CASO CLÍNICO

Infection by human Influenza A (H1N1) in pregnant women. Report of Three cases at the Oaxaca Regional Specialist Hospital.

Chávez-Manzanera Emma Adriana*, Rosas-Saldivar Jessica Magali**,
Velásquez-Paz Arturo Luis***

* 4th Year Resident of Internal Medicine
National Institute of Medical Science and Nutrition "Salvador Zubirán"
** Pregraduate Medical Intern, Medicine Faculty of the Universidad Nacional Autónoma de México; NUCE Group.
Oaxaca Regional Specialist Hospital
*** Investigation Department. Oaxaca Regional Specialist Hospital

DETALLES DEL ARTÍCULO

Recibido el 26 de septiembre de 2009
Aceptado el 6 de noviembre de 2009

Rev Eviden Invest Clin 2010; 3 (1): 61-67

Correspondencia/*Correspondence*

Emma Adriana Chávez Manzanera
National Institute of Medical Science and Nutrition "Salvador Zubirán"
Vasco de Quiroga No. 15 Sección XVI, Delegación Tlalpan, 14000 México D.F.
Tel. 52(55)52352498. 52(55)28431978
emanzanera@hotmail.com

INFECCIÓN POR INFLUENZA HUMANA A (H1N1) EN MUJERES EMBARAZADAS. REPORTE DE 3 CASOS DEL HOSPITAL REGIONAL DE ALTA ESPECIALIDAD DE OAXACA.

Palabras clave: embarazo, influenza estacional, influenza A (H1N1), pandemia, México

RESUMEN

Durante las epidemias y pandemias previas por influenza estacional se ha comprobado una mayor morbilidad y mortalidad en mujeres embarazadas en comparación con las no embarazadas. Se ha registrado a nivel mundial un incremento de hasta siete veces el número de defunciones maternas durante la pandemia de influenza por el virus A (H1N1). Presentamos tres casos de infección por influenza humana A (H1N1) en mujeres embarazadas que se atendieron en la UCI del Hospital Regional de Alta Especialidad de Oaxaca con el objetivo de dar a conocer nuestra experiencia y contribuir a evitar el retraso en la atención médica de este tipo de pacientes.

Key words: pregnancy, Seasonal Influenza, H1N1 influenza, pandemic, Mexico

ABSTRACT

During previous seasonal influenza epidemics and pandemics, a higher morbidity and mortality has been shown in pregnant women when compared to those who were not pregnant. Worldwide, an up to seven fold increase in the number of maternal deaths has been registered during the Influenza pandemic caused by the virus A (H1N1). We present three cases of infection by human Influenza A (H1N1) in pregnant women treated in ICU the Oaxaca Regional Specialist Hospital with the object of sharing our experience and helping to avoid the delay in medical attention offered to this type of patients.

Introduction

In México between February and April of 2009, there was an increase in the number of hospitalizations and deaths due to acute pneumonia, and in the number of cases of suspected influenza. The virus A (H1N1), a new strain of the influenza virus, was identified by the Center for Disease Control and Prevention (CDC) on the 17th of April, 2009.[1] During previous epidemics and pandemics of seasonal influenza, a higher rate of morbidity and mortality in pregnant women has been registered than in women who were not pregnant. However, there are few reports to date on the seriousness of the infection caused by the A (H1N1) influenza virus in pregnant women.[2]

Worldwide, an up to seven fold increase in the number of maternal deaths during the influenza pandemic of the A (H1N1) virus has been registered. The Mexican SINAVE (Immediate Notification System of Maternal Deaths) recorded an increase in the number of maternal deaths caused by pneumonia during the periods from the 1st of January to the 9th of September, 2009, with a total of 682 maternal deaths being registered (estimated cause of maternal death of 46.9 per 100,000 live newborns). Of these 10.3% were due to pneumonia caused by influenza in comparison to 2.5% and 2.9% registered in 2007 and 2008, respectively; this signifies an average of nine deaths per month.[3]

The mechanisms that condition a greater susceptibility and risk of complications and death during pregnancy are those that occur as a physiological compensation during pregnancy, such as hyperventilation, relative anemia and the increase in cardiac output as well in obesity. In this article, we present the following cases of infection by human A (H1N1) influenza virus in pregnant women that were treated in ICU (Intensive Care Unit) the Oaxacan Regional Specialist Hospital with the aim of sharing our experience and helping to avoid the delay in medical attention for this type of patient.

Presentation of Cases

Case 1

The patient was a 37 year old female in the 37th week of gestation and a prior history of obesity. The patient presented respiratory symptoms characterized by rhinorrhea, pharyngeal pain, dry cough and a fever of 38 degrees centigrade. A productive cough and dyspnea were added on the fourth day, for which reason an emergency cesarean was carried out in a private clinic; two days after the cesarean section, the patient presented and increase in dyspnea and hemoptysis, for which reason the patient was sent to our hospital. On being admitted, the patient presented breathing difficulty and acute hypoxemia, for which reason she was intubated. The patient was started on Oseltamivir, Ceftriaxona and Claritromicina; at the beginning the rapid test was negative for which reason real time PCR was carried out, giving a positive result. The X-ray of the thorax presented diffuse bilateral alveolar infiltrates. After 24 hours of being interned in the hospital, the patient presented acute renal insufficiency, hyperkalemia and metabolic acidosis. The patient required Norepinefrina to handle the septic shock. On the sixth day after being interned, the patient presented progressive leukocytosis and refractory hypoxemia with high PEEP and FIO2, outside the lung protective range. On the seventh day, the patient presented ventricular fibrillation that was unresponsive to attempts at cardiopulmonary resuscitation.

Case 2

The patient was a 30 year old female multipara with 38 weeks of gestation, previously healthy with a normal pregnancy. On the 23rd of August, 2009, an elective cesarean section was carried out, and two days later the patient presented a productive cough, whitish expectoration and fever. On the sixth day hemoptysis and dyspnea were added to the symptomatology. The patient was initially sent to a Hospital in Juchitan where the rapid test for influenza was carried out giving a negative result. The patient was treated empirically with Oseltamivir, Cefotaxima, Beclometasona and micro-nebulizations. On the 30th of August, the patient was sent to our institution due to the worsening of the symptomology. During the physical examination, the patient was found to have dyspnea, oxygenation 40%, with bilateral dispersed rales and right baseline consolidation syndrome. The patient was initiated on Tigeciclina, Claritromicina, Oseltamivir and invasive mechanical ventilation. The thorax x-ray showed disseminated infiltrated alveolar and a ground glass appearance. During the hospitalization, the patient presented septic shock with the isolation of Escheri-

chia coli in the bronchial secretion culture that was responsive to Tigeciclina; however the patient continued to show a tendency to leukocytosis and fever, for which reason Voriconazol and Ceftazidima were added to the treatment to cover Pseudomonas. The evolution was unfavorable with Acute Respiratory Distress Syndrome shown in image and arterial blood gas studies, with high ventilation patterns outside of the pulmonary protection range. On the 15th day after being admitted, Vancomicina was added to the treatment and the catheters were removed because the patient continued with fever and leukocytosis. The patient showed a partial response to the treatment. Twenty one days after being admitted, the patient fell into a cardio-respiratory arrest due to acute refractory hypoxemia and did not respond to attempts to resuscitate.

Case 3

The patient was 23 years old, primiparous, with a gestation of 37 weeks and was negative to chronic degenerative diseases. The patient started the eleventh of August 2009, with a dry cough, coryza, rhinorrhea and fever. Later, a productive cough and yellow expectoration were added to the symptoms, for which reason the patient went to a private Hospital where she was admitted for airway infection and febrile illness. The patient received an unspecified treatment for three days and was then released due to clinical improvement. On the third day after having been released, the patient presented dyspnea and a relapse of the fever, for which reason the patient was taken to a second level Hospital where she received an emergency cesarean section on the 23rd of August and was admitted with a diagnosis of multifocal pneumonia with a negative result for the rapid test for influenza. The patient received treatment with 75mg of Oseltamivir every 12 hours for three days, Cefotaxima, Clindamicina, Beclometasona and Salbutamol. The patient was referred to our institution on the fifth day with surgical puerperium due to an acute respiratory deterioration and was intubated on arrival. The tomography of the thorax showed diffuse infiltrated alveolar, consolidation at the right base and right pleural effusion. The patient was treated with Tigeciclina, Claritromicina, Oseltamivir and Drotecogin alfa (recombinant human activated C protein) during the first 24 hours. The patient remained in intensive care for 28 days with invasive mechanical ventilation to treat the ARDS, with diagnostics of long term intubation, septic shock, ARDS sequelaes and pneumonia associated with the ventilator with bronchial secretion culture of Stenotrophomona maltophilia responsive to quinolones. On the 28th of September, the patient was passed to the ward with a tracheostomy and mechanical ventilation with SIMV for the weaning protocol. During the hospitalization, the patient presented Systemic Inflammatory Response Syndrome on various occasions and was treated with Meropenem, Vancomicina and Amikacina with ulterior development of Pseudomonas aeruginosa and Acinetobacter Baumannii from the bronchial secretions responsive to carbapenemics, reducing the fever with the treatment. On the first of October, the patient was successfully weaned off the invasive mechanical ventilator with the help of the tracheostomy reservoir mask as well as physical and pulmonary rehabilitation. The control tomography of the thorax showed pulmonary fibrosis predominantly on the right and bronchiectasis. The patient was discharged on the 43rd day after being admitted.

Discussion

In April, 2009, the World Health Organization (WHO) received reports of cases of infection by a new virus of influenza, the A (H1N1) transmitted from person to person in Mexico and the United States. Among the high risk groups are children under five, senior citizens, pregnant women, and patients with chronic diseases (cardiovascular, respiratory, renal, hepatic diseases, diabetes mellitus and immunosuppressant diseases).[4] The current recommendation of the CDC (Center for Disease Control and Prevention) for the A (H1N1) influenza pandemic is to begin empiric treatment when there are disease symptoms similar to those of influenza and to use chemoprophylaxis with Oseltamivir or Zanamivir in pregnant women who come into contact with infected patients or who are suspected to be infected by the influenza virus and not to wait for the result of the real time PCR. During the period of seasonal influenza, the CDC also recommends applying the vaccine against the flu to all pregnant women after the first trimester.[5-10]

The use of Oseltamivir in the first 48 hours is associated with a reduction in the risk of pneumonia, otitis media and hospitalization versus the control group. It

also reduces the duration of the symptoms in hours with respect to the control group (16.28 vs. 22.75); as well as the time for the return to normal daily activities (34.8 vs. 36.3). (11) Other studies indicate that Oseltamivir can reduce mortality, including when it is ingested >48 hours of the symptoms having started in patients admitted for seasonal influenza.[9] Oseltamivir is the treatment of choice in pregnant women since it has not shown adverse effects. The percentage of malformations was 1.1% in a population of 90 pregnant Japanese women who received a therapeutic dose (75 mg every 12 hours for 5 days) of Oseltamivir during the first trimester. The percentage of malformations due to the use of Oseltamivir was equal to the general population (1- 3%).[12] It is also important to treat the fever with Acetaminofen since fever is related to various adverse fetal and neofetal events (birth defects and prematurity).[13]

The first report of cases of pneumonia for A (H1N1) influenza in pregnant women was made by the CDC (Center for Disease Control and Prevention) of the United States at the end of May with the detection of 20 cases. Three pregnant women required hospitalization, all patients presented symptoms of disease similar to influenza and one patient died. The patient that died was 33 years old with 35 weeks of gestation. On the sixth day of having begun with cold symptoms, the patient presented Acute Respiratory Distress Syndrome (ARDS) and pneumonia and was treated with mechanical ventilation and antibiotics; thirteen days after having started with respiratory symptoms, Oseltamivir was added to the treatment due to a positive result for A (H1N1) influenza using real time PCR, and the patient died on the 19th day.[6] In another series of cases of seven pregnant patients with infection by A (H1N1) influenza admitted to the intensive care unit in the Hospital of Obstetrics and Gynecology in San Francisco, California, five patients were in the third trimester of pregnancy and two in the second trimester. There was only one maternal death, in a 39 year old woman with a previous history of obesity and smoking. The most frequent co morbidity was concurrent bacterial pneumonia. The risk factors found in this group of hospitalized patients were obesity, low socio-economic level, active smoking, gestation in the third trimester and concurrent cardiac disease.[14]

In a retrospective study of 272 confirmed cases of A (H1N1) influenza in hospitalized patients between April and June in the United States, the most affected group were patients under 18 years of age (45%), adults over 65 years of age (5%) and pregnant women (7%). Of the 18 pregnant women, a third had a concurrent illness (asthma and diabetes mellitus). With respect to the number of weeks of pregnancy, 2 patients (11%) where in the first trimester, 3 patients were in the second trimester and 12 (67%) were in the last trimester of pregnancy. Six patients were admitted to the intensive care unit and the most common complications were ARDS, pneumonia and sepsis. Three pregnant women died (50%).[15] In another retrospective study realized in the United States, 34 confirmed cases of pregnant women with A (H1N1) influenza were found. This study showed a higher percentage of admission to hospital compared to the general population 32.4% vs. 4.2%, respectively (0.32 per 100 000 pregnant women vs. 0.076 per 100 000 of population at risk). Of the 45 registered deaths for the pandemic of influenza H1N1 from the 15th of April to the 16th of June, 2009, six people (13%) were pregnant women. Of the pregnant women who died, one was in the first trimester of pregnancy, one was in the second trimester and four were in the third trimester. The time of appearance of the symptoms to the time of presentation for medical attention was in the range of 1-7 days (mean 3.5 days). The time of appearance of the symptoms to the time of antiviral treatment was from 2-14 days (mean 4.5). All of the patients required invasive mechanical ventilation secondary to the development of viral pneumonia and ARDS. In none of the cases, added bacterial infection was demonstrated.[2]

In Mexico, a retrospective study evaluated the mortality and the epidemiological analysis of 122 deaths due to A (H1N1) influenza. 45.1% of the deaths occurred in persons of 20-39 years of age. The lethality was 2.2% (122 deaths among 5, 563 confirmed cases). The death rate was similar in both sexes. In relation to the past medical history, 83% showed a previously diagnosed condition; of these 36.1% presented a metabolic disorder (diabetes mellitus and obesity), 30.3% were smokers, 17.2% had cardiovascular conditions and 7.4% presented respiratory problems, and at a low level, infectious, anti-immunological and neoplastic conditions. The mean time that passed between the onset of the symptoms and the hospitalization was 6.2 days, and of the 122 deaths that were analyzed only 17% received hospital attention in the first 72 hours.[1]

In this article, a descriptive revision of three women with surgical puerperium in the intensive care area was carried out in a third level hospital in the city of Oaxaca. The patients were attended previously in second level hospitals where cesarean sections were carried out due to respiratory failure; therefore we do not know the infection rate of influenza in pregnant women, the number of patients admitted to hospitals or the outcomes. The diagnosis was through real time PCR and in one patient by post mortem pulmonary biopsy. The patients presented a rapid course of progression of the secondary pulmonary condition to infection by the virus of A (H1N1) influenza, requiring in the three cases invasive mechanical ventilation and the management of refractory hypoxemia with goals of ARDSNet (Acute Respiratory Distress Syndrome). The course of the patients was unfavorable with bacterial superinfection at a pulmonary level and bacteremia. The differences that are found between the patient that survived and the two that died were: age, body mass index, absence of hemoptysis, opportune collection of cultures, number of antibiotics used and change to antibiotics with coverage for inpatient microorganisms due to the presence of data of systemic inflammatory response after 48 hours of being admitted. Comparing the patients with the revised medical literature, the percentage of mortality in patients admitted to our hospital is over 66% against 14% to 50% worldwide. They share some characteristics with our patients such as obesity, low socio-economic level, in the third trimester of pregnancy and late starting of treatment with neuroaminidase inhibitors after 48 hours. (Table 1)

Table 1. Variables analyzed in the patients

Variables	Case 1	Case 2	Case 3
Maternal Age (years)	37	30	23
Gravidity	2	4	1
Parity	2	3	Nulliparous
Weeks pregnant at time of infection	37	38	37
Relative with pneumonia or with DSI[§] in the 7 days prior to the onset of the disease	Unknown	Unknown	Unknown
Body Mass Index	43.4	39.2	36.5
DSI[§] Symptoms	Yes	Yes	Yes *
Time between the onset of the symptoms and the use of Oseltamivir	8 days	6 days	13 days
Time between the onset of the symptoms and the hospitalization of the patient	8 days	6 days	13 days
Rapid test for Influenza	NA **	Negative	Negative
Days of inpatient stay	7	23	43
Bacterial superinfection	Yes	Yes	Yes
Number of antibiotics used	2	5	9
Complications	Renal failure, Pneumonia and Bacteremia	Pneumonia associated with ventilator	Pneumonia associated with ventilator

[§]DSI: Disease similar to influenza
*All of the patients presented symptoms of DSI: dyspnea, tachypnea, hypoxemia y hemoptysis. Case 3 didn't present hemoptysis.
**The rapid test for Influenza was not carried out.

Conclusions

It is believed that the principal mechanisms that condition the most susceptibility and risk of complication and death in pregnant women are related to physiological changes that occur during pregnancy as well in obesity. In pregnancy, there is a progressive decrease

in the functional residual capacity (CFR) from 10% to 25% towards the end of the pregnancy. The volume of espiratory reserve also decreases significatively, with total pulmonary capacity being preserved. The ventilation per minute increases markedly during pregnancy; beginning in the first trimester and reaching 20-40% above base levels at the end; the tidal volume increase by approximately 30-35%.[16] Moreover, added to these are the changes due to obesity such as the reduction in the Forced Expiratory Volume in the first second (FEV1), the Forced Vital Capacity (FVC), The Total Lung Capacity (TLC), the Functional Residual Capacity (FRC) and the Espiratory Reserve Volume (ERV) with relation to the progressive increase in the body mass index. With respect to the consumption of O2 and the production of CO2 (VCO2), both are increased in the obese, as a consequence of the increase in metabolic activity due to the excess of fat and the workload to support the tissues. The normocapnia is maintained by the increase in the respiratory volume per minute, which in turn carries a greater cost in oxygen for respiration. The reduction in the caliber of the airways due to the decrease in the pulmonary capacity and the early closing of the small airways predisposes the patient to hypoxemia and hypercapnia in the most advanced cases.[17] Among other theories related to the mechanism of greater susceptibility in pregnant women are the alterations in the cardiovascular system with an increase in cardiac load, relative anemia, immunology, fluid overload and interstitial edema secondary to a reduction in the oncotic pressure.[2,14]
It is important not to wait for the results of the RT PCR test (real time reverse transcriptase) even though it is very sensitive, since the result could take more than a week; moreover the rapid test for influenza should not be relied upon due to its low sensitivity of 30% and specificity of 58%. The delay in treatment is one of the major prognostic factors for the development of complications at a pulmonary level.[18]

The objective of this study is to contribute to an improvement in the early detection and opportune care of cases of acute influenza in pregnant women. The early use of neuraminidase inhibitors in hospitals of first contact (first and second levels of attention) as well as in gynecological hospitals are fundamental for the prognosis of the pregnant patient. These actions added to the administration of the vaccine against A (H1N1) influenza will significantly reduce the rate of morbidity and mortality in pregnant women infected by A (H1N1) influenza in our country.

Acknowledgments:

Dr. Mario Acosta Castellanos, Chief of Hospital Epidemiology; Dr. Gerardo Pérez Bustamante, Subdirector of Clinical Services; and Dr. Daniel Javier Méndez López of the X-Ray Department of the Oaxacan Regional Specialist Hospital for their help in the carrying out of this study.

Referencias

1. Fajardo-Dolci G.E, Hernández-Torres F, Santacruz Varela J, et al. Perfil Epidemiológico de la mortalidad por influenza humana A (H1N1) en México. Salud Pública de México 2009;51(5):361-371.
2. Jamieson Denisem J, Honein Margaret A, Rasmussen Sonja A, et al. H1N1 2009 influenza virus infection during pregnancy in the USA . Lancet 2009;374:451-58.
3. Complicación y muerte en mujeres embarazadas durante la pandemia de influenza. Aviso epidemiológico DGAE/09/007 del 10 de septiembre de 2009 [consultado el 30 de septiembre de 2009]. Disponible en www.dgepi.salud.gob.mx
4. Guidelines for Pharmacological Management of Pandemic (H1N1) 2009 Influenza and other Influenza Viruses. WHO. August 20, 2009.
5. Ayoub DM, Yazbak FE. Influenza vaccination during pregnancy: a critical assessment of the recommendations of the advisory committee on immunization practice (ACIP). J Am Physicians Surg 2006;11:41-7.
6. CDC. Novel Influenza A (H1N1) Virus Infections in Three Pregnant Women. United States , Abril-Mayo 2009.
7. CDC. May 3, 2009. What Pregnant Women Should Know About H1N1 (formerly called swine flu) Virus.
8. CDC. June 30, 2009. Pregnant women and novel influenza A (H1N1 Virus. Considerations for clinicians.
9. CDC. Jul 6, 2009. Considerations regarding novel H1N1 flu virus in obstetric setting.
10. CDC.2008. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP).
11. Gums JG PE, Blumentals WA . Oseltamivir and influenza related complications, hospitalization and healthcare expenditure in healthy adults and children. Expert Opinion on Pharmacotherapy 2008;9:151-61.
12. Tanaka Toshihiro, Nakajima Ken, et al. Safety of neuraminidase inhibitors

against novel influenza A (H1N1) in pregnant and breastfeeding women. CMAJ 2009;181:55-58.
13. Rasmussen SA, Jamieson DJ, et al. Pandemic influenza and pregnant women. Emerg Infect Dis 2008;14:95-100.
14. Saleeby Erin, Chapman Jocelyn, Morse Jessica and Bryant Allison. H1N1 Influenza in Pregnancy. Obstetrics & Ginecology 2009;114:885-89.
15. Jain Seema, Kamimoto Laurie, et al. Hospitalized Patients with 2009 H1N1 Influenza in the United States, April–June 2009. N Engl J Med 2009;361:1-10.
16. Richard Albert, Stephen Spiro, James J. Tratado de Neumología. Harcourt 2001;capitulo 54
17. Midley Alejandro D. Fisiopatología y soporte ventilatorio no invasivo en la falla respiratoria aguda de los pacientes con obesidad. Rev Arg Med Resp 2008; 8: 64-72.
18. Uyeki TM, Prasad R, Vukotich C, Stebbins S, et al. Low sensitivity of rapid diagnostic test for influenza. Clin Infect Dis 2009;48:89–92.