Interval between Births and Risk of Congenital Cytomegalovirus Infection

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(See the editorial commentary by Plotkin on pages 1038–9)

To examine the effect of the interval between maternal cytomegalovirus (CMV) infection and conception on the risk of congenital CMV infection, the congenital CMV infection rate was evaluated relative to the intervals between deliveries in young women. Among mothers who seroconverted between deliveries, the rate of congenital CMV infection among their offspring was highest when the delivery interval was ≤24 months. However, the risk of transmission remained elevated for women with delivery intervals of 25–48 months and for those with delivery intervals >48 months apart.

When primary cytomegalovirus (CMV) infection occurs during pregnancy, transmission of the virus to the fetus occurs in ~30%–40% of the cases [1, 2]. CMV infection in healthy adults is typically clinically silent and chronic, with viral shedding continuing for months or longer [3–5]. It is logical to believe that the risk of congenital CMV infection might increase when primary maternal infection occurs before pregnancy. However, the risk of transplacental transmission of CMV relative to the interval between primary maternal infection and conception has not been determined. To examine the effect of this interval on the risk of congenital CMV infection, the rate of transmission was evaluated relative to the interval between consecutive deliveries in a cohort study involving young mothers.

Patients and methods. The study population comprised women who delivered newborns at University Hospital (Birmingham, AL) between 1993 and 1998 and was the same as that described in a recent report on maternal immunity and the risk of congenital CMV infection associated with subsequent pregnancies [6]. The study was conducted at a time when newborns born at University Hospital were routinely screened for congenital CMV infection by testing for viral shedding. Cord serum samples obtained during deliveries at University Hospital underwent testing for antibody to CMV, the results of which defined maternal immunity at the time of the initial pregnancy and allowed identification of women who acquired antibody to CMV (seroconverted) between deliveries. The study was approved by the institutional review board of the University of Alabama at Birmingham, and written informed consent was obtained from the mothers of infants with congenital CMV infection who attended our follow-up clinic visits.

Between 1993 and 1998, a total of 7558 multiparous women gave birth at University Hospital. Of these women, 4132 had previously delivered at University Hospital, and 3461 had cord serum specimens that were tested for antibody to CMV. The latter group comprised the study population.

CMV-specific IgG antibodies were measured using a commercially available enzyme immunoassay (Abbott ImX). Seroconversion was determined by simultaneously testing for the presence of CMV IgG antibodies in cord serum samples obtained during the most recent delivery and the absence of CMV IgG antibodies in cord serum samples obtained during the immediately preceding delivery. Newborns were screened during the first days of life for congenital CMV infection by testing saliva samples with a rapid culture method based on centrifugation enhancement to detect monoclonal antibody to the major immediate early antigen in virus-infected cells, as described elsewhere [7]. All positive results of newborn screening tests were confirmed by isolation of virus from urine and/or saliva specimens obtained during a follow-up clinic visit 3 weeks after birth. None of the infants with congenital CMV infection were HIV positive, and <0.2% of women in the study population were expected to be HIV seropositive during pregnancy [8].

All 95% CIs were calculated using exact binomial methods. Student’s t test was used to compare the mean interval between pregnancies. All frequencies and data analyses were performed using SAS/STAT software, version 8 of the SAS System for Windows (SAS Institute). Data are mean values ± SD (median values), unless otherwise indicated.

Results. The majority of women in the study population were African American (2781 [80%] of 3461 subjects), a large...
minority were white (653 [19%]), and the remainder were from other racial and/or ethnic groups (27 [1%]). The age of the study population was 24 ± 5 years. Only 562 women (16%) had private health insurance, and 2889 (84%) had Medicaid or no health insurance. All participants had had ≥1 pregnancy before the birth at which the congenital CMV infection rate was determined; 1033 (30%) had had 2, and 1111 (32%) had had >2. As reported elsewhere, antibody to CMV was detected in 2857 mothers (82.5%) at the time of the immediately preceding pregnancy, and 604 (17.5%) were seronegative [6]. Seroconversion occurred in 142 (23.5%) of the 604 mothers who were initially seronegative (95% CI, 20.1–27.1%). The seroconversion rate was 5.9% per year, based on a mean interval between deliveries of 4 years among women who were initially seronegative. All congenital CMV infections occurred in women who seroconverted between deliveries or who were seropositive at the initial study delivery. Congenital CMV infection occurred in 18 (12.7%) of 142 newborns born to initially seronegative mothers (95% CI, 7.7%–19.3%). As reported elsewhere, congenital CMV infection occurred in 28 infants (1%; 95% CI, 0.7%–1.4%) born to the 2857 immune mothers [6].

When congenital CMV infection occurred, the interval between the initial delivery during which CMV serological status was established and the subsequent delivery was shorter in both the seroconverted and immune groups (table 1). Among women who were initially nonimmune and seroconverted between deliveries, the interval ending with the birth of a newborn with congenital CMV infection was 25.8 ± 13.0 months (22 months), compared with 50.7 ± 38.9 months (36.5 months) when the newborn was uninfected (P<.001). Among initially seropositive mothers, the interval ending with the birth of a newborn with congenital CMV infection was 33.7 ± 19.6 months (28.5 months), compared with 51.6 ± 35.8 months (42 months) when the newborn was uninfected (P<.001). Women who seroconverted between deliveries ≤24 months apart were 4 times more likely to deliver a newborn with congenital CMV infection than were women who seroconverted between deliveries >24 months apart (OR, 4.3; 95% CI, 1.4–14.2). Immune mothers who delivered ≤24 months apart also had a 2-fold increased risk of delivering an infant with congenital CMV infection, compared with seropositive mothers who delivered >24 months apart (OR, 2.3; 95% CI, 1.0–5.2).

Discussion. For mothers who were initially nonimmune or immune, a shorter interval between the birth at which CMV serological status was established and the subsequent birth was associated with an increased risk of congenital CMV infection. The association between a shorter interval between births and an increased rate of congenital CMV infection suggests that the risk of congenital CMV infection increases, even when primary maternal infection occurs months and perhaps years before conception. The median interval between births among women who seroconverted between deliveries was almost 4 years. For those who seroconverted and transmitted CMV to their newborns, the median interval between pregnancies was just less than 2 years (range, 0.9–4.8 years). If we assume that the risk of maternal CMV infection in the seronegative group was equal during the interval between births, these results imply that approximately one-half of the maternal primary infections that led to congenital CMV infection occurred >1 year before conception.

Among initially seropositive women, there was also a strong association between an increased prevalence of congenital CMV infection and shorter interval between deliveries. This result is compatible with at least 2 explanations: it is possible that some of the seropositive women had primary infection near the time that their serological status was initially determined, or it is possible that they were reinfected with a new strain of CMV during the interval between pregnancies. The high seroconversion rate among seronegative women in this population suggests that 10%–15% or more of the initially seropositive women would likely have acquired CMV infection within a year or two before antibody testing. The same exposures that contributed to the high rate of primary CMV infection in this population could lead to reinflections. A recent study of mothers who were CMV seropositive before conception and transmitted the virus to their offspring revealed evidence that many of them had been infected with a new strain of CMV [9].

Relating risk of congenital CMV infection to the time at which maternal infection occurred is important for providing counseling to women of childbearing age who acquire CMV infection before conception and seek information on the risk to the fetus. The results in this report estimate a time frame that maternal CMV infection likely occurred but cannot quantify the risk of infection for the fetus, because it is possible that some maternal infections occurred before and others during the pregnancy that led to congenital CMV infection. However, assuming an equal rate of seroconversions during the interval between births, the results support the conclusion that risk of fetal infection is elevated even when maternal infection occurs months before conception. Follow-up observation of a large cohort of seronegative young women for years, with serial test-

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<tr>
<th>Interval between births, months</th>
<th>Seroconverted mothers (n = 142)</th>
<th>Immune mothers (n = 2857)</th>
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<tbody>
<tr>
<td>&lt;24</td>
<td>11/44 (25)</td>
<td>12/711 (1.7)</td>
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<tr>
<td>25–48</td>
<td>5/50 (10)</td>
<td>9/954 (0.9)</td>
</tr>
<tr>
<td>&gt;48</td>
<td>2/48 (4.2)</td>
<td>7/1192 (0.6)</td>
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*a No. of infected women/no. of women tested (%)
ing for CMV infection and virological screening of newborns, will be required to accurately relate the risk of congenital CMV infection to the time of primary maternal infection.

Mothers who are seronegative are at increased risk for having a newborn with congenital CMV infection during the next pregnancy [6]. Results in the present report show that, if seroconversion occurs between pregnancies, the risk of congenital CMV infection is 12%, and this risk increases as the interval between pregnancies decreases.

Should women who are seronegative be screened for seroconversion, and should those who seroconvert between pregnancies be offered prenatal evaluation for fetal CMV infection? In general, the American College of Obstetricians and Gynecologists has not recommended screening for maternal and fetal CMV infection in the United States [10]. However, colleagues in Europe have debated whether screening for CMV infection should be part of prenatal care [11–14]. Prenatal screening for maternal primary CMV infection using IgM antibody assays is of concern, because CMV-IgM antibody tests are sometimes positive during nonprimary infection and because options for intervention are limited to the termination of pregnancy. To overcome the problem of false-positive CMV-IgM results, a prenatal screening approach that used CMV-IgG antibody avidity and detection of IgM antibody to viral proteins in an immunoblot assay accurately identified primary maternal infections [15]. Mothers with proven primary infection were then offered additional prenatal evaluation with amniocentesis for diagnosis of fetal CMV infection; virus load in amniotic fluid and fetal ultrasonography identified infected fetuses at greatest risk or already showing signs of morbidity due to CMV infection [15]. Identifying women with proven primary infection during pregnancy and offering additional prenatal diagnostic screening will likely decrease the number of pregnancies that may be terminated because of maternal CMV infection by identifying the infected fetuses most likely to demonstrate morbidities [12]. Results of the present study suggest that screening women for CMV seroconversion between pregnancies could also identify a group at high risk for fetal transmission of CMV infection that merits further prenatal evaluation.

References