EPIDEMIOLOGIC AND PREVENTIVE STUDIES OF RUBELLA IN FEMALE OFFICE WORKERS

HIROMU NISHIHARA†, HARUO KONDO†† and MANABU HASHIDA†

INTRODUCTION

Maternal rubella infection, especially occurring in the first trimester of pregnancy, is well recognized to cause a teratogenic effect to the fetus and to produce congenital rubella syndrome (CRS). It seems likely, however, that less attention is paid at present to the problem in the field of industrial medicine. A bank, with which the authors are associated, employs a large number of young female workers, exceeding more than 50% of the whole employees, and in addition the population of the married among them is gradually increasing.

Under these circumstances, it seems important to take measures to prevent unfortunate complications associated with the maternal rubella infection. At that time when a large epidemic of rubella spread widely in this country in 1975, we attempted to investigate the immune status of young female workers to rubella in order to prevent the occurrence of CRS. In this report, we present the results of measurement of serum titers of rubella antibody in female office workers and also the effect of attenuated live rubella-virus vaccine given to the susceptible women.

SUBJECTS AND METHODS

Healthy volunteers from female employees working in offices of a bank situated in Tokyo, Kanagawa and Chiba prefectures (termed as Tokyo district) as well as in Osaka Prefecture, Kyoto and Kobe cities (termed as Osaka district) were subjected to titration of serum antibody to rubella. The antibody titers were measured by hemagglutination-inhibition (HI) test. In Tokyo district,
the investigation was carried out with 350 subjects in April and May, 1976. In Osaka district, a total of 615 subjects were tested; 76 women were tested during the period from April to May, 1976, and 323 subjects in March, 1977. The remaining 216 women were investigated in November, 1978. Age distributions of the subjects are shown in Tables 2, 3, 4 and 5.

Rubella vaccine preparations currently licensed in Japan were used for vaccination. The vaccine was prepared from live, attenuated rubella-virus (TCRB19 strain) in primary rabbit kidney cultures. In inoculation, 0.5 ml aliquots of the vaccine were injected subcutaneously. As for the married women, the inoculation was made within several days after the onset of their last menstruation, and they were instructed to take measures to prevent pregnancy for two months thereafter.

RESULTS AND DISCUSSION

The results of titration of rubella antibody with 350 subjects in Tokyo district are shown in Tables 1 and 2. When the presence of a rubella HI titer of 1:8 or greater is regarded as seropositive as well as positive evidence of past rubella infection, 267 of the 350 females (76.3%) in Tokyo district were immune to the disease. The majority of the seropositive group was found to have titers between 1:64 and 1:256. Only 12 out of the 350 subjects tested had experienced clinical manifestations characteristic of rubella, and their estimated titers corresponded to 1:16 in 2, 1:64 in 4, 1:256 in

Table 1. Distribution of rubella HI titers in female office workers in Osaka district by age groups, 1976.

<table>
<thead>
<tr>
<th>Titer</th>
<th>Frequency</th>
<th>Accumulative frequency</th>
<th>Accumulative percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;8</td>
<td>83</td>
<td>350</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>267</td>
<td>76.3</td>
</tr>
<tr>
<td>16</td>
<td>18</td>
<td>249</td>
<td>71.1</td>
</tr>
<tr>
<td>32</td>
<td>32</td>
<td>231</td>
<td>66.0</td>
</tr>
<tr>
<td>64</td>
<td>76</td>
<td>199</td>
<td>56.9</td>
</tr>
<tr>
<td>128</td>
<td>64</td>
<td>123</td>
<td>35.1</td>
</tr>
<tr>
<td>256</td>
<td>44</td>
<td>59</td>
<td>16.9</td>
</tr>
<tr>
<td>≥512</td>
<td>15</td>
<td>15</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Table 2. Seropositive rates of rubella HI antibody in female office workers in Tokyo district by age groups, 1976.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number tested</th>
<th>Seropositive*</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–19</td>
<td>27</td>
<td>15</td>
<td>55.6</td>
</tr>
<tr>
<td>20–29</td>
<td>296</td>
<td>226</td>
<td>76.4</td>
</tr>
<tr>
<td>30–39</td>
<td>25</td>
<td>24</td>
<td>96.0</td>
</tr>
<tr>
<td>Over 40</td>
<td>2</td>
<td>2</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>350</td>
<td>267</td>
<td>76.3</td>
</tr>
</tbody>
</table>

* Defined as HI titers of 1:8 or greater.

Table 3. Seropositive rates of rubella HI antibody in female office workers in Osaka district by age groups, 1976.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number tested</th>
<th>Seropositive*</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–19</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20–29</td>
<td>67</td>
<td>42</td>
<td>62.7</td>
</tr>
<tr>
<td>30–39</td>
<td>9</td>
<td>9</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>51</td>
<td>67.1</td>
</tr>
</tbody>
</table>

* Definition is the same as in Table 2.
Table 4. Seropositive rates of rubella HI antibody in female office workers in Osaka district by age groups, 1977.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number tested</th>
<th>Seropositive*</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–19</td>
<td>28</td>
<td>7</td>
<td>25.0</td>
</tr>
<tr>
<td>20–29</td>
<td>288</td>
<td>167</td>
<td>58.0</td>
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<tr>
<td>30–39</td>
<td>7</td>
<td>6</td>
<td>85.7</td>
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<tr>
<td>Total</td>
<td>323</td>
<td>180</td>
<td>55.7</td>
</tr>
</tbody>
</table>

* Definition is the same as in Table 2.

Table 5. Seropositive rates of rubella HI antibody in female office workers in Osaka district by age groups, 1978.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number tested</th>
<th>Seropositive*</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>18–19</td>
<td>56</td>
<td>30</td>
<td>53.6</td>
</tr>
<tr>
<td>20–29</td>
<td>157</td>
<td>90</td>
<td>57.3</td>
</tr>
<tr>
<td>30–39</td>
<td>3</td>
<td>3</td>
<td>100.0</td>
</tr>
<tr>
<td>Total</td>
<td>216</td>
<td>123</td>
<td>56.9</td>
</tr>
</tbody>
</table>

* Definition is the same as in Table 2.

2, 1 : 512 in 2 and 1 : 1,024 in 2. As shown in Table 2, about a half population of the age group 18–19 and approximately a quarter of the age group 20–29 were susceptible to the disease.

The results of the estimation performed in 1976 with 76 subjects in Osaka district are shown in Fig. 1 and Table 3. The seropositive rate of the total subjects was 67.1% and that of the age group 20–29 was 62.7%. These values were significantly lower than those obtained in Tokyo district. Nine out of the 76 subjects gave a history of rash illness consistent with rubella, and their titers corresponded to 1 : 16 in 3, 1 : 32 in 3, 1 : 64 in 1, 1 : 128 in 1 and 1 : 512 in 1.

The results of the investigation performed in 1977 with 323 females in Osaka district are shown in Table 4. The seropositive rate of the total subjects was 55.7%, and the rates of the age groups 18–19 and 20–29 were 25.0% and 58.0%, respectively. These values were also considerably lower than those obtained in Tokyo district. As shown in Table 5, the estimation of 216 subjects in Osaka district in 1978 presented similar results to those obtained in 1977 (Table 4), except that the seropositive rate of the age group 18–19 increased considerably.

For the purpose to prevent the development of CRS in infants of pregnant women, it is obviously important to investigate the antibody titers of the married females rather than those of the unmarried. In this survey, 159 married women were involved in the total 350 subjects of Tokyo district and 35 of the married were shown to be susceptible (22.0%). On the other hand, 48 out of the 191 unmarried women were susceptible (25.1%). Thus, there was no remarkable difference in the seronegative rate between the married and the unmarried. In Osaka district, the total 615 subjects examined included 92 married women, and 26 of them were found susceptible (28.3%). In contrast, 265 out of the 523 unmarried women were susceptible (50.7%). The considerably higher seronegative rate of the unmarried group indicates that immunization has to be given to them before they reach the child-bearing age.

The immune status of the Japanese in the years of 1969 and 1972 was clarified by countrywide epidemiologic surveys on rubella performed by the Ministry of Health and Welfare, Japan. The surveys documented more than 40% of the population from 15 to 19 years of age to be susceptible in a considerable number of districts, although fairly wide variations in the susceptible rate were seen among the districts investigated. Another epidemiologic survey for the susceptibility to rubella was performed also by the Ministry in 1975 with 4,513 subjects of various ages and residences. An average of 47.0% in the seropositive rate was documented: the rates of the age groups 15–19, 20–24 and 25–29 were 47.8%, 75.0% and 79.4%, respectively. These values are almost consistent with those we obtained. The Ministry’s survey also demonstrated that there were relatively larger populations susceptible to the disease in the district of Kinki, which involves Osaka Prefecture as well as Kyoto and Kobe cities, than in the district of Kanto involving Tokyo, Kanagawa and Chiba prefectures. These findings are also in accordance with ours.

A large, nationwide epidemic of rubella occurred in this country after the spring season of 1975, and it continued until the end of the summer of 1976. Despite that, the data of the Ministry’s surveys in 1972 and 1975 demonstrated that the seropositive rates of younger generations to the disease were not apparently elevated after the epidemic. We also obtained similar findings: in Osaka district, where approximately 1,150 female employees were engaged, 77 women were infected with rubella during the period from January, 1976 to July,
1977, as shown in Fig. 2. No significant changes were observed, however, in the seropositive rates determined in 1976 to 1978, as illustrated in Fig. 3.

We investigated the incidence of rubella infection among the subjects examined in 1976 and 1977 over one-year period following the antibody titration. Then, we found, in Tokyo district, 11 females who had been diagnosed as rubella during the period of time. Their pre-existing titers corresponded to $<1:8$ in 9, $1:8$ in 1 and $1:64$ in 1. In the last case, where a titer of $1:64$ had been estimated, the onset of symptoms was seen within several days following the titration, but no serological tests have been done thereafter. In Osaka district, on the other hand, 2 women were infected with rubella after the titration, and their prior titers were both $<1:8$. These findings suggest the possibility of the occurrence of the infection even in an individual with an HI titer of $1:8$, that is commonly thought to imply the immunized state.

Quantitative serologic laboratory tests currently available for the diagnosis of infectious diseases generally require careful control of assay conditions to keep accuracy. Nevertheless, slight differences between runs would be expected mainly due to a considerable number of constituents and procedures involved in the assay systems. Similarly, in the hemagglutination-inhibition test for rubella, such a difference as two-fold in titer is considered to be within the range of error, and therefore it is recommended that paired serum specimens collected at different stages in the course of the disease should be simultaneously subjected to the test. Subsequently, a four-fold or greater rise in titer between the paired samples can be regarded as positive evidence of current rubella infection. In view of these facts, persons with a titer of $1:8$ may be considered to be susceptible or to be immunized weakly. Furthermore, whereas the actual number of such persons seems to be rather small, we would recommend to give the vaccine to persons with the titer $1:8$ as well as $<1:8$.

An attempt to prevent CRS by vaccination was performed in Osaka district in March, 1977. Live, attenuated rubella-virus vaccine was administered to 42 volunteers of 19 to 34 years of age, including 3 married women. Their HI titers were all $<1:8$. No apparent complications, such as fever, rash, lymphadenopathy, arthralgia and so on, were observed after the inoculation. In February, 1978, HI titers were measured again in the vaccinees and the results are shown in Table 6. A titer of $<1:8$ was demonstrated in one vaccinee and $1:8$ in another, but the remaining 40 women were found immunized substantially. Re-estimation was carried out one month later with the female having

<table>
<thead>
<tr>
<th>Titer</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>$&lt;8$</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
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<tr>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>32</td>
<td>15</td>
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<tr>
<td>64</td>
<td>12</td>
</tr>
<tr>
<td>128</td>
<td>5</td>
</tr>
<tr>
<td>256</td>
<td>1</td>
</tr>
<tr>
<td>512</td>
<td>2</td>
</tr>
</tbody>
</table>
the titer of $<1:8$, producing the same result as before. Although the reason why the woman failed to acquire immunity is obscure, it is supposed that the vaccine used for the female might happen to be inactivated, or more likely that the woman might be somewhat peculiar immunologically in sensitivity to the vaccine; insufficient development of circulating antibodies, or a rapid decline in the levels of antibodies produced. Anyhow, the vaccine has proved very effective, since the rate of seroconversion investigated so far was 97.6\% (41/42) and the mean titer of the seropositive vaccinees was $2^{6.8}$. These values are higher than those reported by Hayakawa et al.,\( ^{12} \) who presented the values of 96.9\% as the seroconversion rate and $2^{4.5}$ as the mean titer in the study of rubella vaccination to 32 female students. They also noted one female who failed to acquire immunity. Thus, there might be some particular persons in whom protective immunity is hardly attainable by the vaccination, so that it is desirable to estimate the serum titer once again after the vaccination to confirm its efficacy. If it would be impractical to adopt such a procedure to all the vaccinees owing to excessive monetary costs needed, re-examination of the antibody titers in pregnant women at the time of their encountering a rubella epidemic is thought to be favourable for preventing the maternal infection completely.

A governmental policy of vaccination for rubella started in Japan from the autumn of 1977; the vaccine is now routinely given to school girls of 13 to 15 years of age. The policy currently practiced in this country is similar to that conducted in the United Kingdom,\( ^{12} \) unlike that in the United States.\( ^{13} \) The former, in contrast to the latter, has the advantage that immunization is performed closer to the child-bearing age, but has a disadvantage that it will take longer time to control the incidence of CRS unless a greater number of susceptible adult females of child-bearing age are also vaccinated.\( ^{11} \) Accordingly, immunization of susceptible adult women of child-bearing age should be emphasized at present in this country for preventing CRS. Positive efforts on this respect in the field of industrial medicine are thought worthy to establish comprehensive health care.

CONCLUSION

Rubella infection occurring in pregnant women is considered to be so hazardous as to produce various malformations, CRS, to the fetus. One can expect to encounter such an unfortunate case even in the field of industrial medicine, especially in the industries employing a large number of females of child-bearing age. On the basis of these facts, we conducted epidemiologic studies of rubella in female office workers of a bank in association with the prevention of CRS by vaccination and the following results were obtained:

1) Serum HI titers for rubella were estimated in a total of 965 female employees, and then approximately 40\% of them were found susceptible to the disease. The seronegative rate was significantly higher in Osaka district than in Tokyo district, and the rate was not apparently altered even after a large rubella epidemic, suggesting that positive efforts to induce protective immunity into the susceptible young women before pregnancy should be done for the prevention of maternal rubella.

2) In administering rubella vaccine, females with a rubella HI titer of $1:8$ are preferable to be regarded as susceptible and to be involved in the vaccination concomitantly with the females with a titer of $<1:8$.

3) Vaccination for rubella using attenuated live virus vaccine has proved effective in raising the HI titers in susceptible women without any apparent complications, but there has been a single case where immunity was unable to be induced. Therefore, previously vaccinated females of child-bearing age or in pregnancy are desirable to be re-examined for HI titers whenever they encounter a rubella epidemic or become contact with the patient.

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和文要旨

Gregg, N.M. の卓見により風疹罹患妊婦に先天異常
見出される危険性が拡張されて以来、先天性風疹症候群
(CRS)に関する知見は数多く蓄積されている。若年婚
女性の多い職場で風疹の流行をみた場合、CRS 発生の
可能性が予測されることもあるが、産業医学あるいは
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