Rubella Susceptibility Predicts Measles Susceptibility: Implications for Postpartum Immunization

Measles and mumps antibody titer were measured in 262 pregnant women who were either positive \((n = 128)\) or negative \((n = 134)\) for rubella antibodies. Susceptibility to measles and mumps was detected in 4.6\% \((12/262)\) and 7.6\% \((14/184)\) of the women, respectively. Of the rubella-susceptible group, 8.2\% were also measles susceptible, whereas only 0.8\% of the rubella-immune women were measles susceptible. Susceptibility to mumps was evenly divided between rubella-susceptible (7.8\%) and rubella-immune (7.4\%) groups.

The goal of rubella immunization is the elimination of the congenital rubella syndrome (CRS). Protection from CRS is accomplished for the large majority of women in developed countries by routine childhood immunization(s) against rubella. A small number of women in their childbearing years, however, remain susceptible to rubella virus because of missed vaccinations (either intentional or unintentional) or vaccine failure. Prenatal screening of pregnant women for rubella antibodies is widely recommended to identify these susceptible women so that they can be offered vaccination postpartum. This strategy aims to eliminate the risk of CRS in the subsequent pregnancies. Whether to offer rubella vaccination alone or in combination with measles vaccine (MR) or measles and mumps vaccines (MMR) has only recently been considered by some national advisory bodies. For example, only the most recent recommendation of the Advisory Committee on Immunization Practices (ACIP) states that MMR vaccine should be offered to all children (1). Whereas recommendation of the Canadian National Advisory Committee on Immunization calls simply for “rubella vaccination” in these women (2).

Young adults are now recognized as a population at risk for measles and mumps viral infections. This age group has not been protected by the recent introduction of 2-dose MMR vaccine policies for children and was not reached by mass measles vaccination strategies where such campaigns have been under-

References

taken [3, 4]. Indeed, several of the most recent measles and mumps outbreaks in North America have started in or have primarily affected this age group [5–7]. If rubella-seronegative women are more likely to be seronegative for measles and/or mumps, then postpartum rubella vaccination with formulations also containing one or both of these vaccines would be of benefit. We therefore studied pregnant women with or without protective levels of rubella antibodies, to determine their susceptibility to measles and mumps infections.

St. Mary’s Hospital (Montreal, Québec, Canada) is a 400-bed community hospital serving a highly mixed urban population, with ~4500 deliveries per year. The screening of pregnant women for rubella antibodies by ELISA is routine practice (IMx; Abbott Diagnostics, Mississauga, Ontario, Canada). With this assay, a value of ≥10 IU is interpreted as a positive (i.e., immune) result.

We recovered all consecutive rubella-negative serum samples (134 samples) submitted to the laboratory for routine testing during a 4-month period in 1994. Consecutive rubella-positive serum samples (128 samples) submitted over 2 weeks during the same period were also recovered. At the time of collection, the samples were held at 4°C until the initial rubella testing was performed (≤3 days). Samples were then aliquoted and frozen at −70°C until ∼18 months later, when they were used in the current study. Samples with insufficient material remaining for additional testing were excluded.

Measles antibodies were measured in a 2-step procedure. Initially, samples were screened by ELISA using a combination of “in-house” and commercial reagents. In brief, 96-well plates were coated with measles antigen and left overnight in carbonate-bicarbonate buffer. Preparation of the measles antigen has been described elsewhere [8]. All washes were performed with PBS containing 0.5% Tween 20 (PBS/T). Plates were washed once and blocked with PBS/T containing 5% goat serum for 2 h at 36°C (Life Technologies, Grand Island, NY). Serum samples were diluted 1:200 in PBS/T and were incubated in duplicate wells overnight at 4°C (50 μL/well). A standard curve using a local control serum calibrated against the World Health Organization (WHO) standard measles serum (5 IU 66/202; WHO International Laboratory for Biological Standards, Hertshire, UK) was included on all plates. The ELISA was completed using a mouse anti-human IgG (ATCC 1757), a biotin-conjugated goat anti-mouse F(ab)2 (Boehringer Mannheim Canada, Laval, Québec, Canada), avidin-conjugated streptavidin (Life Technologies), and ABTS (Boehringer Mannheim). Optical density was read at 405 nm, and titers were estimated by extrapolation from the standard curve (expressed as mIU). Titers ≥200 mIU are thought to be protective in this type of assay. Serum samples from subjects with ELISA values ≤250 mIU were retested by plaque reduction neutralization (PRN) as described elsewhere [9]. PRN values of ≤120 units are thought to indicate susceptibility to measles [10]. Mumps antibodies were measured using a commercial ELISA (Enzygnost; Behring Diagnostics [Canada], Kanata, Ontario). Results in this assay are reported as positive, equivocal, or negative.

A limited amount of demographic information (e.g., age and nation of birth) was obtained from the patients’ hospital records. OR, χ² tests (with Yates correction), and ANOVA were calculated using EpiInfo version 6 (Centers for Disease Control, Atlanta, GA), and both binary and stratified analyses were performed. Logistic regression was performed using SAS for Windows, version 6.10 (SAS Institute, Cary, NC).

A review of laboratory records revealed that, of 4637 women screened antenatally for rubella antibodies, 10.9% were rubella susceptible. We studied a total of 262 patients who were classified as either rubella seronegative (134 patients) or seropositive (128 patients). Age was known for 261 patients (99.6%). Country of origin was known for 181 women (69.1%) and was unknown for 16 (6.1%). An additional 56 (21.4%) women were born outside North America, but the precise country was unspecified. We assumed these women to be from developing countries, on the basis of the ethnic origin of their names, but the results were similar when these women were excluded from analysis. The results are summarized in table 1. Of those whose country of birth was known, 46% were from Canada. Approximately 14% were from the Indian subcontinent, 13% were from Latin America, and 8% were born in Southeast Asia. The remaining women were from countries in both the developed and the developing world.

Sixty-seven samples (26%) had measles titers of <250 mIU according to ELISA, and were tested by PRN. Only 8 women had PRN titers of ≤120; 4 others were considered equivocal (PRN, >120 and <200). We considered these 12 (4.3%) women to be susceptible to measles. Eleven of the 12 subjects susceptible to measles were from the rubella-susceptible group. There was no difference in measles susceptibility between subjects from developed or developing countries (95% and 96%, respectively). Using logistic regression analysis to adjust for age

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rubella seropositive (n = 128)</th>
<th>Rubella seronegative (n = 134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean y ± SE (range)</td>
<td>31.3 ± 0.49 (20–45)</td>
<td>29.4 ± 0.45 (18–44)</td>
</tr>
<tr>
<td>Born in North America or Western Europe</td>
<td>50 (39.1)</td>
<td>45 (33.6)</td>
</tr>
<tr>
<td>Born or presumed born outside North America or Western Europe</td>
<td>72 (56.2)</td>
<td>79 (59.0)</td>
</tr>
<tr>
<td>Unknown place of birth</td>
<td>6 (4.7)</td>
<td>10 (7.5)</td>
</tr>
<tr>
<td>Measles seronegative</td>
<td>1 (0.8)</td>
<td>11 (8.2)</td>
</tr>
<tr>
<td>Mumps seronegative</td>
<td>7 (7.4)</td>
<td>7 (7.8)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients unless otherwise indicated.

a. P < .003.
b. P < .01.
c. n = 95.
d. n = 89.
and birth in a developing country had virtually no effect on the results.

Mumps antibodies were measured in 184 subjects (95 rubella seropositive and 89 rubella seronegative). We excluded those with borderline rubella titers (5–10 IU; 30 patients) and those with insufficient serum remaining (48 patients). Ninety-two percent of our study subjects tested positive for mumps. Fourteen (7.6%) subjects with equivocal or negative results were considered to be susceptible to mumps. These subjects were evenly distributed between the rubella-susceptible and immune groups. Thirteen of the 14 were immune to measles.

Although there is little debate that women with susceptibility to rubella discovered during pregnancy should receive rubella vaccination postpartum, the potential additional benefit of using MR or MMR formulations is not addressed in the literature. A modest association between rubella and measles susceptibility can be inferred from data published from 2 studies involving military serosurveys for various vaccine-preventable illnesses [11, 12]. A third report, which did not provide the raw data, claimed that there was no correlation between susceptibility to measles and susceptibility to rubella [13].

In this study, the association between susceptibility to rubella and susceptibility to measles in pregnant women was strong. We found measles-susceptibility rates of 8% and 0.8% among rubella-susceptible and rubella-immune individuals, respectively. The reasons for this association remain speculative. Among those born in the developed world, measles infection is now relatively rare, and immunity in the childbearing years is largely the result of childhood vaccination. Failure to be properly vaccinated with MMR could explain the simultaneous lack of immunity to measles and rubella. (It would not explain the apparent lack of association between susceptibility to mumps and susceptibility to either rubella or measles.) Such an association between susceptibility to measles and susceptibility to rubella would not have been evident in older studies in adults, because rubella vaccine first appeared only in 1969. The reason for this association among women born in developing countries is less evident, because measles vaccination is now relatively rare, and immunity in the childbearing years is largely the result of childhood vaccination. Failure to be properly vaccinated with MMR could explain the simultaneous lack of immunity to measles and rubella. (It would not explain the apparent lack of association between susceptibility to mumps and susceptibility to either rubella or measles.) Such an association between susceptibility to measles and susceptibility to rubella would not have been evident in older studies in adults, because rubella vaccine first appeared only in 1969.

The cost of adding measles vaccination for women susceptible to rubella is modest. Using bulk purchase contracts, our additional cost per measles-susceptible woman ranges from $12 to $50 (Canadian), depending on whether mumps vaccination is added as well (data not shown). In light of our prevalence of rubella susceptibility of 11%, and measles-susceptibility rates of 8% and 0.8% in the rubella-susceptible and rubella-immune groups, respectively, approximately half of all measles-susceptible women would be vaccinated with such a program. If the association we observed is confirmed in other centers, it would be rational to vaccinate rubella-seronegative pregnant women with a measles-containing vaccine postpartum as has recently been recommended by the ACIP [1].

References