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Original Article

Pandemic Influenza A (H1N1) Infection in Pregnant and Nonpregnant Women in Spain (2009–2010)

María Morales Suárez-Varela[1,2,3]*, Fernando González-Candelas[2,3,4], Jenaro Astray[5], Jordi Alonso[2,6,7], Olatz Garin[2,6,7], Ady Castro[8], Juan C. Galán[2,9], Maretva Baricot[2,10], Jesús Castilla[2,11], Pere Godoy[2,12], Miguel Delgado-Rodríguez[2,13], Vicente Martin[2,14], José M. Mayoral[15], Tomás Pumarola[16], José M. Quintana[2,17], Sonia Tamames[18], Agustín Llopis-González[1,2,3], Àngela Dominguez[2,19], and the CIBERESP Cases and Controls in Pandemic Influenza Working Group, Spain**

[1]Unit of Public Health and Environmental Care, Department of Preventive Medicine, University of Valencia, Valencia;
[2]Centro de Investigación Biomédica en Red (CIBER) in Epidemiology and Public Health (CIBERESP), Madrid;
[3]Center for Public Health Research (CSISP), Valencia;
[4]Research Unit ''Genomics and Health'' CSISP-University of Valencia, Valencia;
[5]Surveillence Branch, Community of Madrid, Madrid;
[6]University Pompeu Fabra, Barcelona;
[7]Institute for Research IMIM-Hospital del Mar, Barcelona;
[8]CIBER Respiratoy Diseases, Madrid;
[9]Ramón y Cajal University Hospital, Madrid;
[10]University of Girona, Girona;
[11]Public Health Institute of Navarra, Navarra;
[12]Departament of Health, Generalitat of Catalonia, Barcelona;
[13]University of Jaen, Jaen;
[14]University of León, León;
[15]Security Service of Andalusia, Andalusia;
[16]Red Española de Investigación en Patología Infecciosa (REIPI), Madrid;
[17]Basque Fundation for Health Innovation and Research, Barakaldo;
[18]Department of Public Health, Development and Innovation, Junta de Castilla y León; and
[19]Department of Public Health, University of Barcelona, Barcelona, Spain

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SUMMARY: The present study aimed to compare the main features of infection with pandemic influenza A virus in pregnant and nonpregnant women admitted to hospitals in Spain during the first waves of the 2009–2010 influenza pandemic. This was a prospective (November 2009 to June 2010), multicenter observational study. All cases were women of reproductive age who had not been vaccinated against seasonal or pandemic influenza A. Influenza infection was confirmed by reverse transcription-polymerase chain reaction (RT-PCR). The sociodemographic and clinical data of all cases were reviewed. A total of 219 inpatients, including 49 pregnant women and 170 nonpregnant women, were enrolled in the study upon admission to participating hospitals. The most substantially different symptoms between the groups were respiratory distress and unilobar consolidation, both of which were more frequent among nonpregnant women. Antibiotics and systemic corticosteroids were more frequently used in nonpregnant women; however, there were no differences in the rates of treatment with antivirals. Our findings indicated that the compared with nonpregnant women, pregnant women in this study did not have significantly different symptoms and were not at increased risk of complications from pandemic influenza virus infection.

INTRODUCTION

In May 2009, the second documented death caused by a novel virus strain, the influenza A (H1N1)pdm09 virus, occurred in a previously healthy pregnant woman in the United States (1,2). The influenza A (H1N1)pdm09 virus quickly spread to all continents, and Spain was the first European country to report a case of pandemic influenza (3). According to the World Health Organization (WHO) (4–6), pregnant women were at increased risk for complications from the new

*Corresponding author: Mailing address: Unit of Public Health and Environmental Care, Department of Preventive Medicine, University of Valencia, Avda. Vicente Andrés Estellés s/n, 46100 Burjassot, Valencia, Spain. E-mail: maria.m.morales@uv.es

**Members of the CIBERESP Cases and Controls in Pandemic Influenza Working Group are listed in the Appendix.

influenza A virus, which led to recommendations that this population should be hospitalized upon infection with the new viral strain. Early findings specific to the 2009 pandemic demonstrated that pregnant women were not only disproportionately admitted to hospitals but also represented an above-average proportion of influenza-related deaths (7). In addition, it was noted that among patients who acquired this infection, pregnant women were approximately 4–5 times more likely to develop severe disease than nonpregnant women (8). Since then, our knowledge about influenza infection during pregnancy has greatly expanded with regard to both diagnostic and treatment information, and much more attention has been focused on the issue of influenza in pregnancy (9–11).

Although the severity of this illness ranges from mild to severe, little has been reported on how this infection affects pregnant women globally rather than individually (2,12). Before the emergence of the influenza A (H1N1)pdm09 virus, much of what we knew about influenza in pregnant women was based on indirect evidence, including studies that used acute respiratory hospitalizations during the influenza season as a proxy for influenza illness (7,11,13,14) and case series of pregnant women from previous pandemics who were not necessarily representative of all pregnant women with influenza (15–17).

The U.S. Centers for Disease Control and Prevention (CDC) subsequently developed prevention, treatment, and control recommendations for pregnant women in the event of an influenza pandemic (18,19). During the pandemic (20), experts debated the most appropriate treatments for use in pregnancy; however, limited data were available at that time (21–23).

Since then, several studies (11,13,14) have shown that pregnant women accounted for a greater proportion of morbidity and mortality from influenza A (H1N1)pdm09 virus infection than the general population. Moreover, the increased severity of infection in pregnant women with this virus than in the general population has been documented carefully and consistently in a wide variety of clinical settings (24). Unfortunately, most of these analyses have compared pregnant women with the general population rather than with more appropriate control groups such as nonpregnant women of a similar age. In fact, a thorough literature search did not yield any studies comparing influenza A (H1N1)pdm09 infection between pregnant and nonpregnant women of the same age who were hospitalized.

The present study aimed to describe the major features of infection with influenza A (H1N1)pdm09 virus in nonvaccinated pregnant women compared with those in nonvaccinated nonpregnant women of the same age range who were hospitalized in Spain during the first waves of the 2009–2010 influenza pandemic. We specifically tested the hypothesis underlying the initial recommendation of hospitalizing pregnant women who became infected with the pandemic virus, i.e., pregnant women are at an increased risk for complications and more severe development of the disease than nonpregnant women. We only included nonvaccinated women in the study because the influenza vaccine may alter the clinical features of the disease. The findings of our study may be beneficial for informing prevention and control strategies of novel A (H1N1)pdm09 influenza viruses and possibly other influenza virus strains during pregnancy.

MATERIALS AND METHODS

Procedures: The present study was part of a multicenter matched case-control study of influenza A (H1N1)pdm09 infection that was conducted in 28 hospitals in 7 autonomous Spanish communities (Catalonia, Andalusia, Madrid, Basque Country, Valencian Community, Castile and León, and Navarre) between November 1, 2009 and February 28, 2010 (25).

Participants: In total, 1,165 women between 15 and 44 years of age (1) visited the participating hospitals during the study period with an infection with influenza A (H1N1)pdm09 virus that was confirmed by reverse transcription polymerase chain reaction (RT-PCR) assays. Of these, 219 women were hospitalized for more than 24 h, including 49 women who were pregnant at the time of hospitalization and 170 nonpregnant women. None of these 219 women had been vaccinated against seasonal or pandemic influenza virus during that season; therefore, all were enrolled in the study.

Data confidentiality and ethical issues: The study was conducted in accordance with the requirements of the Ethics Committees and data inspectorates of the participating regions. All the women enrolled in the study signed an informed consent approved by the Ethics Committees of the participating hospitals.

Variables: The recruitment questionnaire for pregnant women consisted of items assessing demographic variables (e.g., age, weeks of gestation, racial/ethnic status, country of birth); social factors (e.g., employment status, education level); and behavioral variables (e.g., method of preventing infection use of alcohol-based hand sanitizers, living conditions, number of cohabitants and size of living area, smoking habits, occupation, travel prior to influenza infection). We also gathered information regarding medical conditions (personal care, daily activities, and clinical background, e.g., obesity, asthma, pneumonia, diabetes, chronic obstructive pulmonary disease, renal failure, arterial hypertension, chronic cardiovascular disease, heart failure, disabling neurological disease, human immunodeficiency virus infection); illness-induced limitations (e.g., mobility, personal care, daily activities); and prior medical care (e.g., previous admission with H1N1-infection, days of hospitalization, initial diagnostic results, length of hospitalization, treatment, and complications during hospitalization). The same variables were recorded for nonpregnant women (referred to also as ''controls'' in the ensuing text), except for those related to pregnancy. The medical conditions were retrieved from the patients' medical records, and the remaining variables were obtained from face-to-face or telephone interviews with the patients.

Statistical analysis: All data were entered and analyzed using the SPSS version 19 software program. Chi-square tests were performed to compare differences between pregnant and nonpregnant women, and normally distributed continuous variables between pregnant and nonpregnant women were compared by means of *t*-

tests. P-values < 0.05 were considered to be statistically significant.

RESULTS

Table 1 shows the demographic characteristics of pregnant women ($n = 49$) and nonpregnant women ($n = 170$) infected with pandemic influenza virus who were admitted to participating hospitals in Spain during the study period. The groups differed significantly ($P < 0.001$) in their age distributions, with more pregnant women in the <20 and 30–34 years groups and more nonpregnant women in the 20–29 and >34 years groups. More than 75% of the pregnant women with influenza infection during the present study were in their third trimester (weeks 26–40) of pregnancy. Significant differences between the groups were also found with regard to ethnicity (more minority ethnic groups were represented among pregnant women) and education level (a larger proportion of pregnant women had advanced education). There were no differences in smoking habits or in the proportion of women in each group who had been vaccinated against seasonal influenza in the previous year; the proportion was low (around 7%) as expected for this age group. Similarly, the women did not differ significantly with regard to occupation, although a higher proportion of the infected pregnant women worked in the healthcare industry.

One particular preventing infection measure showed significant differences ($P = 0.003$) in frequency between cases and controls: the use of a respiratory mask was considerably more common among nonpregnant women (65.7%) than among pregnant women (34.3%). Most women in both the groups had received information about the use of influenza prevention measures (87.0% of nonpregnant women, 83.7% of pregnant women), a minority washed their hands more than 10 times a day (24.6% of nonpregnant women, 35.4% of pregnant women), and the majority never used alcohol-based sanitizers (64.8% of nonpregnant women, 51.1% of pregnant women).

No significant differences were observed between pregnant and nonpregnant women with regard to housing conditions, including the number of cohabitants and the size of living quarters. Interestingly, pregnant women were significantly more likely to report having traveled before getting sick (12.2%) than nonpregnant women (3.5%) ($P = 0.019$). All the 6 nonpregnant women who had traveled before developing pandemic influenza infection were of white ethnicity, while of the 6 pregnant women who had traveled, 5 were Caucasian and 1 was Arabian.

Table 2 summarizes the study subjects' underlying medical conditions. One statistically significant difference was observed between the groups when asked to self-evaluate the occurrence of problems with personal care prior to contracting influenza ($P = 0.009$): pregnant women reported significantly fewer problems (100% reported "no problems") than nonpregnant women (84.1%). The groups did not differ significantly with regard to self-reported difficulty in performing activities of daily living before the onset of illness (11.1% of pregnant women and 19.3% of nonpregnant women reported "some problems"). No significant differences

Table 1. Demographic and sociological characteristics of hospitalized women infected with influenza A (H1N1)pdm09 virus in Spain (2009–2010)

	Nonpregnant (%)[1)]	Pregnant (%)[1)]	P[2)]
Total no.	170	49	
Age group (yr)			
<20	20 (11.8)	14 (28.6)	
20–29	70 (41.2)	3 (6.1)	
30–34	19 (11.2)	19 (38.8)	0.001
>34	61 (35.9)	13 (26.5)	
Trimester of pregnancy			
First (weeks 1–12)	—	4 (8.2)	
Second (weeks 13–25)	—	8 (16.3)	
Third (weeks 26–40)	—	37 (75.5)	
Ethnicity			
Caucasian	140 (83.8)	36 (73.5)	
Romanian	2 (1.2)	0 (0)	
Hispanic	20 (12.0)	8 (16.3)	
Arabian or north African	5 (3.0)	2 (4.1)	
Other	0 (0.0)	3 (6.1)	0.017
Education level			
No/primary studies	59 (36.4)	4 (8.2)	
Secondary/superior	103 (63.6)	45 (91.8)	<0.001
Smoking habits			
Non-smoker	110 (70.5)	32 (65.3)	
Smoker	34 (21.8)	11 (22.4)	0.596
Former smoker	12 (7.7)	6 (12.2)	
2008-09 vaccine	13 (7.6)	3 (6.1)	0.685
Prevention			
Information	147 (87.0)	41 (83.7)	0.554
Use of mask	46 (65.7)	24 (34.3)	0.003
Hand-washing (frequency)			
1–4	64 (38.3)	11 (22.9)	
5–10	62 (37.1)	20 (41.7)	0.112
>10	41 (24.6)	17 (35.4)	
Use of alcohol solutions			
Never	105 (64.8)	24 (51.1)	
Occasionally	27 (16.7)	10 (21.3)	0.362
Frequently	19 (67.9)	9 (19.1)	
Always	11 (6.8)	4 (8.5)	
Housing conditions			
No. of cohabitants			
0	4 (2.4)	0 (0)	
1–2	24 (14.5)	14 (29.2)	
3–5	123 (74.5)	31 (64.6)	0.077
6–8	14 (8.5)	2 (4.2)	
≥9	0 (0)	1 (2.1)	
Area (m^2)			
≤50	6 (3.9)	4 (9.1)	
51–70	43 (27.7)	9 (20.5)	
71–100	73 (47.1)	18 (40.9)	
101–120	10 (6.5)	7 (15.9)	0.364
121–150	8 (5.2)	4 (9.1)	
≥151	15 (9.7)	2 (4.5)	
Occupation			
Non health-related	95 (55.9)	23 (46.9)	0.093
Health worker	6 (3.5)	4 (8.2)	0.158
Self-worker	19 (11.2)	6 (12.24)	0.835
Unemployed	69 (40.6)	22 (44.9)	0.589
Travel before H1N1	6 (3.5)	6 (12.2)	0.019

[1)]: Percentages are referred to the actual number of responses/data for each group.
[2)]: Chi-square test.

Table 2. Underlying medical conditions of hospitalized women infected with influenza A (H1N1)pdm09 virus in Spain (2009–2010)

	Nonpregnant (%)[1)]	Pregnant (%)[1)]	P[2)]
Background			
Personal care			
No problem	101 (84.16)	40 (100)	
A problem	19 (15.83)	0 (0.0)	0.009
Daily activity			
No problem	117 (80.68)	40 (88.88)	
A problem	28 (19.31)	5 (11.11)	0.577
Clinical background			
Obesity	19 (65.5)	10 (34.5)	0.061
Asthma	38 (22.5)	6 (12.2)	0.116
Pneumonia (<2 years ago)	19 (14.6)	2 (4.9)	0.098
Diabetes	10 (5.9)	1 (2.0)	0.275
COPD	5 (3.0)	2 (4.1)	0.700
Renal failure/nephritic syndrome	3 (1.8)	2 (4.1)	0.342
Arterial hypertension	8 (4.8)	1 (2.1)	0.406
Chronic cardiovascular disease	5 (3.0)	0 (0)	0.222
Heart failure	4 (2.4)	0 (0)	0.277
Neurological disease	2 (1.2)	1 (2.0)	0.654
AIDS/HIV infection	3 (1.8)	1 (2.1)	0.889

Footnotes are in Table 1.
COPD, chronic obstructive pulmonary disease.

were observed between pregnant and nonpregnant women with regard to clinical background prior to infection with influenza A (H1N1)pdm09 virus, although nonpregnant women noted a slightly higher prevalence of certain pathologies. For example, obesity was more prevalent in the nonpregnant group than in the pregnant group (65.5% vs. 34.5%), although the difference was not statistically significant ($P = 0.061$).

A comparison of symptoms developed as a result of pandemic influenza A virus infection is presented in Table 3. No statistically significant differences were observed between pregnant and nonpregnant women with regard to self-declared mobility limitations caused by the illness ($P = 0.209$), although 16.3% of pregnant women and 25.3% of nonpregnant women reported that they needed to stay in bed.

When the subjects were asked about their ability to perform personal care and daily activities once they had contracted influenza infection, statistically significant differences were found between pregnant and nonpregnant women with regard to personal care ($P = 0.010$), and borderline significant differences ($P = 0.054$) were observed with regard to daily activities, with nonpregnant women reporting more limitations in both areas. Self-reported challenges with personal care and daily activities in both the groups were twice as frequent as those reported before influenza infection (Table 2).

The symptoms characterizing seasonal influenza that were reported by pregnant and nonpregnant women were essentially the same, with the exception that nonpregnant women experienced significantly higher rates of respiratory distress (64.4% vs. 40.4%, $P = 0.003$), hypoxemia (39.5% vs. 12.5%, $P = 0.002$), and unilobar consolidation (21.3% vs. 5.9%, $P = 0.038$) than pregnant women. Similarly, subjects' reported duration

Table 3. Symptoms at presentation in hospitalized women infected with influenza A (H1N1)pdm09 virus in Spain (2009–2010)

	Nonpregnant (%)[1)]/ Mean ± SD	Pregnant (%)[1)]/ Mean ± SD	P[2)]
Mobility			
In bed	43 (25.3)	8 (16.3)	
No problem	55 (32.4)	23 (46.9)	0.209
Some problems	32 (18.8)	10 (20.4)	
Personal care			
No problem	81 (74.7)	34 (69.3)	0.010
A problem	54 (31.8)	10 (20.4)	
Daily activity			
No problem	51 (30.0)	26 (53.1)	0.054
A problem	56 (32.9)	11 (22.4)	
Temperature (fever)	162 (96.4)	47 (95.9)	0.868
Days of fever	3.61 ± 2.09	2.47 ± 2.94	0.030
Cough	144 (86.7)	40 (81.6)	0.371
Malaise	103 (78.6)	33 (80.5)	0.798
Days of malaise	4.02 ± 3.71	2.33 ± 1.89	0.011
Respiratory distress	105 (64.4)	19 (40.4)	0.003
Days of respiratory distress	4.14 ± 3.63	3.13 ± 2.22	0.195
Headache	87 (53.0)	28 (57.1)	0.614
Days of headache	3.88 ± 3.75	2.61 ± 2.00	0.112
Myalgia	64 (50.8)	23 (56.1)	0.555
Days of myalgia	4.13 ± 4.11	2.65 ± 1.96	0.111
Hypoxemia	47 (39.5)	5 (12.5)	0.002
Days of hypoxemia	3.83 ± 2.76	2.40 ± 1.67	0.240
Rhinorrhea	43 (33.9)	16 (39.0)	0.547
Days of rhinorrhea	3.33 ± 2.65	2.56 ± 1.93	0.286
Odynophagia	35 (27.6)	15 (38.5)	0.194
Days of odynophagia	4.05 ± 3.13	2.33 ± 1.98	0.051
Vomiting	30 (23.6)	7 (17.1)	0.379
Days of vomiting	4.31 ± 5.57	3.43 ± 2.50	0.684
Unilobar consolidation	26 (21.3)	2 (5.9)	0.038
Interstitial infiltrate	24 (19.0)	6 (17.6)	0.853
Diarrhea	12 (9.4)	3 (7.3)	0.677
Days of diarrhea	5.0 ± 3.61	2.67 ± 0.57	0.106
Pleural effusion	8 (6.3)	0 (0)	0.132
Consciousness alteration	7 (5.6)	1 (2.4)	0.417
Days of consciousness alteration	4.09 ± 2.94	2.0 ± 0.0	—
Seizures	7 (4.3)	1 (2.0)	0.464
Days of seizures	3.44 ± 1.81	5 ± 0.0	—
Pneumothorax	1 (0.8)	0 (0)	0.602

Footnotes are in Table 1.

of symptoms generally indicated a worse course of the disease in nonpregnant women than in pregnant women, with statistically significant differences being observed in the duration of fever, malaise, hypoxemia, and odynophagia.

No pregnant women required hospitalization before being infected by the pandemic influenza virus, whereas 2 nonpregnant women required hospitalization before the infection (Table 4); this difference was not statistically significant ($P = 0.446$). Most women visiting hospitals with pandemic influenza infection required subsequent hospitalization, and there were no significant differences between pregnant and nonpregnant women (87.7% vs. 87.7%). Despite a slight trend

Table 4. Medical care and treatment in hospitalized women infected with influenza A (H1N1)pdm09 virus in Spain (2009–2010)

	Nonpregnant (%)[1)]	Pregnant (%)[1)]	P[2)]
Medical care			
Previous hospital admission with H1N1 infection	2 (1.2)	0 (0.0)	0.446
Days of hospitalization			
≤3	52 (33.1)	24 (55.8)	
4–7	66 (42.0)	13 (30.2)	
8–14	28 (17.8)	5 (11.6)	0.458
15–21	5 (3.2)	0 (0.0)	
22–30	2 (1.3)	1 (2.3)	
≥31	4 (2.5)	0 (0)	
Initial diagnostic			
Primary care	63 (37.1)	13 (26.5)	0.078
Home care	3 (1.8)	2 (4.1)	0.109
Occupational medical care	0 (0.0)	1 (2.0)	0.057
Hospital emergency unit	44 (25.9)	6 (12.2)	0.027
Emergency primary care	23 (13.5)	5 (10.2)	0.677
Treatment			
Antibiotic	95 (73.1)	16 (39.0)	0.001
Systemic corticosteroids	44 (38.3)	2 (4.9)	0.001
Anti-inflammatory antipyretic	96 (76.2)	33 (80.5)	0.569
Antiviral	112 (65.9)	34 (69.4)	0.623
Oseltamivir	110 (98.2)	32 (94.1)	0.840
Other	2 (1.8)	2 (5.9)	—

Footnotes are in Table 1.

toward shorter inpatient stays among pregnant women, there were no statistically significant differences (P = 0.458) in the length of hospitalization between the 2 groups.

After the initial examination, 37.1% of nonpregnant women and 26.5% of pregnant women were referred to primary care; however, this difference was not statistically significant (P = 0.078). The only significant difference in destination between the 2 groups was found in subsequent referrals to emergency units (P = 0.027), where 25.9% of nonpregnant women and only 12.2% of pregnant women were addressed (Table 4).

There were significant differences between groups with regard to the proportion of influenza-infected women who were treated with antibiotics (73.1% vs. 39.0%, $P < 0.001$) and systemic corticosteroids (38.3% vs. 4.9%, $P < 0.001$). However, no differences were observed in the rates of treatment with anti-inflammatory antipyretics (76.2% vs. 80.5%, P = 0.569) and antiviral drugs (65.9% vs. 69.4%, P = 0.623), among which oseltamivir was the most commonly used treatment in both the groups (98.2% vs. 94.1%, P = 0.840).

DISCUSSION

In the present study, we analyzed differences between pregnant and nonpregnant women aged 15–44 years who were hospitalized in Spain between November 1, 2009 and February 28, 2010 because of influenza A (H1N1)pdm09 infection. The results showed that pregnant women in Spain who were hospitalized with pandemic influenza virus infection during the study period were mainly in the third trimester of pregnancy and that compared with nonpregnant women, they were younger, had a higher proportion of non-Spanish origin, had a higher education level, and were more likely to report traveling before the onset of influenza symptoms. Pregnant women had fewer difficulties with personal care than nonpregnant women both before and during influenza infection; however, with regard to daily activities, pregnant women had fewer problems prior to illness than nonpregnant women; however, the rate of problems during the influenza episode was similar.

The medical records of nonpregnant women in the present study showed a higher incidence of obesity and pneumonia than those of pregnant women. Fever was the most common symptom of influenza infection; however, nonpregnant women experienced it longer than pregnant women; the same was true for malaise. Pregnant women also showed less hypoxemia and unilobar consolidation. They required approximately the same hospitalization rate as nonpregnant women; however, they were less frequently referred to emergency units and were administered fewer drugs.

All of aforementioned results suggest that compared with nonpregnant women, pregnant women in Spain did not have an increased risk of complications from influenza A (H1N1)pdm09 virus infection. This finding is inconsistent with the notion that pregnant women were more likely than other population groups to suffer severe complications. Moreover, none of the pregnant women enrolled in the present study died or required intensive care as a consequence of pandemic influenza infection.

The present study included pregnant subjects who were hospitalized for pandemic influenza infection in all 3 trimesters of pregnancy; however, a substantially higher proportion of pregnant women in our subject pool was in the third trimester. Similar results have been reported from other studies of seasonal (13,14) and pandemic influenza (2,11). These findings suggest that the risk of contracting influenza infection may be higher in the third trimester of pregnancy.

The attenuated severity of influenza A (H1N1)pdm09 virus infection in pregnant women compared with nonpregnant women that we found in the present study is in apparent contradiction with several previous studies (1,26–28). One possible explanation for these results is as follows: as in the case of most influenza patients, the majority of the pregnant women (94.1%, 32/34) and the nonpregnant women (98.2%, 110/112) in our patient population were treated with oseltamivir. This is the primary variable that differentiates our study results from others; however, additional factors such as early or delayed treatment (27,29) could also help explain these conflicting results (1). However, we should also point out that nonpregnant women were often treated with antibiotics (73.1%), unlike pregnant women (39%); it is likely that pregnant women did not require antibiotics because they were diagnosed with influenza A (H1N1)pdm09 virus.

In 2009, vaccination against seasonal influenza was available in Spain beginning in late September and for pandemic influenza beginning in mid-November. Therefore some people received 1 or the other or both or none. To minimize the confounding effect of different vaccination regimens, we considered only nonvaccinat-

ed women in the present study. Moreover, only those cases with laboratory-confirmed infection with influenza A (H1N1)pdm09 virus were included in the present study.

Our data show that the demographic features of pregnant and nonpregnant women attending hospitals in Spain because of influenza A (H1N1)pdm09 infection were largely similar. The most remarkable differences were found in the age distribution, ethnicity, education level, and travel history prior to infection. We also observed that the duration of symptoms prior to seeking healthcare among pregnant women was much shorter than among nonpregnant women. This finding may be attributable to the pregnant woman's heightened concern about their health because of the possible consequences of the illness on their fetuses. Unfortunately, the delay in reporting to the hospital that was observed among the nonpregnant women in our study resulted in more clinical complications, an increased need for hospital emergency care, and the increased use of drugs.

The differences in the age distribution between the 2 groups were mainly due to the low proportion of pregnant women in the 20–29 years group (6.1%) and the high proportion in the less than 20 years group (28.6%). This younger group appears to have been overrepresented in the present study because only 2.4% of births in Spain in 2010 occurred to mothers in this age group (30). The high proportion of younger women in the pregnant group may indicate a higher risk for influenza infection in this age group or it may be the result of excessive medical attention to these young women during pregnancy. Moreover, both of these hypotheses may be involved, and they should not be considered mutually exclusive. On the other hand, the 20–29 years group is most likely underrepresented in our study sample because mothers in this age group accounted for 29.7% of births in Spain in 2010 (30). Optimal physical and medical conditions in this age group may explain the observed deviation and low incidence of influenza infection requiring inpatient care in this population. However, sporadic cases, including the first death in Spain from pandemic influenza, fell into this age category and received much media attention.

Several previous studies (26) have noted differences in the severity of influenza infection depending on the ethnic background, with minorities tending to be overrepresented in the more severe groups. In the present study, more pregnant women of foreign origin than nonpregnant women sought hospital care as a result of pandemic influenza infection, which may be explained by better medical coverage of pregnant women, regardless of their economic or immigration status.

Secondary changes occur in the immune system during pregnancy. The body shifts from a cell-mediated to a humoral-based immune response and becomes somewhat immunocompromised, which increases susceptibility to influenza virus and may be responsible for more severe complications associated with influenza infection (31,32). Therefore, prevention measures are particularly important for pregnant women. A majority of women in both the study groups reported having received information about measures to prevent infection by pandemic influenza. Nevertheless, the proportion of women adopting any of these protective measures was very low in both the groups. Apparently, prevention campaigns in Spain at this time were rather effective in delivering the message of how to prevent influenza infection; however, they were much less successful in convincing individuals to change their behaviors accordingly.

When it became available, vaccination was an essential component of the public health response to influenza A (H1N1)pdm09 (33) and Spain guidelines placed pregnant women in a high-priority group for receiving of influenza A (H1N1)pdm09 vaccine (34). The low level of use of influenza A (H1N1)pdm09 vaccine in pregnant women in Spain was similar to that in other countries (35) and it is disconcerting and has important implications for future pandemic influenza vaccination planning with special interest in pregnant women. In addition to the protection provided to mothers, influenza vaccination also seems to provide benefit to the infant (27,36,37).

No significant differences were observed between pregnant and nonpregnant women with regard to living conditions, employment, and smoking habits. With regard to the indoor environment (number of people living together and size of living area), daily activities, and the impact of job duties on health, no significant differences were observed between pregnant and nonpregnant women. Therefore, our study did not identify any risk factors for influenza infection that could be targeted for increasing prevention.

From analysis of self-evaluated health conditions before the development of influenza infection, it can be observed that pregnant women reported to be in a better condition than nonpregnant women. However, the clinical manifestations of the infection did not reveal differences between the 2 groups, apart from respiratory distress, hypoxemia, and unilobar consolidation. These 3 symptoms were significantly more prevalent among nonpregnant women. The main complications in both the groups were respiratory tract disease and exacerbation of underlying conditions with the former being most common. This could be because during pregnancy, physiological changes occur in the cardiovascular and respiratory systems, particularly during the second and third trimesters. With the progression of pregnancy, a woman's diaphragm is pushed upward, resulting in decreased lung capacity, which makes respiratory disease in pregnant women more dangerous (12).

Influenza infection can result in severe limitations on self-care and daily activities for both pregnant and nonpregnant women; however, no differences were observed between the 2 groups in this regard. This may result in part from sample bias because only women admitted to hospitals were considered in the present study. In fact, most of these women (approximately 87% in both the groups) required subsequent hospitalization, an indication of the severity of their infection at the time they visited the hospital.

Underlying diseases did not differ between pregnant and nonpregnant women, except for obesity, a finding similar to those of other studies (27,38–41). The clinical situation was also worse in the nonpregnant women. This could be due to their delayed arrival at the hospital, with a more evolved clinical picture. A complementary explanation could be the social, familial, and labor roles

of women aged 15 to 44 that may lead them to seek healthcare only when the disease is more advanced. It should be noted that in our study, we found no deaths of pregnant or nonpregnant women resulting from influenza infection.

Because the pregnant women enrolled in the present study were still pregnant when they completed the surveys, we are unable to gather data about the effects of influenza A (H1N1)pdm09 virus infection on the subjects' offspring. Furthermore, the effects of seasonal influenza A (H1N1)pdm09 on the health of fetuses and infants are not well understood. We propose that future studies on this topic are necessary. For example, maternal fever, which was a very common symptom in our study, has been associated with an increased risk of neural tube defects, neonatal seizures, hypoxic ischemic encephalopathy, cerebral palsy, neonatal death, and other complications (42–46) as well as with other adverse neonatal and developmental outcomes, when occurring later in pregnancy (47–49). In the present study, 95.9% of the pregnant women were febrile at some point during treatment; however, their fever lasted for a lesser time than that of nonpregnant women, probably because of a more rapid initiation of treatment. In pregnant woman with influenza, prompt treatment of fever with acetaminophen is recommended to reduce the risks to the fetus (50).

WHO recommends that pregnant women with suspected or confirmed influenza, regardless of the stage of pregnancy, should be treated with antiviral therapy (51,52). No differences were observed in the present study with regard to the frequency or nature of antiviral treatment between pregnant and nonpregnant women. Probably, early identification and treatment were the most important factors in the evolution of illness in both the groups of patients. Most authors recommend oseltamivir as the preferred treatment for pregnant women (11,21–23), and this was the antiviral of choice for most cases in our study.

We also have found some justification for the treatment of pregnant women with influenza (27), given the positive evolution of these patients. Among pregnant women, influenza A (H1N1) vaccination coverage in 2009 increased from its consistently low pre-pandemic levels (53); these higher levels appear to have been sustained during the 2010–2011 influenza season (54). Since the pandemic, we have witnessed a renewed interest in many topics related to pregnancy, including the immunology of pregnancy, the behavior of pregnant women in adhering to influenza vaccination recommendations, and the clinical management of critically ill pregnant women. However, it is still necessary to continue working to build on recent advances in this area. For example, further studies are required on best practices to maximize influenza vaccination coverage among pregnant women in order to meet the Healthy People 2020 objective of 80% participation for annual influenza vaccination coverage among pregnant women (55).

Our investigation has some limitations. The most important limiting factor is our sample size, despite being a nationwide study. Future studies would benefit from a larger sample size because size limits prevented us from performing deeper analyses. However, this is a common problem also observed in other studies (1). It should be kept in mind that many pregnant women with influenza infection may directly report to their obstetrician; therefore, they would not be treated at the hospital (33) unless they develop serious complications. Another limitation we acknowledge is the lack of complete information about the antiviral treatments administered to patients enrolled in the study. Future studies should seek strategies for controlling for this potential information bias.

In conclusion, given that influenza viruses are the most common cause of serious respiratory illnesses in winter around the world, the findings of the present study may be important to public health planners for planning influenza prevention strategies for both pregnant and nonpregnant women of reproductive age.

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Appendix The following are the members of the CIBERESP Cases and Controls in Pandemic Influenza Working Group: Andalusia: E. Azor, J. Carrillo, R. Moyano, J.A. Navarro, M. Vázquez, F. Zafra (Red de Médicos Centinela), M.A. Bueno, M.L. Gómez, M. Mariscal, B. Martínez, J.P. Quesada, M. Sillero (Complejo Hospitalario de Jaén), M. Carnero, J. Fernández-Crehuet, J. del Diego Salas (Hospital Virgen de la Victoria), M. Delgado Rodríguez (CIBERESP, Universidad de Jaén), V. Fuentes (Hospital Costa del Sol), V. Gallardo, E. Pérez (Servicio de Epidemiología, Junta de Andalucía), R. López (Hospital Infanta Elena, Huelva), J.R. Maldonado (Hospital de Torrecárdenas), J.M. Mayoral (Servicio de Vigilancia de Andalucía), Á. Morillo (Hospital Virgen del Rocío), J.M. Navarro, M. Pérez (Laboratorio de Referencia de Gripe), S. Oña (Hospital Carlos Haya), M.J. Pérez (Hospital Virgen de Valme), M.C. Ubago (Hospital Virgen de las Nieves), M. Zarzuela (Hospital Puerta del Mar). Valencian Community: J. Blanquer (Hospital Clínico Universitario), F. González Candelas (CIBERESP, CSISP-Universitat de Valencia), M. Morales (CIBERESP, CSISP-Universitat de Valencia, Hospital Doctor Peset). Castile and León: D. Carriedo, F. Díez, I. Fernández, S. Fernández, M.P. Sanz (Complejo Asistencial Universitario de León), J.J. Castrodeza, A. Pérez, S. Tamames (Dirección General de Salud Pública, Desarrollo e Innovación, Junta de Castilla y León), V. Martín (CIBERESP, Universidad de León), A. Molina (Instituto de Biomedicina, Universidad de León), J. Ortiz de Saracho (Hospital del Bierzo), R. Ortiz de Lejarazu (Centro Nacional de Gripe, Valladolid), A. Pueyo, J.L. Viejo (Complejo Asistencial, Burgos), P. Redondo (Servicio Territorial de Sanidad y Bienestar Social, León). Catalonia: A. Agustí, A. Torres, A. Trilla, A. Vilella (Hospital Clínic de Barcelona), J. Alonso (CIBERESP, UniversitatPompeuFabra, IMIM-Instituto Recerca Hospital del Mar), F. Barbé (Hospital Arnau de Vilanova), M. Baricot, N. Soldevila (CIBERESP), L. Blanch, G. Navarro (Hospital de Sabadell), X. Bonfill, J. López-Contreras, V. Pomar, M.T. Puig (Hospital de Sant Pau), E. Borràs, A. Martínez, Núria Torner (Dirección General de Salud Pública, Generalitat de Catalunya), C. Bravo, F. Moraga (Hospital Valld'Hebrón), F. Calafell, O. Garín (Universitat Pompeu Fabra), J. Caylà, C. Tortajada (Agencia de Salud Pública de Barcelona), À. Domínguez (CIBERESP, Universitat de Barcelona), I. Garcia, J. Ruiz (Hospital GermansTrias i Pujol), J.J. Garcia (Hospital Sant Joan de Deu), (Universitat Pompeu Fabra), J. Gea, J.P. Horcajada (Hospital del Mar), P. Godoy (CIBERESP, Departament de Salut Generalitat de Catalunya), N. Hayes (Hospital Clínic-CRESIB), T. Pumarola (REIPI, Universitat de Barcelona), A. Rosell (Hospital de Bellvitge), M. Sáez (CIBERESP, Universitat de Girona). Madrid: Carlos Álvarez, M. Enríquez, F. Pozo (Hospital 12 de Octubre), J. Astray (Subdirección de Vigilancia, Comunidad de Madrid), F. Baquero, R. Cantón, J. C. Galán (CIBERESP, Hospital Ramón y Cajal), A. Robustillo, M.A. Valdeón (Hospital Universitario Ramón y Cajal), E. Córdoba, F. Domínguez, J. García, R. Génova, E. Gil, S.

Jiménez, M.A. Lopaz, J. López, F. Martín, M.L. Martínez, M. Ordobás, E. Rodríguez, S. Sánchez, C. Valdés (Area de Epidemiología de la Comunidad de Madrid), J.R. Paño, M. Romero (Hospital Universitario La Paz). Navarra: J. Castilla (CIBERESP, Instituto de Salud Pública de Navarra), P. Fanlo, F. Gil, V. Martínez Artola, M. Ruiz (Complejo Hospitalario de Navarra), J. Gamboa, F. Pérez-Afonso M. Sota, M.E. Ursua, M.T.Virto (Red de Médicos Centinela), A. Martinez, L. Martínez (Instituto de Salud Pública). Basque Country: U. Aguirre, A. Caspelastegui, P.P. España, S. García (Hospital Galdakao), J. Alustizac (Hospital Mendaro), J.M. Antoñana, I. Astigarraga, J.I. Pijoan, I. Pocheville, M. Santiago, J.I. Villate (Hospital de Cruces), J. Arístegui, A. Escobar, M.I. Garrote (Hospital Basurto), A. Bilbao, C. Garaizar (Fundación Vasca de Innovación e Investigación Sanitarias), G. Cilla, J. Korta, E. Pérez Trallero, C. Sarasqueta (Hospital Donostia), F. Esteban, J.L. Lobo, C. Salado, E. Tato (Hospital Txagorritxu), J.M. Quintana (CIBERESP, Fundación Vasca de Innovación e Investigación Sanitarias).

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