Maternal Immunity and Prevention of Congenital Cytomegalovirus Infection

Karen B. Fowler, DrPH
Sergio Stagno, MD
Robert F. Pass, MD

Congenital cytomegalovirus (CMV) infection remains a major public health problem in the United States because of its frequency and its role as a cause of sensorineural hearing loss, cognitive impairment, cerebral palsy, and visual impairment.1,2 Congenital cognitive impairment, cerebral palsy, a cause of sensorineural hearing loss, because of its frequency and its role as the United States.2-4 Development of a nervous system damage in children is the leading infectious cause of central sensorineural hearing loss in children and CMV infection is a leading cause of sensorineural hearing loss in children and CMV infection was listed as a top priority by the Institute of Medicine of the National Academy of Sciences in an analysis of cost of disease and impact on quality-adjusted life-years.5

Virus can be transmitted to the fetus during primary maternal infection during pregnancy, but it also can be transmitted even when maternal infection occurred years prior to conception.6 Whether maternal immunity decreases the frequency of transplacental transmission of CMV has not been previously studied. Uncertainty over the ability of naturally acquired immunity to prevent future infection is a major impediment to development of vaccines for prevention of congenital CMV infection. To test the hypothesis that preconception maternal immunity reduces the risk of congenital CMV infection, we compared rates of congenital CMV infection according to maternal serological status in a population with a high rate of congenital CMV infection who delivered newborns screened for congenital CMV infection between 1993 and 1998, and whose cord serum specimen from a previous delivery could be retrieved and tested for antibody to CMV.

Main Outcome Measure Congenital CMV infection according to maternal immune status, age, race, parity, and socioeconomic status.

Results Of 604 newborns born to initially seronegative mothers, congenital CMV infection occurred in 18 (3.0%). In contrast, of 2857 newborns born to immune mothers, congenital CMV infection occurred in 29 (1.0%) Two factors, preconception maternal immunity (adjusted risk ratio, 0.31; 95% confidence interval, 0.17-0.58) and maternal age of 25 years or older (adjusted risk ratio, 0.19; 95% confidence interval, 0.07-0.49), were highly protective against congenital CMV infection. No other factors were associated with a reduction in the risk of congenital CMV infection.

Conclusion Naturally acquired immunity results in a 69% reduction in the risk of congenital CMV infection in future pregnancies.

Context Vaccine development to prevent congenital cytomegalovirus (CMV) infection has been impeded by the uncertainty over whether maternal immunity protects the fetus.

Objective To determine whether the presence of maternal antibodies to CMV significantly reduces the risk of congenital CMV infection in future pregnancies.

Design, Setting, and Participants Cohort study of 3461 multiparous women from a population with a high rate of congenital CMV infection who delivered newborns screened for congenital CMV infection between 1993 and 1998, and whose cord serum specimen from a previous delivery could be retrieved and tested for antibody to CMV.

METHODS Study Population

Women who delivered a newborn at the university hospital in the southern part of the United States between January 1993 and December 1998 were included in the study population if the following criteria were met: (1) the newborn was screened for congenital CMV infection; (2) the mother had 1 or more previous live births at the university hospital; (3) a cord serum specimen from a previous delivery could be retrieved and tested for IgG antibody to CMV. Cord serum specimens were stored at −20°C in a repository. The study was approved by the institutional review board at the University of Alabama, Birmingham. Written informed consent was obtained from the mothers of infants with congenital CMV infection who attended follow-up clinics. The institutional review board waived consent for those without CMV infection.

Between 1993 and 1998, 7558 multiparous women delivered at the university hospital (FIGURE). Of these women, 4132 had a prior delivery at the university hospital, and 3461 had available cord serum specimens. The latter group comprises the study population. The 671 women who delivered between January 1993 and December 1998...
RESULTS

Characteristics of the study population according to maternal CMV antibody status at the time of the previous pregnancy are shown in Table 1. Overall, 2857 mothers (82.5%) had CMV antibodies at the time of the previous pregnancy, and 604 (17.5%) were seronegative. The majority of both groups were black, although seronegative mothers were more likely to be white (33.4%) than were seropositive mothers (15.8%). Slightly more seronegative mothers (22.0%) compared with seropositive mothers (15.3%) had private health insurance, a difference that was statistically significant (P < .001). Not surprisingly, the initial pregnancy at which serological status was determined was the first pregnancy for more of the seronegative group. Seronegative mothers were younger by less than 1 year in mean age, a difference that was statistically significant (P = .001).

Overall, congenital CMV infection occurred in 46 infants (1.3%) born to study mothers. Of 604 newborns born to initially seronegative mothers, congenital CMV infection occurred in 29 (1.0%). In contrast, of 2857 newborns born to immune mothers, congenital CMV infection occurred in 17 (0.6%). In the initially seronegative group, 142 women (23.5%) seroconverted between deliveries. All of the congenital CMV infections among the initially seronegative group occurred in the infants of mothers who seroconverted between pregnancies.

Risk factors for delivering an infant with congenital CMV infection were examined for the entire study population (Table 2). Black race and lower socioeconomic status (Medicaid or no insurance for hospital stay) were both associated with increased risk of congenital CMV infection. However, the 95% CIs for both factors included 1.0. Older maternal age (>25 years) and gravidity (>2) were associated with de-

Table 1. Study Population Characteristics by Serostatus During Prior Pregnancy*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Seropositive (n = 2857)</th>
<th>Seronegative (n = 604)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>2382 (83.4)</td>
<td>399 (66.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Other</td>
<td>451 (15.8)</td>
<td>202 (33.4)</td>
<td></td>
</tr>
<tr>
<td>Insurance status for hospital stay</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medicaid or no insurance</td>
<td>2421 (84.7)</td>
<td>471 (78.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Private insurance</td>
<td>436 (15.3)</td>
<td>133 (22.0)</td>
<td></td>
</tr>
<tr>
<td>No. of prior pregnancies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1020 (35.7)</td>
<td>297 (49.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2</td>
<td>853 (29.9)</td>
<td>180 (29.8)</td>
<td></td>
</tr>
<tr>
<td>&gt;2</td>
<td>984 (34.4)</td>
<td>127 (21.0)</td>
<td></td>
</tr>
<tr>
<td>Maternal age, mean (SD), y</td>
<td>24.6 (5.2)</td>
<td>23.8 (5.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Gestational age at delivery, mean (SD), wk</td>
<td>38.2 (2.9)</td>
<td>38.2 (2.8)</td>
<td>.67</td>
</tr>
</tbody>
</table>

*Values are expressed as number (percentage) unless otherwise indicated.
increased risk of congenital CMV infection. The presence of maternal antibody at the previous delivery was highly protective against delivering a future newborn with congenital CMV infection (RR, 0.32; 95% CI, 0.17-0.62).

Maternal immune status at previous birth, maternal age, race, insurance status, and gravidity were evaluated in a logistic regression model to simultaneously assess the effects of these factors on the risk of congenital CMV infection. Once maternal immune status at previous birth and maternal age of 25 years or older were included in the model, none of the other potential risk factors changed these estimates and they were not independently associated with congenital CMV infection. Even after adjustment for age, maternal immunity remained strongly protective against congenital CMV infection (adjusted RR, 0.31; 95% CI, 0.17-0.58). Maternal age of 25 years or older remained strongly associated with reduced risk of congenital CMV infection after adjustment for maternal immunity (adjusted RR, 0.19; 95% CI, 0.07-0.49).

**COMMENT**

This study shows that young women who have immunity to CMV from naturally acquired infection are 69% less likely to give birth to an infant with congenital CMV infection in the future than are those who are initially CMV seronegative. Among mothers CMV seronegative at a previous delivery, seroconversion between deliveries is common (23.3% in this study). When seroconversion occurs between deliveries, the risk of congenital CMV infection is high. We found a rate of congenital CMV infection of 12.7% for offspring of mothers who seroconverted during the interval (average, 3 years) between deliveries.

The major limitation of this study is that it included only multiparous women. Ideally, in testing the ability of immunity from naturally acquired CMV infection to prevent congenital CMV infection, a cohort of young women prior to their first pregnancy would be enrolled after determining their CMV immune status. These women would be followed up through subsequent pregnancies, all offspring would be tested for congenital infection, and maternal seroconversions would be defined by repeat CMV antibody testing. The expense and logistical difficulties associated with enrollment and follow-up of such a cohort of young women would likely make this type of study impossible to conduct. Our study was limited to women who had at least 1 pregnancy prior to their first pregnancy because this initial pregnancy was used as the starting point for determining immunity to CMV prior to the subsequent pregnancy. The exclusion of younger primiparous women may have led to an underestimation of the proportion of congenital infections due to primary maternal infection, and therefore underestimation of the protective effect of maternal immunity. Since the prevalence of maternal antibody increases rapidly with age in young women, it is likely that a greater proportion of younger women would have been seronegative near the time of their first pregnancy. It is possible that our study has actually underestimated the ability of naturally acquired immunity to prevent future congenital CMV infection by selecting an older multiparous population in which fewer seroconversions will occur.

The current study is the first to compare rates of congenital CMV infection based on maternal immunity status at a point prior to conception. The study population, mothers who had more than 1 pregnancy with delivery of a live newborn at the university hospital, was predominantly black (80%) and young, with a mean age of 24 years. Previous studies of this delivery population have reported a relatively high rate of congenital CMV infection (1.25%), a high rate of primary infection during pregnancy, and the occurrence of congenital CMV infection in women known to have been infected 1 year or more prior to conception. Published reports indicate that exposure to young children and sexual activity are important sources of CMV infection for young women. Those exposures were not assessed in the current study and the only demographic variable significantly associated with acquisition of CMV among seronegative women was race. Considering the entire study population (seropositive and seronegative women), maternal immunity and older maternal age were associated with protection from congenital CMV infection. None of the other suggested demographic or maternal risk factors were independently associated with congenital CMV infection in this population.

Although the occurrence of congenital CMV infection in offspring of women who are known to have been infected long before conception has been previously reported, the current study probably provides the most accurate estimate for congenital CMV infection rate. Of 2857 immune mothers from a predominantly low-income, young, black

### Table 2. Factors Associated With Delivering a Newborn With Congenital CMV Infection in Multiparous Women

<table>
<thead>
<tr>
<th>Factor</th>
<th>Congenital CMV Infection (n = 46)</th>
<th>No Infection (n = 3415)</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black</td>
<td>41 (89.1)</td>
<td>2740 (80.2)</td>
<td>2.02 (0.79-6.57)</td>
</tr>
<tr>
<td>Maternal age ≥25 y</td>
<td>5 (10.9)</td>
<td>1419 (41.6)</td>
<td>0.17 (0.05-0.44)</td>
</tr>
<tr>
<td>Medicaid or no insurance</td>
<td>43 (93.5)</td>
<td>2649 (83.4)</td>
<td>2.85 (0.91-14.39)</td>
</tr>
<tr>
<td>&gt;2 Prior pregnancies</td>
<td>6 (13.0)</td>
<td>1105 (32.4)</td>
<td>0.31 (0.11-0.75)</td>
</tr>
<tr>
<td>Seroregime during prior pregnancies</td>
<td>28 (60.9)</td>
<td>2829 (82.8)</td>
<td>0.32 (0.17-0.62)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; RR, risk ratio.
population in the United States, 29 (1.0%) transmitted congenital CMV infection. Previous studies from this institution reported a rate of 3.4% in women who were immune prior to conception; this was based on a smaller sample size (n = 208) and a more highly selected study population. However, some have reported high rates (1.2%-2.9%) of congenital CMV infection in populations in which almost all women of childbearing age were seropositive, but they did not define congenital CMV infection rates based on maternal immunity documented prior to conception. However, even a rate of congenital CMV infection of 1.0% is of great concern because the majority of young women from the study population are immune to CMV, and recent studies report that some congenital CMV infections in newborns born to immune mothers are associated with central nervous system disease. A better understanding of the factors that influence occurrence of congenital CMV infection and disease in offspring of immune mothers is needed, both for planning preventive strategies and to estimate the potential effectiveness of vaccines.

Results reported here are of importance in planning strategies for prevention of congenital CMV infection. Based on the reduction in risk of congenital CMV infection associated with maternal immunity, a vaccine that could achieve protection similar to that from immunity from naturally acquired infection would be expected to reduce the rate of congenital CMV infection by at least 70%. Young maternal age was strongly associated with increased risk of congenital CMV infection as has been observed in previous reports.

Our findings along with previous reports indicate that postponing pregnancy until age 20 years or older could substantially reduce the rate of congenital CMV infection.

Author Contributions: Study concept and design: Fowler, Pass. Acquisition of data: Fowler, Stagno, Pass. Analysis and interpretation of data: Fowler, Stagno, Pass. Drafting of the manuscript: Fowler, Pass. Critical revision of the manuscript for important intellectual content: Fowler, Stagno, Pass. Statistical expertise: Fowler. Obtained funding: Fowler, Stagno, Pass. Administrative, technical, or material support: Fowler, Stagno, Pass. Study supervision: Fowler, Pass.

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