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Pregnancy, obesity and other risk factors for complications in influenza A(H1N1) pdm09 infection

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ABSTRACT

Although influenza is usually a self-limited disease, patients who develop complications are at increased risk of hospitalization, intensive care unit admission and death. Since preventive and early therapeutic measures should be prioritized in higher risk patients, identification of the risk factors for severe infection is important from a public health perspective. Risk factors for complications in pandemics may show some differences with regard to seasonal influenza. During the influenza A(H1N1)pmd09 pandemic, although many cases occurred in younger adults, the risk factors identified for severe infections and complications were similar to those for seasonal influenza, including chronic respiratory, renal, liver, and heart diseases. Aged patients, although less frequently affected, were also at higher risk. Obesity, and particularly morbid obesity (>40 body mass index) has been noted as a significant risk factor for severe disease in the 2009 influenza pandemic. Some interesting recent studies provide insights into the biological reasons behind the poor outcomes in morbidly obese patients. In terms of pregnancy, the studies have shown contradictory results due to variations in methodology and medical care. However, it seems that pregnancy, particularly during the third trimester, increases the risk of complications, and that early antiviral treatment is associated with improved outcomes.

Embarazo, obesidad y otros factores de riesgo asociados al desarrollo de complicaciones de la infección por gripe A(H1N1)pdm09

Palabras clave:
Infección de gripe
A(H1N1)
Gripe pandémica
Gripe estacional
Complicaciones de la gripe
Factores de riesgo
Resultados

RESUMEN

Aunque la gripe es habitualmente una enfermedad autolimitada, el desarrollo de complicaciones se asocia con mayor riesgo de ingreso, de necesidad de cuidados intensivos y de muerte. Dado que las medidas preventivas y terapéuticas deben priorizarse en los pacientes de mayor riesgo, el conocimiento de los factores de riesgo tiene gran importancia desde la perspectiva de la salud pública. Los factores de riesgo de enfermedad grave pueden ser distintos en las pandemias; los factores identificados durante la pandemia 2009 A(H1N1), a pesar de que muchos de los casos ocurrieron en personas jóvenes, son similares a los de la infección estacional, incluyendo las enfermedades respiratorias, renales, hepáticas y cardíacas crónicas. Los pacientes ancianos, aunque menos frecuentemente afectados, también mostraron mayor riesgo. La obesidad, sobre todo la mórbida (índice de masa corporal > 40) ha sido también un factor de riesgo significativo durante esta pandemia. Recientemente se han publicado datos interesantes sobre las posibles explicaciones biológicas de este hecho. Con respecto al embarazo, los datos de los estudios son contradictorios debido a diferencias metodológicas y de atención sanitaria. Sin embargo, parece que el embarazo, particularmente durante el tercer trimestre, aumenta el riesgo de complicaciones, y que el tratamiento antiviral precoz mejora el pronóstico.

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Introduction

Influenza is an acute illness mainly affecting the respiratory tract that typically starts abruptly with a high fever, myalgia, sore throat, nasal discharge, and non-productive cough. However, the spectrum of the disease is broad. Some patients suffer a mild disease similar to a common cold while others have limited involvement of the respiratory tract and systemic symptoms predominate. Uncomplicated influenza, although quite uncomfortable, is a self-limited disease usually lasting 2 to 5 days. However, some patients suffer complications that can be life-threatening.[1] The most important complications of influenza are shown in Table 1.

The frequency with which complications develop in influenza infection is difficult to ascertain as it depends on the population studied, the diagnostic criteria, the setting, the definition of complications, the immunological status of the population, etc. However, even though only a minority of infected patients develops serious complications, the population-burden of morbidity and mortality among the highest risk groups is substantial due to the high numbers of people that may be infected during seasonal and epidemic influenza.[2] In the case of infections due to the influenza A(H1N1)pmd09 virus, the rate of hospitalization has been estimated at around 2-7% of infections during the first wave of the pandemic, with 6-15% of admitted patients requiring intensive care unit (ICU) admission.[3] In Spain, 43% of admitted patients had pneumonia.[4]

Recognition of persons at high risk of developing complications is relevant from a public health perspective for 2 reasons: first, vaccination campaigns can be targeted to persons at higher risk of developing complications; and second, since influenza may present with non-specific symptoms, diagnosis testing and early antiviral therapy may be prioritized for these patients. Certain underlying conditions have been traditionally recognized as risk factors for complications in seasonal influenza but there may be some differences during pandemics. Next we review the risk factors for complicated infection due to influenza A(H1N1)pmd09, with a specific emphasis on pregnancy and obesity.

Table 1
Main complications in influenza infections

Organ affected	Complications and comments
Respiratory tract	Pneumonia is the most frequent and severe complication
	Classified into primary (caused by influenza virus), secondary or bacterial (*Streptococcus pneumoniae, Staphylococcus aureus, Haemophilus influenzae*, etc.) or mixed
	Chronic pulmonary disease and asthma acute exacerbation
Muscle	Myositis and rhabdomyolysis
	Mainly in children
	Distinct from typical and usual myalgia
Central nervous system	Encephalitis, seizures, transverse myelitis, aseptic meningitis, and Guillain-Barré syndrome (direct etiological relationship with influenza virus not established)
Heart	Myocarditis, pericarditis (indirect effect)
	Myocardial infarction (epidemiological association)

Pregnancy and complicated influenza

Pregnancy has classically been considered a risk factor for severe disease among women with both seasonal and previous pandemics influenza. Nevertheless, the supporting evidence for this association in seasonal influenza is indirect, as it has been mainly obtained through ecological studies using proxy indicators such as respiratory illness-associated hospitalizations or deaths among pregnant women during flu seasons or pandemics. The influenza A(H1N1)pmd09 pandemic provided an opportunity to better delineate the relationship between pregnancy and complicated influenza. Three important circumstances concurred during this pandemic: the widespread availability of a reliable and real-time method for microbiological diagnosis, the broad availability of antiviral therapy, and the performance of cooperative, multicenter clinical studies.

Early during the influenza A(H1N1)pmd09 pandemic, several authors found pregnancy to be clearly associated with severe disease[5-10] while others, including us, did not.[11-14] The main results from these studies are summarized in Table 2. Methodological issues may partially explain this discrepancy. Estimating the burden of complicated influenza during pregnancy requires establishing a comparison between the rate of complications among pregnant and non-pregnant women of reproductive age who are infected. Although other non-validated clinical definitions have been proposed, severe disease has most commonly been defined in the various studies as one or several of the following: hospitalization, admission to an intensive care unit (ICU), or death. However, hospitalization and ICU admission are subject to both selection and clinical management bias; pregnant women might have been more easily admitted to the hospital and ICU just because they were already considered to be at increased risk for complications. In addition, administration of early antiviral therapy even in the absence of complicated influenza may have been more frequent.[6,11,13] Moreover, severe disease may be overestimated in pregnant women in comparison with non-pregnant women if patients are included by passive reporting. Mortality should be a less biased outcome variable to evaluate differences in the severity of disease, although again passive reporting may bias the results.

Researchers from the Spanish Network for Research in Infectious Diseases (REIPI) specifically investigated the impact of pregnancy on the severity of influenza A(H1N1)pmd09 infection by comparing the severity of presentation and the outcomes in pregnant and non-pregnant women of reproductive age within the REIPI multicenter prospective cohort of hospitalized patients with confirmed pandemic influenza.[13] We found a low frequency of severe complications in the 98 consecutive pregnant women admitted to the 13 participant Spanish hospitals. Overall, only 2 (2%) patients required ICU admission (both of them had comorbid conditions) and neither died. When controlled for confounders either by multivariate analysis or comparison of matched cohorts, pregnancy was not found to be independently associated with an increased risk of severe complications. As explained above, a lower threshold to hospitalization was evident among pregnant women, since hospital admission was considered to be "clinically-driven" only in 33% of pregnant women as compared to 66% among non-pregnant women. In addition, pregnant women were admitted earlier after the onset of symptoms, and antiviral therapy was also administered earlier, which we believe influenced the outcomes. The SEMICYUC multicenter sub-cohort including women of reproductive age with pandemic influenza admitted to 148 Spanish ICUs, showed a significant overrepresentation of pregnant women as compared with non-pregnant women, with a higher likelihood of pneumonia among the former.[10] Nevertheless, no statistically significant differences in mortality or in the need for mechanical ventilation were observed between the 2 groups. Interestingly, the proportion of pregnant women receiving early antiviral therapy was markedly lower in the SEMICYUC than in the REIPI cohort (14% vs. 41%).[10,13]

Since most complicated cases occurred during the third trimester of pregnancy, delivery and neonatal outcomes are other relevant issues. In a systematic review, Mosby et al.[15] found that in 3 of 4 series reporting more than 50 pregnancy outcomes, preterm birth rates approximated or exceeded 30% as compared with an average worldwide rate of preterm delivery of approximately 10%. Cesarean

Table 2
Summary of data from studies reporting outcome data of pregnant women with influenza A(H1N1)pmd09 infection

Reference	Design and setting	No. of PWI	No. of admitted PWI (%)	No. of PWI with clinically-driven admission (%)	No. of PWI admitted to ICU (%)	No. of dead PWI (%)	No. of PWI receiving early (<48 h) antiviral therapy (%)
					RR or OR for ICU admission (95%CI)*	RR or OR for death (95% CI)*	
6	Population-based case series (passive reporting), USA	788	509 (64.59%)	NA	115 (22.6%)	30 (5.9%)	148 (45.3%)
					3.7 (1.9-7.2)	NA (5% of influenza deaths)	
14	Population-based case series (passive reporting of hospitalized patients), Japan	181	NA	NA	1.1%	0	105 (58%)
					NA	NA	
9	Population-based cohort study (consecutive ICU admitted patients), Australia and New Zealand	62	NA	NA	NA	7 ICU-admitted patients	NA (median days until antiviral therapy: 6)
					7.4 (5-10)	NA (11% of ICU-admitted PW)	
10	Multicenter cohort study (consecutive ICU-admitted patients), Spain	50	NA	NA	NA	7 (14%)	7 (14%)
					Na (22% of ICU-admitted WRA)	NA (NS differences)	
6	Multicentre cohort study (consecutive hospitalized patients), Australia	43	NA	18 (42%)	8 (18.6%)	1 (0.55%)	12 (43%)
					NA	NA	
11	Single-center cohort study (consecutive hospitalized and non-hospitalized patients), Singapore	211	62 (29.4%)	35 (56.4%)	1 (1.63%)	0	70 (33.2%)
					NA	NA	
12	Single-center cohort study (consecutive hospitalized and non-hospitalized patients), La Réunion	141	85 (60%)	NA	1 (1.18%)	0	NA (median days until antiviral therapy: 2)
					0.4 (0.0-2.6)	NA	
13	Multicenter cohort study (consecutive hospitalized patients), Spain	98	NA	32 (33%)	2 (2.04%)	0	40 (41%)
					0.2 (0.05-1.5)	NA	

ICU: intensive care unit; NA: not applicable/not available; NS: no statistically significant; OR: odds ratio; PWI: pregnant women with influenza; RR: relative risk; SD: severe disease; WRA: women of reproductive age.
*Reference: non-pregnant women of reproductive age.

delivery was frequently reported in case series and cohort studies. Siston et al.[8] found cesarean delivery to be more common than vaginal delivery (58% vs. 42%), while the average cesarean delivery rate in USA was 38%.[15] In the aforementioned systematic review, maternal hypoxemia was found to be the most commonly reported indication for cesarean delivery.[15] Regarding neonatal outcomes, a low proportion of neonates born from infected pregnant women tested positive for influenza. Mosby et al. found that among the 45 neonates whose influenza status was reported in the literature, only 6 (13%) were positive. Therefore it is likely that the impact of prematurity on neonatal outcomes was more relevant than neonatal influenza infection. Finally, no relevant adverse events related to oseltamivir therapy have been reported among pregnant women.

Of note, influenza A(H1N1)pmd09 vaccination rates among pregnant women have been repeatedly reported to be low (<40%).[16,17] Recent data regarding the safety of vaccinations in this subset of population are reassuring.[18,19]

In summary, pregnancy is likely to be a significant risk factor for severe disease among women infected with influenza A(H1N1) pmd09. Increased clinician awareness leading to early diagnosis and antiviral therapy probably contributed to improvements in the prognosis for pregnant women with pandemic influenza in some studies. Infection with the pandemic strain during pregnancy was associated with premature delivery although the rate of vertical transmission was apparently not very high. Although the influenza A(H1N1)pmd09 vaccine was expected to be safe, as demonstrated afterwards, the vaccination rate was low, representing an opportunity for further improvement.

Obesity and the outcome of influenza infection

Obesity has become a worldwide epidemic. More than 30% of Americans are obese, as are more than a quarter of men and women in several European countries.[20] In recent years, the prevalence of

obesity in the Spanish population has risen to 17%.[21] Numerous health problems and chronic diseases have been related to obesity, including type 2 diabetes mellitus, hypertension, dyslipidemia, certain cancers, and cardiovascular diseases.[22]

Emerging data indicate an association between obesity and the risk of acquiring some infectious diseases or worsening their outcomes. However the mechanisms underlying these findings are not well established, and a number of potential factors may be involved. Immune system dysregulation, decreased cell-mediated immune responses, related comorbidities, respiratory dysfunction and pharmacological issues have been proposed as possible mechanisms.[23] In addition, excessive weight gain (≥18 Kg) may increase the risk of developing community-acquired pneumonia.[24] In obese patients, a disproportionately high percentage of total body oxygen consumption is allocated to respiratory work, resulting in reduced functional residual capacity and expiratory volume. Thus, a subsequent ventilation-perfusion abnormality may decrease ventilatory reserves and predispose this group to respiratory failure after even mild pulmonary challenges.[25] Obstructive sleep apnea is present in 40% of obese persons and is associated with systemic hypertension, pulmonary hypertension, and *cor pulmonale*.[26] In addition, obese persons are at increased risk of developing pulmonary emboli and aspiration pneumonia. Extremely obese persons may develop a sustained increase in arterial carbon dioxide tension due to chronic hypoventilation and chronic inflammation of the respiratory tract.[26,27] These are factors that may affect the outcome of acute lung injury which, if these patients need intensive care, may require prolonged mechanical ventilation and hospitalization.

As early in the pandemic as June 2009, severe pulmonary complications in 10 patients, of whom 9 had a body mass index (BMI) ≥30, and 7 had a BMI ≥40, were reported from Michigan.[28] After that, data from various studies (including the REIPI cohort) suggested that obesity and morbid obesity (BMI ≥40) affects the course of the disease and increases the hospitalization, intensive care admission and mortality rates.[29-42] One prospective, observational, multicenter Spanish study performed on ICU patients indicated that obesity was associated with a higher consumption of ICU resources, prolonged mechanical ventilation, a longer stay in the ICU and longer hospitalization.[43] Interestingly, obesity has been shown to be a particularly significant risk factor among patients <60 years of age.[33] Obesity has also been associated with pneumonia in patients with influenza A(H1N1)pmd09 infection in one study,[44] and a risk factor for mortality in hospitalized patients with community-acquired pneumonia due to influenza A(H1N1)pmd09 in another.[45] A recent systematic review and meta-analysis confirmed that obesity is associated with higher risks of ICU admission and death in patients with influenza A(H1N1)pmd09 infection.[46] In addition, a recent multinational study conducted by the World Health Organization including some 70,000 confirmed cases of H1N1 from the registries of nearly 20 countries found a clear association between obesity and poor outcomes in H1N1.[47]

The mechanisms underlying these findings have not been fully established. Obesity has been shown to have substantial effects on immune surveillance. Adipocytes produce cytokines, growth factors, and adipokines that promote macrophage activation. Among adipokines, leptin is considered to be pro-inflammatory and is elevated in obese individuals, whereas adiponectin reduces macrophage activity and pro-inflammatory cytokine production which, in these patients, is produced in decreased amounts. As a result, the innate immune system of obese individuals is hyperresponsive to pathogens.[48,49] Excessive pro-inflammatory cytokine release is a key determinant in severe influenza A(H1N1) pmd09 infection, and the pathogenesis of severe influenza infection shares properties similar to those in sepsis syndrome.[50] Sheridan et al.[51] reported that influenza vaccine antibody levels decline significantly and CD8+ T-cell responses are defective in the obese in comparison to healthy weight individuals. Thus, obese individuals may be at risk for a suboptimal vaccine response. In animal studies, diet-induced obese mice have been shown to be more susceptible to morbidity and mortality during influenza infection than lean mice due to altered innate immune responses[52] and impaired influenza-specific memory T-cell function in the lungs.[53]

The higher rates of mortality in obese patients have raised concerns about the adequacy of the standard dose of oseltamivir. However, standard dosing of oseltamivir may be adequate for obese patients, even for those that are critically ill, and dose adjustments are not required for individuals with obesity.[54-56]

In summary, although obese persons may have multiple co-morbidities that contribute to the risk of severe influenza, persons with BMI ≥30, and particularly with a BMI ≥40, are at higher risk for severe disease, influenza pneumonia, hospitalization, ICU admission, and death due to H1N1 infection, independently of other risk factors. Prompt empiric antiviral treatment for influenza may be advisable in these patients during influenza seasons. Oseltamivir doses should not be increased. Severely obese individuals should receive influenza vaccinations annually, although vaccinations may be less effective in the rest of the population.

Other risk factors for complicated influenza

Additional risk factors for complicated influenza, both seasonal and epidemic, have been recognized. Risk factors for severe disease following seasonal influenza infection include older age and chronic comorbid conditions such as pulmonary, cardiovascular, renal, liver, neuromuscular, hematologic, and metabolic diseases, as well as some cognitive conditions, and immunodeficiency.[2, 57]

When interpreting the studies, it is important to take into account that the population studied may be different (outpatients, admitted patients, or patients admitted to ICU), and the criteria for defining complicated disease may also vary. Outcomes evaluated included hospital admission, pneumonia, ICU admission, and death.

As for the 2009 pandemic, the results from the REIPI cohort identified the following variables as independent predictors for severe infection among hospitalised patients with influenza A(H1N1) pmd09 infection (defined as ICU admission or death): younger age (16-49 years), comorbid conditions, morbid obesity, and bacterial co-infection, while early antiviral therapy was protective. Among comorbid conditions, chronic obstructive pulmonary disease, obstructive sleep apnea syndrome, and chronic heart disease were more frequent in patients with severe influenza A(H1N1)pmd09 infection.[38] Other studies found asthma to be an important risk factor for hospitalisation and severe disease, particularly in children.[47,58,59] This variable was not associated with an increased risk of ICU admission or death either in the REIPI cohort[38] or in the international study;[47] our interpretation is that patients with asthma may have sought medical attention earlier and although admitted to the hospital, their subsequent evolution was better, probably because antiviral therapy was started early. In a Spanish study on patients admitted to the ICU, hematological diseases and continuous renal replacement therapy were also factors independently associated with poorer outcomes.[60] Other chronic conditions such as diabetes, neurological diseases and liver disorders appeared in only a few studies as a risk factor for severity.[41,59,61,62]

The aforementioned large multinational study found that older age, chronic respiratory tract, cardiac, liver, or renal diseases, immunosuppression, morbid obesity, pregnancy (third trimester), and asthma were associated with a higher probability of hospital admission; the same variables except for pregnancy and asthma, plus diabetes mellitus, and neurological diseases were associated with an increased probability of death.[47] This important study is a pooled analysis of patients included in national registries and the results were not controlled for confounders.

In a recent case-control study from China, chronic underlying diseases and poor psychological health were 2 important risk factors for severe disease.[63] In children, neurological and/or neuromuscular diseases and patients whose parents had less than a secondary educational level were at increased risk of hospitalization.[64]

An interesting risk factor to consider is the patient age. Unfortunately the results vary in the revised articles; as stated above, age <50 years was an independent predictor of severe disease in the REIPI cohort;[38] in fact, pneumonia was less frequent among patients >65 years, although no significant differences in mortality were found.[65] In New Mexico, mechanical ventilation was significantly more frequent in young adults (≥25 years).[62] In Canada the risk of a severe outcome was elevated in those ≥20 years of age.[66] Overall, all series reporting the data from the 2009 pandemic found a higher number of severe cases among young adults, which was attributed to the fact that older adults may have been partially immunized in their youth during previous circulations of other A(H1N1) viruses. However, in the previously mentioned multinational study, patients >64 years of age had the highest risk of death,[47] suggesting that while infection rates were very low in the oldest age group, their risk of death once they became infected was higher, as happens with seasonal influenza. Interestingly, a REIPI comparison of the hospitalised patients with infection due to influenza A(H1N1)pmd09 during the pandemic with those during the first post-pandemic season found the latter to be older, and comorbidities were more frequent; in addition, ICU admission rates and mortality were higher.[67] A similar trend was found among ICU-admitted patients in Spain.[60] Another recent study from China found that patients >65 years of age had the highest death-hospitalization ratio, and children <5 years the highest mortality rate.[33] In another study in California, adults aged 50-59 years had the highest fatality rate due to 2009 H1N1; however, for those hospitalized in intensive care, case-fatality ratios were high for all adults, but especially for those over 60 years of age.[69]

As for other potential risk factors that have been more inconsistently found in studies, male gender has been associated with an increased risk of death in one study;[62] young non-white patients without medical insurance were disproportionately likely to require ICU care in Utah (EEUU)[59] and in Manitoba (Canada)[70] and New Mexico,[62] ethnicity appeared to be related with severe infection.

Clearly, immunosuppression is a risk factor for complications.[38,71] However, we will not discuss immunosuppression or the protective effect of antiviral therapy here, because they are the subject of other articles included in this supplement.

Conclusions and areas for future research

Despite differences in methodology and biases, the available evidence suggests that risk factors for complicated infection were similar (except for age) during the 2009 influenza pandemic as those in seasonal influenza. Pregnancy appears to be, as in previous pandemics, associated with an increased risk for severe infection, particularly in the third trimester. Also, obesity, and especially morbid obesity, has been clearly recognized a risk factor during the pandemic. These populations should be prioritized as targets for preventive actions such as vaccination campaigns, early diagnosis and antiviral therapy.

Areas for future research include the characterization of pregnancy and obesity as risk factors in seasonal influenza, the performance of population-based studies rather than hospital-based studies to identify risk factors for complications, and the identification of potential genetic features of the host and virulence factors of the virus that are associated with an increased risk of complications.

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Conflicts of interest

JRB has been a consultant for Roche and Merck, and has been a speaker for Merck. JRPP, EMR and FSP declare no conflicts of interest.

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