Rubella Vaccination of Unknowingly Pregnant Women During 2006 Mass Campaign in Argentina

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We report a prospective study of 56 pregnant women inadvertently vaccinated with rubella vaccine during the 2006 campaign performed in Argentina. Of these patients, 48 (87%) were immune, whereas the remaining 9 (16%) were susceptible. In the latter group, 7 presented with a primary reaction to the vaccine confirmed through immunoglobulin (Ig) G antibody avidity testing or seroconversion of IgG titers. During the clinical and laboratory follow-up, newborns did not present evidence of infection or malformations compatible with congenital rubella syndrome.

Rubella is a highly contagious acute exanthematous disease that affects both children and adults, with minor morbidity and few complications. The highest risk occurs when susceptible pregnant women are exposed to the virus during the first months of pregnancy, when infection with the virus can cause congenital rubella syndrome (CRS) and may have disastrous effects on the fetus.

Since the vaccination against rubella was introduced in the United States, the incidence of the disease has decreased by 99%. Similar results have occurred in many countries of the Americas that have obligatory vaccination schemes, such as Argentina. The measles-mumps-rubella vaccine with viral type RA27/3 attenuated virus was introduced in Argentina in 1998; subsequently, a major decrease was noted in the number of reported cases of rubella [1].

In September 2003, the 44th Directing Council of the Pan American Health Organization (PAHO) adopted as a goal to eliminate rubella and CRS by 2010 [2]. In line with this strategy, from September to December 2006, the Argentine Ministry of Health implemented nationwide measles-rubella vaccination of women of childbearing age (15–39 years). A total of 6 718 314 women were vaccinated during the campaign, and 98.8% coverage was achieved. The rubella vaccine is composed of an attenuated strain and can cause viremia (the duration of which is shorter than that of the natural infection). The vaccine virus could also cross the placental barrier and reach the fetus [3, 4].

The main purpose of the study was to evaluate the serological status and the embryo-fetal adverse effects in unknowingly pregnant women who had been vaccinated against rubella. Most pregnancies were followed up, and the newborns were evaluated.

MATERIALS AND METHODS

This prospective study performed in Argentina was launched during the 2006 vaccination campaign. The study included pregnant women (age, 15–39 years) who were vaccinated with measles-rubella–containing vaccine.

To validate the sample, an active search for cases that met the inclusion criteria was done. A total of 56

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pregnant women were studied. The age range was 16–38 years (mean, 26 years).

The largest percentage of pregnant women lived in the Buenos Aires capital district (67.8 %), followed by the province of Buenos Aires (28.7%), and thirdly the province of Santa Cruz (3.5%). Patients in Buenos Aires capital district were monitored clinically by the Centro Nacional de Genética Médica (CENAGEN), a center for the prevention and treatment of birth defects.

The source of health consultations was not random but corresponded to patients seen in some health care centers of the country, most likely representing a small sample of the total number of pregnant women who were vaccinated. The total population of Argentina, according to the last census conducted (2001), is 36 260 130 people; the city of Buenos Aires represents 7.6%, the province of Buenos Aires represents 38.1%, and Santa Cruz represents 0.5%.

Maternal serum was tested for rubella-specific immunoglobulin (Ig) G and IgM using a commercial enzyme-linked immunoserologic assay (ELISA) and rubella (IgM) capture ELISA. Maternal serum samples were also studied with the rubella IgG avidity assay. All equipment used was developed by Radim. Results were calculated on the basis of the specifications of the kits.

Women were grouped according to their immunity against rubella laboratory results (IgM negative and IgG positive) and susceptibility if they were IgM positive after the vaccination.

To confirm primary maternal infection with the vaccine virus, cases considered susceptible were studied using the avidity technique and on the basis of seroconversion (Table 1). Clinical follow-up was conducted among the susceptible pregnant women. The newborns of susceptible women were clinically evaluated to identify CRS-compatible signs or symptoms. These signs or symptoms were characterized by (1) cataracts, congenital glaucoma, congenital heart disease (most commonly ductus arteriosus or peripheral pulmonary artery stenosis), hearing impairment, or pigmentary retinopathy; and/or (2) purpura, hepatosplenomegaly, jaundice, microcephaly, developmental delay, meningoencephalitis, and/or radiolucent bone disease. A case was considered to have been clinically confirmed if a medical doctor identified 2 complications in group 1 or one complication from group 1 and another complication from group 2. Serum samples were collected from the newborns to identify the presence of IgM antibodies.

Table 1. Follow-up of Suspected Cases With Primary Reaction to the Vaccine

Patient	Maternal IgG/IgM status	Maternal avidity percentage	Case classification	Newborn IgM status
1	+/+	5	Susceptible	Negative
2	+/+	11	Susceptible	Negative
3	+/+	12	Susceptible	Negative
4	+/+	14	Susceptible	Negative
5	+/+	29	Susceptible	Not determined
6	+/+	32	Susceptible	Not determined
7	+/+	53	Indeterminate	Not determined
8	+/+	71	Immune	Not determined
9	+/+	Not determined	Susceptible[a]	Negative

NOTE. Case classification by avidity test: susceptible, low avidity (<50%); indeterminate, intermediate (50%–60%); and immune, high (>60%). IgG, immunoglobulin G; IgM, immunoglobulin M.

[a] Determined on the basis of positive IgG serological conversion.

RESULTS

Of 56 pregnant women, 83.9% were IgG and IgM negative and the remaining 9 (16.1%) were IgG and IgM positive. In 7 patients (13%), primary reaction to the vaccine was confirmed (susceptible) by means of IgG antibody avidity testing or seroconversion of IgG titers. Of the remaining patients, one was immune and the other was determined to be indeterminate by avidity testing (Table 1).

None of the patients studied ($n = 56$) presented with immediate clinical symptoms compatible with rubella (rash and fever), with the exception of 1 patient who belonged to CENAGEN in whom both symptoms were observed after vaccination. However, the patient's serological status was IgG positive and IgM negative; for reason it was determined that the symptoms were not associated with the vaccine.

In the subgroup of patients from the city of Buenos Aires (38 patients) who were seen by clinics outside of CENAGEM, clinical follow-up was performed for 28 patients to determine whether there was a delayed onset of symptoms associated with the vaccine. Through the follow-up, 1 molar pregnancy and 5 abortions were found that corresponded to the group of patients with prior rubella immunity.

Of the patients classified as susceptible, 4 were from the province of Buenos Aires, 2 were from Santa Cruz, and 1 was from the city of Buenos Aires. For 5 of them, the pregnancy was followed up clinically until birth. All newborns had normal clinical evaluation findings; no signs of CRS were present, and IgM results were negative in all cases.

DISCUSSION

To eliminate congenital rubella, Argentina implemented a vaccination campaign targeting women aged 15–39 years from September to November 2006. Our purpose was to determine the serological status and embryo fetal adverse effects, especially CRS, in a sample of unknowingly pregnant women who had been vaccinated. In a previous study that included 680 women exposed to the vaccine against rubella (3 months prior to the pregnancy or during its course), no malformations compatible with CRS were found [5]. In another prospective study

performed in Iran in 2003, among women who had been vaccinated during pregnancy, 5 neonates were born with IgM-positive cord blood whose signs were also not compatible with CRS. In a serological study involving 149 newborns of susceptible mothers, 10 infants (6.7%) had anti-rubella antibodies; none presented with CRS-related congenital defects in the medical re-examinations at birth and at 3 months of age [4].

In the total patient sample we studied, a maternal immunologic response to the rubella vaccine was noted in 13% of the pregnant women studied. The number of women of childbearing age who were susceptible to rubella are much higher than the previous estimates obtained in our country. Although these values may be overestimated, given the small sample size, they indicate the need for having implemented a mass vaccination campaign in our population.

After the use of the vaccine, no adverse effects were seen in the newborns or in the offspring of susceptible women, and no CRS cases or asymptomatic IgM-positive cases presented. Therefore, we believe that these results, although they should be extended to include a larger number of cases, contribute to the evidence that vaccine RA27/3 is safe.

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