectively) compared with women with noninfluenza ARI (24% and 5%, respectively; all $P < .001$ (Table 2). Illness duration was similar for women with influenza and noninfluenza ARI (mean, 9.3 vs 10.3, respectively).

Women with influenza sought medical care sooner: 53% within 2 days of illness onset, compared with 35% among women with noninfluenza ARI ($P < .001$; Table 2). Slightly more women with influenza reported using OTC medications (92% vs 81%; $P < .05$), but few in either group were prescribed or used antibiotic or antiviral medications. In fact, few women with influenza were prescribed antiviral medications (8%), and there was no difference in the likelihood of either group to be prescribed antibiotic medications (11% vs 16%).

In multivariate analyses adjusting for site, season, age, vaccination status, and days since illness onset, several variables showed significant differences between influenza and noninfluenza ARI (Table 4). The adjusted odds of having a temperature greater than 38.9°C or severe subjective feverishness was greater than 4-fold higher among women with influenza. The adjusted odds were 2 times higher for activity impairment, early care-seeking behavior, a higher 12 symptom severity score, severe subjective cough, and chills.

Impact of vaccination status, comorbidities, and trimester on influenza illness severity

Among 100 women with influenza illnesses, illness severity did not differ by trimester, receipt of influenza vaccine, or the presence of comorbidities (Supplemental Table). Within the same group, a temperature of 38.9°C or greater was more common among those vaccinated vs unvaccinated (40% vs 17%, $P < .01$), but the severity of subjective symptoms did not differ among those vaccinated vs unvaccinated (data not shown).

Secondary analyses

Despite the small number of influenza cases by influenza (sub)type, we conducted exploratory analyses to compare severity indicators by influenza type and subtype. The mean symptom severity score was higher for influenza B illnesses than either influenza A(H3N2) (19.7 vs 17.4, $P < .05$) or influenza A(H1N1) pdm09 (19.7 vs 17.2, $P < .05$; Figure 3). There were no significant differences in illness duration (means, 9.4 days for influenza B, 8.0 for A[H3N2], and 8.5 for A[H1N1]pmd09 virus infections).

In a sensitivity analysis, we limited participants to those with illness onset of 4 days or less from the home visit and respiratory specimen collection and noted no difference in the direction or pattern of effects. We also excluded non–medically attended illnesses and found it also did not change the main findings.

Comment

We found that pregnant women with influenza illnesses described some symptoms as more severe (especially cough, myalgia, fever, and chills), reported greater subjective impairment, and were more likely to seek care earlier and to have highly elevated temperatures. Among the women infected with influenza, influenza vaccination was not associated with less severe illness.

We found a median symptom severity score of 18 (of 36) for influenza illnesses in pregnant women, which was within the range that Belongia et al[10] reported using for the same measure for nonhospitalized adults infected with 3 different influenza A strains, using the same scale. Women with influenza were more likely to seek medical care within 2 days of onset, which suggests that severe symptoms present more rapidly after onset. More than half of episodes (53%) were associated with an medical encounter within the first 2 days of onset, similar to previously reported estimates of 45-60% for influenza A among community-dwelling adults and children.[12] Women with influenza rated the impairment caused by their illness as greater than those with noninfluenza ARI, similar to a recent study with health care workers using the same measures.[11]

This study has several strengths. We directly compared the epidemiological and clinical characteristics of influenza and noninfluenza ARI in the same population of pregnant women using identical enrollment, laboratory diagnostics, and follow-up methods. We used EMRs to conduct surveillance to identify women eligible for testing and to determine vaccination status and comorbidities, thereby reducing recall biases, and we used RT-PCR testing, collection of detailed data regarding clinical and subjective manifestations of illness, and quick response time between illness

TABLE 2
Clinical characteristics associated with influenza vs noninfluenza ARIs among pregnant women

Characteristics	Noninfluenza ARI (n = 192)		Influenza (n = 100)		*P* value
Illness and specimen collection timing					
Days from onset to swab, mean days ± SD	4.7	±1.8	4.2	±2.0	< .05
Subjective symptom severity and impact					
12-symptom severity score, median/IQR [a]	16	12-20	18	14-20	< .05
Overall subjective severity, mean score ± SD [b]	4.7	±1.8	4.3	±2.0	NS
Subjective impairment, mean score ± SD[c]	4.8	±2.3	5.9	±1.9	< .001
Illness duration, mean days ± SD[d]	10.3	±4.8	9.3	±4.2	NS
Fever severity					
Any fever, ≥37.8°C	47	(24)	63	(63)	< .001
Highly elevated fever of ≥38.9°C	9	(5)	20	(20)	< .001
Highest recorded temperature, mean °C ± SD	37.2	±0.8	38.0	±1.0	< .001
Medical utilization during illness					
Any medical visit for ARI[e]	156	(81)	88	(88)	NS
Two or more medical visits for ARI	76	(40)	42	(42)	NS
Early care-seeking behavior[f]	68	(35)	53	(53)	< .001
First medical encounter, mean days ± SD[g]	3.0	±2.1	2.4	±2.2	< .05
Emergency department visits	15	(8)	12	(12)	NS
Illness-associated hospitalization	7	(4)	5	(4)	NS
Use of medications					
Antibiotic prescription					
Prescribed	30	(16)	11	(11)	NS
Self-reported use	21	(11)	9	(9)	NS
Antiviral prescription					
Prescribed	2	(1)	8	(8)	NS
Self-reported use	6	(3)	10	(10)	NS
OTC medications, self-reported use	155	(81)	92	(92)	< .05

Data are counts (column percentage), unless otherwise indicated. *P* values are from Pearson χ^2, Fisher exact, or Student *t* tests.

ARI, acute respiratory illness; *ICD-9, International Classification of Diseases, ninth revision*; *IQR*, interquartile range; *NS*, not statistically significant; *OTC*, over-the-counter medications.

[a] Summed subjective severity of 12 symptoms: cough, fatigue, feverishness, congestion, headache, myalgia, sore throat, chills, wheezing, ear pain, nausea, and vomiting. Each symptom was rated as absent (0), mild (1), moderate (2), or severe (3), except for cough, which did not have a response option (0); [b] Participants were asked to rate their health during their illness (0, normal health; 9, worse possible health); [c] Participants were asked to rate their ability to perform activities during their illness (0, able to perform usual activities; 9, unable to perform usual activities; severe was defined as an impairment rate of ≥6); [d] Mean illness duration was calculated using only the response from those participants who could recall the date their illness ended (noninfluenza ARI [n = 139] and influenza [n = 75]); [e] Medically attended acute respiratory illness visits that occurred between onset and recovery date with at least 1 of these ICD-9 codes: 460-466, 480-488 or 490-491; [f] Medically attended 2 days or less following onset; [g] Days between illness onset and first medical visit (includes only those people who had medical encounters).

Sokolow. Influenza severity in pregnant women. Am J Obstet Gynecol 2015.

detection, testing for influenza, and then interviewing participants about their illness.

Our study also has several limitations. The highest fever reached during the illness was an important measure of severity; however, we had to rely on the highest reported temperature, which may understate the true severity of fever if women are not consistently and repeatedly taking their temperature. We were also unable to determine the duration of fever. Our focus on febrile ARI with cough prevented us from considering mild or atypical manifestations of influenza illness. A report of 2 seasons may reflect the clinical manifestations of circulating influenza viruses during those seasons and may not be generalizable to other strains or seasons. The small number of influenza

TABLE 3
Self-reported symptom severity measures associated with influenza vs noninfluenza ARIs among pregnant women

Characteristics	Percentage self-reported as severe				
	Noninfluenza ARI (n = 192)		Influenza (n = 100)		*P* value
Upper respiratory symptoms					
Nasal congestion	90	(47)	42	(42)	NS
Sore throat	65	(34)	23	(23)	NS
Ear pain	17	(9)	11	(11)	NS
Lower respiratory symptoms					
Cough[a]	57	(30)	46	(46)	< .01
Wheezing	11	(6)	4	(4)	NS
Systemic symptoms					
Fatigue	66	(34)	41	(41)	NS
Myalgia	26	(14)	28	(28)	< .005
Feverishness	9	(5)	18	(18)	< .001
Chills	25	(13)	25	(25)	< .01
Headache	48	(25)	18	(18)	NS
Gastrointestinal symptoms					
Vomiting	15	(8)	5	(5)	NS
Nausea	18	(9)	5	(5)	NS

Data are counts (column percentage), unless otherwise indicated. *P* values are from Pearson χ^2, Fisher exact, or Student *t* tests.

ARI, acute respiratory illness; *NS*, not statistically significant.

[a] Ten participants reported cough as absent during their illness: in these instances, their responses were recoded as 1 (mild) because a cough was present at the time they were deemed eligible to participate in the study.

Sokolow. Influenza severity in pregnant women. Am J Obstet Gynecol 2015.

illnesses available for analysis limited our power to examine differences among influenza (sub)types, vaccination status, trimester at onset, or more serious illness outcomes (eg, hospitalization). We were unable to disentangle the contributions of host, agent, and environment in influencing the risk of infection or manifestations of disease.

With a larger sample size, it would be useful to explore whether a combination of symptoms and severity could effectively rule in or rule out influenza prior to receiving test results. The relatively small number of influenza and noninfluenza illnesses examined in this study limited the precision of our findings; future studies with more precise estimates of the positive and negative predictive value of illness symptoms may facilitate potential clinical applications.[13]

Medication usage could have affected severity and clinical outcomes. Use of antiviral and antibiotics was similar across groups; however, more influenza-positive women took OTC medications, which could have masked severity. Some self-reported data (eg, symptom severity, use of OTC medications, smoking status, and self-reported vaccine status for the 14 women vaccinated outside the Kaiser Permanente system [5%]) could not be verified.

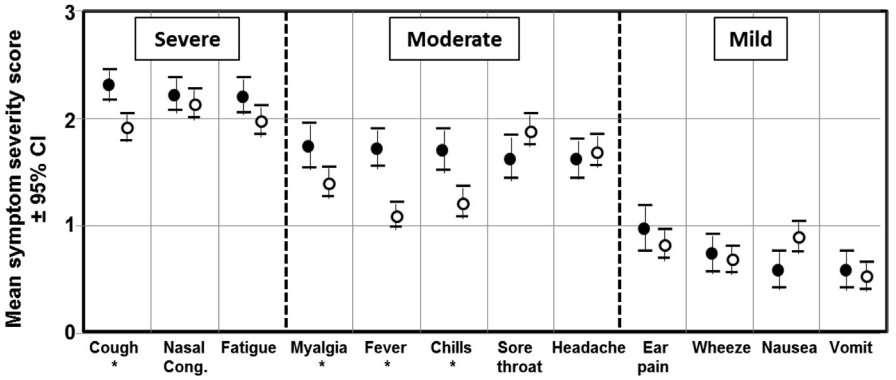
Comparisons of influenza and noninfluenza ARI severity

This study indicates that influenza and noninfluenza ARIs in pregnant women are distinguishable based on subjective and EMR-based severity measurements. These differences persisted after adjusting for site, season, age, vaccination status, and days since illness onset. Our logistic regression analyses revealed a strong association between an influenza-positive illness and severe cough and/or fever. Overall, our findings generally are consistent with prior studies of influenza illnesses.[10-12]

Although most influenza and noninfluenza ARI illnesses involved fever, feverishness, or chills, records of highly elevated temperature (>38.9°C) were much more common among influenza (20% vs 5% noninfluenza ARI). High fever is a cause for concern because a temperature elevation of 1.9°C over normal (37.0°C) is the threshold for assessing teratogenic risk (eg, neural tube defects).[14,15] There is little information on the effects of higher temperature elevations for short exposures or more modest elevations for longer periods of time, although both situations can yield a similar thermal dose (ie, length and intensity of fever). We were unable to measure fever duration; however, 20% of influenza illnesses reached the temperature risk threshold. After adjusting for site, season, age, vaccination status, and days since illness onset, we found the odds of reaching or exceeding this risk threshold were greater than 4.5-fold higher among influenza-positive women.

Although antiviral medications may reduce complications of influenza illness and shorten symptom duration,[16-18] few women in our study with influenza illnesses (10%) were prescribed antivirals; this is a somewhat lower rate of use than was reported previously (15-22%) for nonpregnant adults.[10,12] The reasons for this relatively low level of antiviral use probably include the fact that only 36% of women in our study sought medical care within 2 days after illness onset and within the ideal window for antiviral treatment. The lower use of antiviral medications in some integrated care systems[19] and the hesitancy of pregnant women to take medications in general[20] may have also contributed.

FIGURE 2
Mean response to self-reported severity ranking of 12 symptoms



Mean response to self-reported severity ranking of 12 symptoms, with 95% confidence intervals. Symptoms are sorted by mean severity score: severe, ≥2; moderate, 1—1.9; mild, >1. *Vertical line* with *solid circle* indicates influenza illnesses; *vertical line* with *open circle* indicates noninfluenza ARI. *Asterisk* indicates symptoms with statistically different responses between influenza and noninfluenza ARI ($P < .01$).

ARI, acute respiratory illness.

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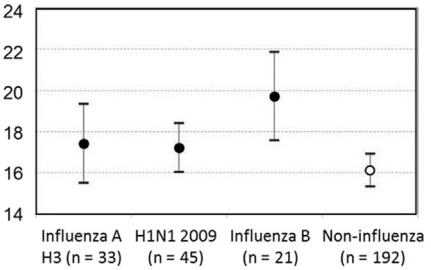
FIGURE 3
Mean sum of 12 self-reported symptoms by influenza virus type/subtype



Mean sum of 12 self-reported symptoms by influenza virus type/subtype compared with noninfluenza illnesses, with 95% confidence intervals shown. Individual summed scores ranged from 6 to 29. One case with an unsubtypable influenza illness has been excluded from this figure. Mean severity scores for influenza B and noninfluenza are statistically different. Symptoms include cough, fatigue, feverishness, congestion, headache, myalgia, sore throat, chills, wheezing, ear pain, nausea, and vomiting. Each symptom was rated as absent (0), mild (1), moderate (2), or severe (3), except for cough, which did not have a mild response option.

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TABLE 4
Results of logistic regression of factors associated with influenza vs noninfluenza acute respiratory illnesses among 292 pregnant women, 2 sites, 2010-2012

Characteristics	aOR [95% CI][a]	*P* value
Site (referent, KPNC)	1.66 [0.98—2.82]	.062
Season (referent, 2010-2011)	0.76 [0.45—1.27]	.288
Age at illness onset (referent, <31 y)	0.78 [0.48—1.27]	.317
Vaccination status in current season (referent, unvaccinated)	0.58 [0.35—0.96]	.034
Influenza test 6 days or longer after onset (referent, <6 d)	0.75 [0.44—1.28]	.289
Highest recorded temperature ≥38.9°C (referent, <38.9°C)	4.51 [1.92—10.56]	< .0001
Activities greatly impaired (referent, not greatly impaired)	2.43 [1.42—4.18]	.001
Early care-seeking behavior (referent, visit >2 d after onset)	2.28 [1.36—3.82]	.002
12 symptom severity score (referent, not severe)	2.06 [1.10—3.87]	.025
Subjective feverishness severe (referent, not severe)	4.08 [1.71—9.70]	.002
Subjective cough severe (referent, not severe)	2.05 [1.21—3.46]	.007
Subjective chills severe (referent, not severe)	2.01 [1.06—3.80]	.032

aOR, adjusted odds ratio; *CI*, confidence interval; *KPNC*, Kaiser Permanente Northern California.

[a] Adjusted for site, season, age, vaccination status, and days from illness onset to influenza testing.

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Impact of trimester and vaccination status on influenza illness severity

We found no evidence that influenza vaccination was associated with lower subjective symptom severity. Vaccinated women were more likely to have a high fever of 38.9°C or greater (40% vs 17%; $P < .01$); we cannot explain this finding. Power for analyzing the impact of vaccination on other illness severity characteristics was low because of the small number of influenza illnesses when separated by vaccination status (42 vaccinated and 58 unvaccinated).

Patients were diagnosed in all trimesters of pregnancy, and we found little evidence that influenza illnesses in third-trimester pregnant women were more severe than those that occurred earlier. Women with third-trimester illnesses did have fewer severe nausea symptoms, but it is difficult to differentiate typical early pregnancy nausea from nausea caused by influenza.

Impact of influenza type/subtype on illness severity

Women infected with influenza B viruses were more likely to have severe symptoms than either influenza A subtype (mean severity score, 19.7 vs 17.4 for influenza A[H3N2] and 17.2 for influenza A[H1N1]pdm09). Although the severity of influenza B virus infections among adults is debated,[21] this finding differs from some published studies. For example, Irving et al[12] found that over 4 seasons in 2007−2011, influenza B illnesses were milder than influenza A. The discrepancy could reflect seasonal variation in the virulence of influenza B viruses.[21]

Conclusion

Influenza had a greater negative impact on pregnant women than noninfluenza ARIs. This finding adds to a growing literature indicating that illness caused by influenza virus infection, even among those not requiring hospitalization, is moderately more severe than illnesses caused by other respiratory pathogens and reinforces the importance of influenza prevention and control efforts among pregnant women and women planning to become pregnant in the next 12 months.[9] ■

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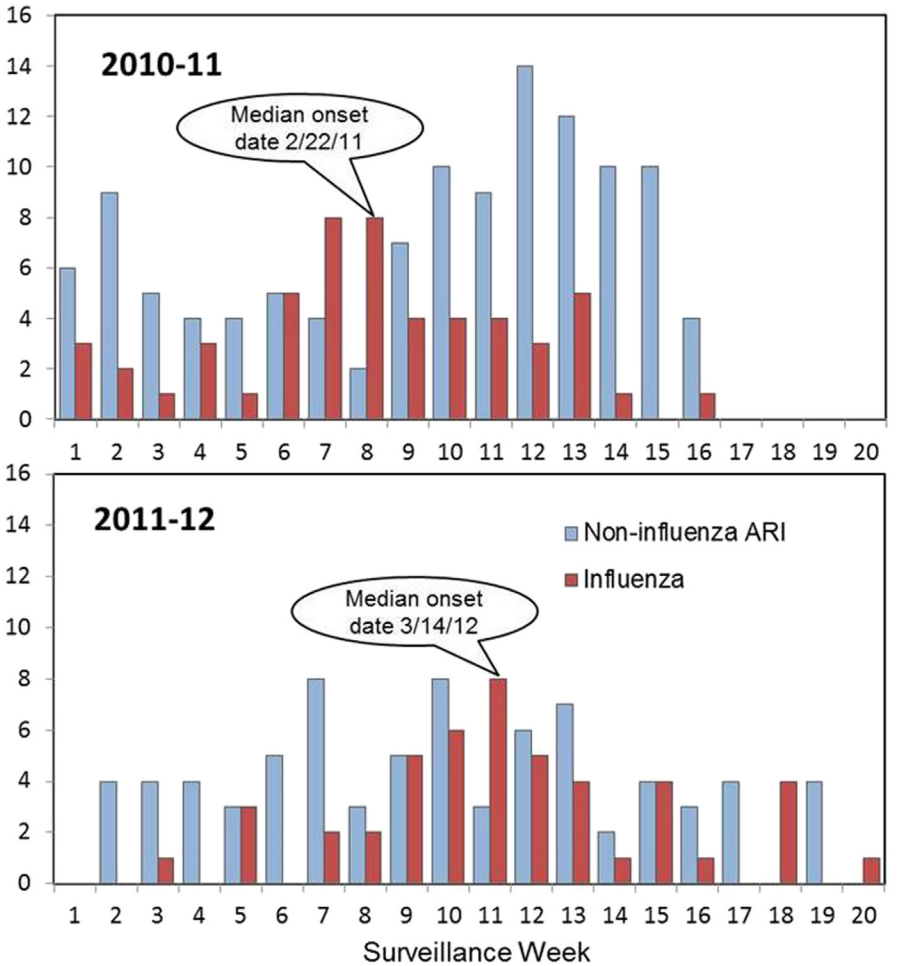
Appendix

SUPPLEMENTAL FIGURE
Pregnant women with febrile acute respiratory illness



Number of pregnant women with febrile acute respiratory illness (ARI) who tested positive or negative for influenza by week of testing during 2010-2011 and 2011-2012 seasons.

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SUPPLEMENTAL TABLE

The influence of selected factors on self-reported symptom severity measures among 100 pregnant women with laboratory-confirmed influenza during 2010-2012 influenza season, 2 sites

Severity	Illness severity[a]				*P* value	Total	
	Mild or moderate (n = 54)		Severe (n = 26)			(n = 100)	
Trimester at illness onset							
First or second trimester	42	(74)	15	(26)	NS	57	(100)
Third trimester	32	(74)	11	(26)		43	(100)
Current season vaccination status[b]							
Vaccinated	43	(74)	15	(26)	NS	58	(100)
Not vaccinated	31	(74)	11	(26)		42	(100)
Comorbidities							
None	60	(72)	23	(28)	NS	83	(100)
One or more	14	(82)	3	(18)		17	(100)

Data are counts (row percentage). *P* values are from Pearson χ^2 or Fisher exact test.

NS, not statistically significant.

[a] Summed subjective severity of 12 symptoms were defined as severe if score was 22-29; [b] Current-season vaccination status defined as receipt of vaccine at least 14 days prior to illness onset.

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