Rubella vaccination during the preconception period or in pregnancy and perinatal and fetal outcomes

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The rubella vaccine is contraindicated in pregnancy. Between July and August 2009, the Turkish Republic Ministry of Health implemented a vaccine program to eradicate rubella in women in the reproductive period. In this program, many pregnant women were also vaccinated inadvertently. In this study, 62 pregnant women applied to our clinic who were vaccinated either during pregnancy or within one month before the last menstrual period. Seventeen of them were followed until the end of the pregnancy by fetal echocardiography and detailed ultrasonography. Rubella immunoglobulin (Ig) M and IgG antibodies were studied in the cord blood obtained at birth. All fetuses were examined by a pediatrician, an ophthalmologist and a pediatric cardiologist. A hearing test was also performed on all neonates. No signs of congenital rubella syndrome could be found.

Key words: rubella vaccination, preconception period, outcome.

Rubella virus is an enveloped, positive strand, non-segmented RNA virus, and has a single major antigenic type. Its incubation period is 14-21 days. Contamination occurs mainly by the respiratory route. Retroauricular and occipital lymphadenopathies are the most typical signs seen in the second week of the disease. Rashes are first seen on the face and neck, then cover all of the body. Fever, arthralgia, arthritis, thrombocytopenia, encephalitis, and panencephalitis can also be seen; spontaneous abortion and stillbirths are the main obstetric complications[1-3]. Rubella may cause serious congenital infections if seen in early pregnancy, especially in the first trimester, designated as congenital rubella syndrome (CRS)[1,4]. Congenital cataracts, congenital heart defects, sensorineural deafness, and mental retardation are the most common and important features of CRS[1,4,5]. The other features are listed in Tables I and II. CRS affects 110,000 children each year in developing countries[6]. As a result, many countries that are members of the World Heath Organization (WHO) have started to use rubella-containing vaccines in their national immunization programs. The number of these countries has increased since 2009[7]. In this study, we aimed to measure the fetal and perinatal outcomes of rubella vaccination during pregnancy or within one month before the last menstrual period.

Material and Methods

In July-August 2009, the Turkish Republic Ministry of Health implemented a vaccine program to eliminate rubella in women of reproductive age (18-35 years) and to eradicate CRS. In this study, 17 women applying to the Ege University Obstetrics and Gynecology Department (İzmir) who were inadvertently vaccinated (R-VAC, Keymen Pharmaceuticals) during the first trimester of pregnancy or within one month before the last menstrual period were included. All of the patients recognized their pregnancies in the first trimester and 1-3 months after vaccination. They also applied to our clinic in the first trimester. Pregnancies were confirmed with serum beta-human chorionic gonadotropin (β-hCG) test and ultrasonography. At the first visit, all patients were informed about the potential risks and previous studies mentioned in the literature, and pharmacology counselling was done. None of patients wanted

Table I. Congenital Rubella Syndrome (Common Features)

Temporary	Permanent	Late-Onset/Developmental
Hepatosplenomegaly	IUGR	Psychomotor retardation
Conjugated hyperbilirubinemia	PDA	Hypotonia
Purpura	Pulmonary stenosis	Diabetes mellitus
Thrombocytopenia	Cataracts	Behavioral abnormalities
"Blueberry-muffin" rashes	Microphthalmia	
Lymphadenopathy	Retinopathies	
Meningoencephalitis	Sensorineural deafness	
Radiolucencies in bones	Microcephaly	
Abnormal EEG		

IUGR: Intrauterine growth restriction. PDA: Patent ductus arteriosus.

to terminate their pregnancies. These patients were examined by fetal echocardiography for related cardiac defects and detailed sonography for anomaly screening between 18-22 weeks of gestation. Rubella immunoglobulin (Ig)M and IgG antibodies were assessed by rubella ELISA IgM and IgG kits (Abbott Laboratories) from the pregnant women at the first visit and from the fetal cord blood obtained at birth. After birth, all fetuses were examined by a team of pediatricians, ophthalmologists and otolaryngologists. Laboratory criterion for the diagnosis of CRS was demonstration of rubella-specific IgM antibodies in the cord blood. The clinical evaluation consisted of examinations directed by a pediatrician and an ophthalmologist. In addition, all infants underwent auditory screening by otoacoustic emission. Patients who had been vaccinated earlier than one month before the last menstrual period were not included into this study[8].

Results

The mean maternal age was 26.58 ± 4.04 (range: 21-35) years. All mothers were healthy, and none had hypertension or diabetes, etc. No history of opiate abuse, smoking, or alcohol or teratogenic exposure during pregnancy was reported. Serological evaluation of mothers prior to vaccination was not available, but all mothers were rubella IgG (+), with high avidity (<60%) after vaccination. Mean rubella IgG level was 112.73 IU/ml (range: 40.2-284.5 IU/ml). The rubella IgM level was weakly positive in only one patient, and the avidity of rubella IgG was 45.7%. In the pregnancy follow-up, detailed (level-II) ultrasonography could be performed on 11 patients and fetal echocardiography on 10 patients. All of the results were normal. No pregnancy complications such as preeclampsia, gestational diabetes mellitus, preterm birth, or preterm rupture of membranes, etc. were reported. Mean birth weight was 3418.125 ± 456.16 g (range: 2700-4510 g). None of the

Table II. Congenital Rubella Syndrome (Rare Symptoms)

Temporary	Permanent	Late-Onset/Developmental
Prematurity	VSD	Autism
Myocarditis	ASD	Interstitial pneumonia
Hepatitis	Glaucoma	Chronic progressive panencephalitis
Interstitial pneumonia	Intracranial calcifications	Hypo-hyperthyroidism
Hemolytic anemia	Hypertension	Thyroiditis
Leukopenia	Thymic hypoplasia	Precocious puberty
Diarrhea	Abnormal teeth	Growth hormone deficiency
		Keratitis, keratoconus
		Subretinal neovascularization

VSD: Ventricular septal defect. ASD: Atrial septal defect.

neonates had clinical evidence of intrauterine growth restriction (IUGR) or cardiovascular, ophthalmologic, central nervous system, or other system abnormalities. All auditory screenings were normal. IgM anti-rubella antibodies were negative in the cord blood obtained at birth in all neonates. Mean rubella IgG antibody titer was 90.38 ± 63.81 IU/ml (range: 7-251 IU/ml).

Discussion

The prevalence of women susceptible to rubella infection differs throughout the world, ranging from 6-25%[9]. In Turkey, according to Aksakal et al.[10], the seropositivity of rubella IgG was 95.5% among women in the reproductive age group and 96.2% among pregnant women in a rural region of Ankara, the capital of Turkey. In a cross-sectional study by Sasmaz et al.[11], rubella seroprevalence was 55% for women in the reproductive age group (15-49 years) in Mersin, Turkey. In a study performed in North Carolina, 9.4% of pregnant women were reported to be susceptible to rubella infection[12]. Because of susceptibility to rubella infection among women of child-bearing age and the risk of CRS, active immunization with the live attenuated rubella vaccine is recommended for young women[13,14]. However, the problem is that young women may be unknowingly pregnant at the time of vaccination or may become pregnant shortly after vaccination. This may cause great stress for both the mother and the physician regarding CRS. This topic has been discussed in many studies. In the studies performed in 1985 by Enders et al.[15] and Preblud et al.[16], and in 1990 by Burgess[17], any cases of CRS reported in the population had been vaccinated less than three months before pregnancy or after conception. The CDC (Centers for Disease Control and Prevention) then decreased the interval between the vaccination and pregnancy from three months to one month[8]. Similar vaccine campaigns were performed in other countries, such as in Costa Rica (2001), Brazil (2002) and Iran (2003). Badilla et al.[18] designed a study in the population inadvertently vaccinated during the mass campaign in Costa Rica in 2001. One thousand one hundred and ninety-one mother and child pairs were analyzed in the study, and no adverse pregnancy outcomes such as miscarriage or CRS were documented in women who were vaccinated and unknowingly pregnant. In a prospective study by Minussi et al.[19], 171 pregnancies were successfully followed up to the end of the pregnancy. 11.1% (19/171) ended in spontaneous miscarriage. In 6.7% of the infants (10/149), serological tests showed the presence of anti-rubella IgM antibodies, a sign of vaccine virus infection during pregnancy, but clinical evaluations and complementary tests did not reveal any sign of CRS at birth and at three months of age. In another prospective study from Iran by Nasiri et al.[20], who followed 60 pregnant women who were inadvertently vaccinated during the 1-4 week periconceptional period, no signs of CRS were found in the neonates based on systemic physical exam at birth and one month later, and cord blood anti-rubella IgM antibody tests were negative in all. Like in all the aforementioned studies, no signs of CRS could be found in our study. All of the cord blood anti-rubella IgM titers were negative. However, it is difficult to generalize these results to cover all populations, as the number of participants was very low in this study. Due to ethical considerations, controlled and randomized studies to determine the risk of vaccine administration before conception or during gestation are nearly impossible. Hence, the current recommendations on rubella vaccination during pregnancy are based mainly on case reports and some observational studies[21]. Another limitation of this study is that the immune status of mothers before vaccination was unknown. There are conflicting data in Turkey in which rubella seropositivity varies from 5% to 45% in different regions[10,11]. Serum IgG levels were all positive and IgM levels were negative after vaccination except in one mother. Avidity was high (<60%) in all. In one mother, the IgM level was weakly positive and the avidity of IgG was 45.7%. In this study, we wanted to emphasize the inadequate organization and the consequent side effects of the rubella vaccine program in Turkey. In order to not cause confusion regarding the effects of the rubella vaccine in pregnancy, patients must be screened for pregnancy before vaccination and should be informed regarding contraception for the first month after vaccination.

In conclusion, the rubella vaccine in pregnancy seems to be safe. Even though we cannot say that the rubella vaccine can be given safely

during pregnancy, if it is done inadvertently, the patient or the physician should not be concerned about CRS. The patient should be informed about the possible risks but also about the safety of the vaccine in light of the literature. Rubella vaccination in pregnancy should not be a reason for pregnancy termination.

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