Seroprevalence of Rubella Antibodies and Effects of Vaccination among Healthy University Women Students in Korea

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Since the introduction of rubella vaccination in Korea in 1982, several outbreaks of rubella have occurred. In order to examine the current seroepidemiology of rubella virus infection in Korean women of child-bearing age, the healthy university women students of Yonsei University in Seoul aged 18~26 years were chosen as a model population. A survey was carried out in the time of routine annual physical check-up. Serum specimens of 242 volunteers of healthy women university students were randomly sampled for screening rubella-specific IgG/IgM antibodies by an automated enzyme immunoassay system (Vitek System VIDAS, bioMerieux Vitek, Inc., Lyon, France).

A total of 177 subjects were positive for rubella-specific IgG antibody, giving a prevalence of 73.1%. The mean ± standard deviation of rubella-specific IgG antibody was 99.3 ± 95.3 IU/mL. In this study, the efficiency of a vaccination was about 88%. With such a relative high proportion of susceptibility (26.9%) among university women students in child-bearing age, a extensive rubella vaccination program should be enforced to prevent possible outbreaks of congenital rubella syndrome in the future.

Key Words: Rubella vaccination, rubella-specific IgG/IgM antibodies, enzyme immunoassay, congenital rubella syndrome

Rubella infection in pregnant women may cause congenital rubella syndrome, so it is now widely accepted that the vaccination should be offered to all susceptible women of child-bearing age. In Korea, however, the usual seroprevalence and titers of rubella antibodies among women of child-bearing age has not been yet clarified making it difficult for many obstetricians to serodiagnose the rubella infection in pregnant women.

The aim of this study was to estimate current seroprevalence among college students representing healthy adolescent women in Korea and to investigate serological changes after vaccination of seronegative individuals in order to gather a preliminary data to set up a vaccination policy of rubella virus for the school health program.

MATERIALS AND METHODS

Study population

The study subjects were chosen among the healthy women students of Yonsei University, Seoul, Korea. Each student was asked with a questionnaire consisting of some questions regarding her current health status and previous vaccination history. Two hundred and forty-two volunteers were recruited. Their
ages ranged from 18 to 26 years. Individuals
with a rubella vaccination history were ex-
cluded.

Five milliliters of venous blood were collect-
ed and the sera were separated within two
hours, frozen at -40°C, and tested for rubella-
specific IgG and IgM assay.

Among the individuals with rubella-specific
IgG negative or low positive results, sixty-
three volunteers were vaccinated. Six and 12
months later, rubella-specific antibody tests
were repeated in some volunteers.

Methods

Rubella-specific antibody tests were per-
formed by enzyme-linked immunosorbent
assay (ELISA) with VIDAS system (bioMe-
rieux Vitek, Inc., Lyon, France). Vidas RUB
IgG and IgM are automated assays which en-
able anti-rubella IgG and IgM in human
serum to be quantitatively measured. The IgM
antibodies are specifically detected after the
capture of the sample IgM on the solid phase.
These assays combine the indirect enzyme
immunoassay method with a final fluorescent
detection (ELFA). When the assay is comple-
ted, the results are analyzed automatically and
the index (ratio of sample’s fluorescent signal
to the memorized standard signal) is calculat-
ed by the machine.

The assays were performed according to the
manufacturer’s procedure manual. Rubella-spe-
cific IgG level was quantitated as Interna-
tional Unit (IU)/mL. The results not greater
than 20 IU/mL were reported as negative, while
30 IU/mL was taken as the positive cutoff
value. Those results between 20 and 30 IU/mL
were regarded as low or borderline positive.
The results of rubella-specific IgM test were
reported negative when the ratio of sample
fluorescent signal to standard signal was 0.8
or lower and positive when the ratio was 1.2
or higher. The results between the cutoff val-
ues were regarded as equivocal.

RESULTS

The results of rubella-specific antibody tests
among healthy university students

The mean rubella-specific IgG level of 242

![Graph showing distribution of rubella-specific IgG antibody levels among 242 healthy women students. Bars represent the number (frequency) of students and line means cumulative percentage of the level.]

Table 1. The results of five students who showed positive or equivocal positive for rubella-specific IgM antibody among 242 healthy university women students

<table>
<thead>
<tr>
<th>Age</th>
<th>Rubella-specific IgG Ab (IU/mL)</th>
<th>Result</th>
<th>Rubella-specific IgM Ab (Ratio to Sample/Standard)</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>113</td>
<td>positive</td>
<td>1.67</td>
<td>positive</td>
</tr>
<tr>
<td>20</td>
<td>124</td>
<td>positive</td>
<td>5.11</td>
<td>positive</td>
</tr>
<tr>
<td>18</td>
<td>129</td>
<td>positive</td>
<td>0.84</td>
<td>equivocal</td>
</tr>
<tr>
<td>21</td>
<td>147</td>
<td>positive</td>
<td>0.87</td>
<td>equivocal</td>
</tr>
<tr>
<td>19</td>
<td>284</td>
<td>positive</td>
<td>0.95</td>
<td>equivocal</td>
</tr>
</tbody>
</table>

* Ratio means sample’s fluorescent signal to the standard signal.
healthy individuals was $99.3 \pm 95.3$ IU/mL and the distribution is shown in Fig. 1. Sixty-five participants seemed not to have sufficient immunity for rubella virus (55 negatives and 10 low positives) and vaccination was recommended, of which 63 were actually immunized.

### Table 2. The changes in the rubella-specific antibodies of thirty-three students' paired sera after vaccination

<table>
<thead>
<tr>
<th>Student's Name</th>
<th>Rubella-specific IgG Ab (IU/mL)</th>
<th>Rubella-specific IgM Ab Ratio*Sample/Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 month</td>
<td>12 month</td>
</tr>
<tr>
<td>KGS</td>
<td>276</td>
<td>231</td>
</tr>
<tr>
<td>KGH</td>
<td>71</td>
<td>93</td>
</tr>
<tr>
<td>KNM</td>
<td>33</td>
<td>37</td>
</tr>
<tr>
<td>KMH</td>
<td>63</td>
<td>110</td>
</tr>
<tr>
<td>KSA</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>KSJ</td>
<td>80</td>
<td>95</td>
</tr>
<tr>
<td>KSO</td>
<td>96</td>
<td>126</td>
</tr>
<tr>
<td>KEH</td>
<td>35</td>
<td>63</td>
</tr>
<tr>
<td>KJE</td>
<td>150</td>
<td>185</td>
</tr>
<tr>
<td>KHG</td>
<td>53</td>
<td>44</td>
</tr>
<tr>
<td>PSW</td>
<td>28</td>
<td>42</td>
</tr>
<tr>
<td>BHG</td>
<td>165</td>
<td>141</td>
</tr>
<tr>
<td>BSJ</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>BEK</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>STE</td>
<td>27</td>
<td>372</td>
</tr>
<tr>
<td>SER</td>
<td>41</td>
<td>46</td>
</tr>
<tr>
<td>SEJ</td>
<td>63</td>
<td>121</td>
</tr>
<tr>
<td>SJS</td>
<td>129</td>
<td>190</td>
</tr>
<tr>
<td>SMS</td>
<td>128</td>
<td>221</td>
</tr>
<tr>
<td>OSN</td>
<td>270</td>
<td>233</td>
</tr>
<tr>
<td>RKI</td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td>YSI</td>
<td>129</td>
<td>176</td>
</tr>
<tr>
<td>LSY</td>
<td>95</td>
<td>81</td>
</tr>
<tr>
<td>LEK</td>
<td>105</td>
<td>100</td>
</tr>
<tr>
<td>LJS</td>
<td>400</td>
<td>353</td>
</tr>
<tr>
<td>LJE</td>
<td>238</td>
<td>178</td>
</tr>
<tr>
<td>LHH</td>
<td>55</td>
<td>37</td>
</tr>
<tr>
<td>LAK</td>
<td>154</td>
<td>107</td>
</tr>
<tr>
<td>JMY</td>
<td>130</td>
<td>77</td>
</tr>
<tr>
<td>JJH</td>
<td>159</td>
<td>140</td>
</tr>
<tr>
<td>CJY</td>
<td>49</td>
<td>12</td>
</tr>
<tr>
<td>HMJ</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>HKS</td>
<td>298</td>
<td>80</td>
</tr>
</tbody>
</table>

Total $123.4 \pm 104.2^\circ$ $128.3 \pm 101.3$ $0.22 \pm 0.22$ $0.17 \pm 0.14$

* Ratio means sample's fluorescent signal to the standard signal.

**: Equivocal (all the results of rubella-specific IgM Ab in this table except this one were negative).

**: Mean ± S.D
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with rubella vaccine. Meanwhile, rubella-specific IgM revealed two positives and three equivocal positives, whose rubella-specific IgG levels ranged from 113 to 284 IU/mL (Table 1). The majority of the participants (97.9%) were IgM-negative.

The results of rubella-specific antibody tests six months after vaccination

Forty-two individuals were subjected to follow-up test six months after vaccination. The rubella-specific IgG level ranged from 11 to 400 IU/mL, on the average 120.4 IU/mL. Thirty-seven (88.1%) showed seroconversion while two were still negative and three were in the range of low positivity. Among 42 women, two showed IgM equivocal positive results whose IgG level was 80 and 116 IU/mL respectively.

The results of rubella-specific antibody tests twelve months after vaccination

Forty-nine individuals were subjected to follow-up test twelve months after vaccination. The IgG level ranged from 12 to 400 IU/mL, on the average 129.8 IU/mL. The seroconversion rate was 87.8% (43/49). Four were IgG-negative and two were low positive. Only one student showed IgM-positive whose IgG level was 327 IU/mL.

The results of rubella-specific antibody tests who participated in both follow-up tests at sixth and twelfth months after vaccination

The number of participants joined both follow-up serological tests sixth and twelfth months after vaccination was thirty-three. The paired samples showed increases in IgG levels and decreases in IgM ratios with time. The average IgG level at the sixth month after vaccination was 123.4 IU/mL and that at the twelfth month was 128.3 IU/mL, respectively (paired t-test, p<0.05). And the average IgM ratio at the sixth month after vaccination was 0.22 and that at the twelfth month was 0.17, respectively (Table 2). The values after 6 month and 12 month were significantly different.

One individual who showed IgM-equivocal result at six months after vaccination turned negative another six months later, and her IgG level increased from 80 to 95 IU/mL during that time.

![Fig. 2. Changes in rubella-specific IgG Ab titers before and after vaccination.](image)

**Table 3. Rubella-specific antibodies after vaccination**

<table>
<thead>
<tr>
<th>Rubella-specific antibodies</th>
<th>Patients’ Group</th>
<th>Six-month after vaccination (n=42)</th>
<th>Twelve-month after vaccination (n=49)</th>
<th>Overall (n=91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubella-specific</td>
<td>Overall</td>
<td>120.4 ± 97.4</td>
<td>129.8 ± 10.8</td>
<td>125.5 ± 102.3</td>
</tr>
<tr>
<td>IgG Ab(IU/mL)</td>
<td>Follow-up (n=33)</td>
<td>123.4 ± 104.2</td>
<td>128.3 ± 101.3</td>
<td></td>
</tr>
<tr>
<td>Rubella-specific</td>
<td>Overall</td>
<td>0.23 ± 0.22</td>
<td>0.21 ± 0.26</td>
<td>0.22 ± 0.24</td>
</tr>
<tr>
<td>IgM Ab(Ratio)</td>
<td>Follow-up (n=33)</td>
<td>0.22 ± 0.22</td>
<td>0.17 ± 0.14</td>
<td></td>
</tr>
</tbody>
</table>

*: Ratio means sample’s fluorescent signal to the standard signal.

+: Mean ± S.D.

**Follow-up means the group of paired serum samples.**

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Overall results of rubella-specific antibody tests after vaccination

Among the 63 volunteers vaccinated for rubella virus, 53 individuals were tested for rubella-specific antibody tests either six or twelve months after vaccination. Thirty-three were joined at both times, nine were only at the sixth month, and sixteen were only at the twelfth month. Their serological findings are summarized in Table 3.

Fig. 2 shows the rubella-specific IgG antibody levels of 63 subjects before vaccination and 49 subjects after vaccination (12 months post-vaccination). As is shown in the figure, the rubella-specific IgG antibodies after vaccination significantly increased.

DISCUSSION

Rubella (German measles) is a common contagious disease with mild constitutional symptoms and generalized rashes, but exposure during the first trimester of pregnancy may result in congenital defects (Chernesky and Mahony, 1995; Ekbblad, 1995). The triad of anatomic abnormalities including cataracts, neurosensory deafness and congenital heart disease has been referred to as the congenital rubella syndrome (Ewert et al. 1992; Fogel et al. 1996). Thus, serological tests to determine the immune status in women and tests to diagnose recent rubella virus infection in pregnant women are of great importance (Ahmed, 1992; Chernesky and Mahony, 1995). The epidemiology of rubella infection has been studied in many areas of the world (Ahmed, 1992; Fraser et al. 1993; Garcia et al. 1993; Legrande, 1993; Lin and Chen, 1993; Pelissero et al. 1993; Lin and Chen, 1994; Miller et al. 1994; Souza et al. 1994; Janes, 1995; Saldanha and Azevedo, 1995), and mass immunization programs conducted in many countries have successfully decreased the infection with a concurrent reduction in congenital rubella syndrome (ACOG, 1993; Condon and Bower, 1993; Gay et al. 1994; Szilagyi et al. 1994; Penson, 1995; Matter et al. 1995).

Rubella infections can be transmitted from mother to fetus resulting in so-called congenital rubella syndrome. When the pregnant woman has sufficient immunity to the rubella virus, the congenital infection can be prevented (Weber et al. 1993). So, the vaccination for rubella virus is now included in a regular vaccination program. Vaccine is given to girls routinely at fifteenth month after birth and at the age of three. In Korea, however, the nation-wide vaccination program was started at 1982, so at the present time, most adolescent and young women of child-bearing age (over 16 years old) did not have the chance to be vaccinated for the rubella virus. In order to analyze risk factors for seronegativity to rubella and to assess the efficacy of a rubella screening and vaccination in women of child-bearing ages, we analyzed rubella serology and the effects of a vaccination in healthy women university students.

Our study revealed that 26.9% of the healthy women from 18 to 26 years old were needed a vaccination because they did not have sufficient immunity for rubella virus. They had negative or low positive anti-rubella IgG levels.

The postvaccination seroconversion rate was 88.1% and 87.8% after 6 and 12 months respectively. These findings suggest that serological follow-up and decision making whether or not to offer reinforcing vaccination should be an essential part in the vaccination program for rubella virus (Marsack et al. 1995).

From the current viewpoint of diagnostic virology, there are now a variety of methodologies available (Ahmed, 1992; Chernesky and Mahony, 1995). As well as commonly performed serological detection methods of antiviral antibodies, various approaches to detect viral antigens from viral culture techniques to molecular biological methods such as polymerase chain reaction have been developed (Bosma et al. 1995). Nevertheless, even such a highly sophisticated method does not give physicians satisfaction with regard to diagnostic sensitivity or specificity, namely, diagnostic accuracy. Moreover, such modalities are not easy to perform and expensive as well to be used as a routine diagnostic test. Thus, the
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serological tests for specific antiviral antibodies are still the first-line choice for the diagnosis of viral infection because they represent the functional immune status of the host and have advantages such as simple procedure, standardization, and cost-effectiveness.

Until now, the vaccine was not recommended for boys or men in Korea. In temperate climates, rubella is endemic throughout the year, but there is a regular seasonal peak between March and May (Horstmann, 1989). Before the widespread use of the vaccine, rubella was most commonly found among children, but many susceptible adolescents and young adults were also infected (Horstmann, 1982). After 1977, a change in the epidemic pattern of rubella was identified. The regular cycle of rubella epidemics no longer existed. The change deserves further investigation with the current seroprevalence of rubella infection being examined.

From this study, the titer of rubella-specific IgG antibody was increased and turned positive in 88% of the test subjects after 6 months of vaccination. And after 12 months, the positive rate was similar to the 6 months’ data but the titer of rubella-specific IgG antibody more significantly increased (p<0.05). We concluded that the rubella vaccination program should be extended to include seronegative women of reproductive age.

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