Rubella is an exanthematous illness characterized by nonspecific signs and symptoms, including transient erythematous and sometimes pruritic rash, postauricular or suboccipital lymphadenopathy, arthralgia, and low-grade fever\(^1\). Clinically similar exanthematous illnesses are caused by parvovirus, adenoviruses, and enteroviruses\(^2\). Moreover, 25-50 per cent of rubella infections are subclinical\(^3\). Rubella is typically a mild disease with minor morbidity and a few complications unless it is contracted by a pregnant woman (particularly during the first trimester)\(^2,3\). In such cases, rubella often leads to foetal death or severe congenital defects including blindness, deafness, cardiovascular anomalies, and mental retardation [congenital rubella syndrome (CRS)]\(^2,4\).

Although the burden of CRS is not well characterized in all countries, it is estimated that more than 100,000 cases occur each year in developing...
countries alone\textsuperscript{5-7}. Caring for CRS cases is costly because of the permanent disabilities caused by the condition\textsuperscript{8}.

Rubella vaccination is included in national immunization programmes in most countries and territories of the world. The vaccines are highly protective and without significant adverse effects\textsuperscript{9}.

However, as rubella vaccines contain live attenuated viruses, there is concern that vaccination of women later found to be pregnant might result in foetal infection and deformity\textsuperscript{9-11}. The currently recommended approach to vaccinating women of childbearing age is to ask them if they think they are pregnant or may become pregnant in the next 3 months. If the answer is “yes”, they should not receive the vaccine; if the answer is “no”, they should be vaccinated\textsuperscript{9,10}.

In December 2003, the Ministry of Health and Medical Education of the Islamic Republic of Iran implemented a nationwide campaign to vaccinate about 33,000,000 people aged between 5 and 25 yr with a combined measles and rubella (MR) vaccine (Measles; Edmonston Zagreb strain/Rubella; RA27/3 strain, Serum Institute of India Ltd., Pune, India\textsuperscript{12}. Unfortunately, during the campaign some pregnant women received vaccine during the first trimester of pregnancy or some others became pregnant shortly thereafter.

We undertook this study to evaluate the risk of CRS among the infants born to vaccinated mothers.

**Material & Methods**

The study conducted in Vali-e-Asr multispeciality hospital affiliated to Birjand University of Medical Sciences and Health Services, Birjand, East Iran, receiving referral patients from South Khorasan province.

For the purpose of the study, we followed up all women who had received the MR vaccine during nationwide campaign while they were in the first trimester of pregnancy or had become pregnant within 3 months thereafter, during November 2003 - November 2004, and agreed for evaluation. The exclusion criterion for the study group were documented previous history of rubella infection or vaccination, and delivery outside the hospital. During the initial counselling session, details of the exposure were obtained, including the date of rubella vaccination as well as maternal demographics and obstetrical history.

The mothers were followed up until delivery. At delivery the mothers’ blood and infants’ cord blood samples were collected aseptically. Another sample of infant’s blood was collected at the 8\textsuperscript{th} wk of age. Sera was separated and stored at -20\textdegree C until analyzed.

Relevant information regarding antepartum and intrapartum factors that could have a bearing on neonatal condition was collected. All infants were examined during the first 24 h of life by a pediatrician to find any clinical signs of CRS.

IgM rubella antibody was evaluated qualitatively in mothers’ and infants’ blood using indirect ELISA method. IgG rubella antibody was also evaluated quantitatively in cord blood and second blood specimen of infants. All serologic tests were performed using the same ELISA kits in the same laboratory by the same person. ELISA kits used were Enzygnost\textsuperscript{®} Anti-Rubella-Virus/IgM (Dade Behring, Marburg, Germany) and Rubella IgG ELISA Kit (Genesis, UK).

The endpoint of interest was the incidence of CRS. CDC’s clinical criteria for diagnosis of CRS were used\textsuperscript{2,3}.

Laboratory criteria for diagnosis of CRS were: demonstration of rubella-specific IgM antibody in cord blood, or demonstration of rubella-specific IgM antibody in infant blood at 8\textsuperscript{th} wk of age, or infant rubella antibody level persisting at a higher level and for a longer period than expected from passive transfer of maternal antibody (i.e., rubella titre that does not drop at the expected rate of a two-fold dilution per month)\textsuperscript{2,3}.

A comparison group of women who did not receive rubella vaccine or received it more than 3 month before conception, were also followed up in a similar way. Outcomes of interest were compared between the study and comparison groups with the t test, chi- square test and Fisher’s exact test.

The ethical committee of the university approved the study. A written informed consent was obtained from each participant after the study objectives were explained.

**Result**

A total of 106 exposed women and 40 controls were followed. Of these, only 60 women (all in the exposed group) agreed on their infants’ blood sampling at 8\textsuperscript{th} wk of age. There were no statistically significant differences in maternal age, rate of smoking, alcohol
consumption and recreational drug use between the exposed and control group. There were no statistically significant differences in obstetric history, gravidity and parity in the two groups.

Seventy one (66.98%) women in the exposed group received MR vaccine before conception and the remaining received it during the first trimester.

There were 107 live births (two twins) and one still birth in the exposed group and 42 live births (two twins) in the control group. There were no significant differences between the two groups in mean birth weight, height and head circumference of newborns (Table I).

None of the children exhibited signs of congenital rubella syndrome. There were no significant differences between the two groups in the rates of still birth and major malformations or in rates of prematurity (Table II). Two newborns had major malformations; one had congenital hip dislocation and the other had chest deformity with ascites. Mothers of these two malformed children in the exposed group received the vaccine during the first trimester.

Serological study showed no IgM rubella antibody in the maternal and infant cord blood in any of study subjects; it was not found in the second blood specimens of 60 infants that were also tested. IgG rubella antibody was positive in all infants’ cord blood but it decreased in the 60 blood specimen of newborns tested after 8 wk.

**Table I.** Demographic data of newborns in the study and control groups (Data are mean ± SD)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Exposed group (n=107)</th>
<th>Control group (n=42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight(g)</td>
<td>3092.67±493.777</td>
<td>3022.50±427.418</td>
</tr>
<tr>
<td>Height(cm)</td>
<td>49.074±3.647</td>
<td>48.925±2.702</td>
</tr>
<tr>
<td>Head circumference (cm)</td>
<td>34.470±2.812</td>
<td>34.063±1.340</td>
</tr>
</tbody>
</table>

**Table II.** Pregnancy outcome in exposed and control groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Exposed group N (%)</th>
<th>Control group N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still birth</td>
<td>1(0.94)</td>
<td>0</td>
</tr>
<tr>
<td>Rate of malformations</td>
<td>2(1.88)</td>
<td>0</td>
</tr>
<tr>
<td>Gestational age Term</td>
<td>98(92.45)</td>
<td>39(92.86)</td>
</tr>
<tr>
<td>Pre term</td>
<td>8(7.55)</td>
<td>3(7.14)</td>
</tr>
</tbody>
</table>

**Discussion**

Data from earlier studies indicated no cases of congenital rubella syndrome (CRS) among infants born to women who were vaccinated inadvertently against rubella within 3 months or early in pregnancy\textsuperscript{13-17}. Based on the “Vaccine in Pregnancy (VIP) Registry” report, between 1979 and 1988 no evidence of CRS occurred in the offspring of the 272 susceptible women who received the RA 27/3 rubella vaccine between 3 months before and 3 months after conception and continued their pregnancy to term\textsuperscript{18}.

The primary end point of this study was the occurrence of congenital rubella syndrome, which was not seen in any of the cases exposed to the vaccine.

Based on the results, none of the children in the exposed group showed serological evidence of CRS. However, our results are different from those of some other studies in that a minority of newborns showed serological evidence of CRS without clinical signs or symptoms\textsuperscript{13,18,19}. A possible explanation for this disagreement may be that in our study all exposed women, both susceptible against rubella before vaccination, and those who were pre-immune, were included, while in other studies, only susceptible women were included. Many studies have shown that about 70-85 per cent of 15-25 yr old women had been immune without vaccination because of clinical or subclinical infection, and thus their response to rubella vaccine should be regarded as a secondary immune response\textsuperscript{6,12,20-22}. Though there are several reports of CRS due to rubella re-infection after exposure to wild rubella virus despite of previous history of vaccination or natural immunity in mothers, there is no report of CRS due to vaccination in such mothers\textsuperscript{23-26}. In conclusion, none of the infants born to mothers vaccinated during the first trimester of pregnancy or those who became pregnant less than three months after vaccination, showed serological evidences of CRS.

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**References**


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