Primary Maternal Cytomegalovirus Infection During Pregnancy: Do We Have a Treatment Option?

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(See the Major Article by Visentin et al, on pages 497–503.)

A primary maternal infection with cytomegalovirus (CMV) during early pregnancy accounts for the majority of congenital disease due to CMV. This is a major public health problem, and in the United States approximately 9000 children are born each year with severe disabilities caused by this placental and intrauterine infection [1]. Immunity induced by infection with wild-type CMV affords women a high degree of protection against acquisition of a second CMV infection and protects the fetuses from severe postnatal neurosensory deafness and neurologic damage. For women who are immune to CMV before conception, the intrauterine fetal infection rate is approximately 1%, and >90% of infants are healthy. For women who acquire CMV during pregnancy, the fetal infection rate varies from 33% to 75% as gestation progresses, and the disease rates may be as high as 50% if infection occurs during the first half of pregnancy [2, 3]. These observations suggest that an active CMV vaccine is feasible and that it has no theoretical or biological obstacles. Both active and passive immunization experiments have been successful in a guinea pig model of congenital infection [4–7]. There have been 2 human trials of active immunization whose end points were the prevention of maternal infection. One trial of a live attenuated vaccine, conducted in the early 1990s, failed because of poor antibody levels associated with a vaccine dose that was too low [8]. A second trial, reported in 2009, used a protein vaccine (gB/MF59). This vaccine was 50% effective in preventing maternal infection in nonpregnant women [9]. A third trial of gB/MF59 that involves a similar study design is ongoing.

Unlike in the United States, in Italy most pregnant women are tested serologically for CMV at the first prenatal visit and, if seronegative, are retested monthly until late during gestation. The initial rationale for this serologic testing was that if seroconversion occurred, especially during early gestation, termination of pregnancy was an option. For those who seroconverted but chose not to terminate, no options were available. With the recognition that immunoglobulin therapy has been used safely in pregnancy for decades [10], primarily to treat blood group incompatibilities but also for passive immunization against rubella virus, hepatitis A and B virus, varicella virus, and measles virus, and because antibodies appeared important for protecting the fetus, in 1996 Giovanni Nigro and colleagues initiated a prospective, nonrandomized, controlled phase I-II safety and immunogenicity study, using passive immunization for women who seroconverted to CMV during pregnancy [3]. There were 2 study protocols, one for prevention of fetal infection and one for treatment of infected fetuses.

A total of 55 women with primary CMV infection had polymerase chain reaction–positive amniotic fluid, suggesting fetal infection. They were offered treatment with CMV-specific hyperimmune immunoglobulin (Cytotect 200 U/kg per infusion). Thirty-one women elected treatment, and 14 did not. Of the 31 treated women, only 1 had a child with abnormalities at follow-up. This result differed from that for the 14 nontreated women (P < .001); of their 14 infants, 2 died postnatally, and 5 were severely affected at follow-up at ≥2 years of age.

The efficacy of immunoglobulin therapy was further supported by a recent case-control study [11]. The subjects were 64 congenitally infected children whose mothers had a confirmed primary infection at ≤20 weeks gestation. Cases were 32 children with either hearing deficit and/or psychomotor retardation. Controls were 32 congenitally infected children who were healthy. Case and controls were matched by the week of maternal gestation (±1 week) at time
of the mother’s infection and by the child’s age (±1 year) at evaluation. Of the 32 cases, only 4 mothers received CMV immunoglobulin, compared with 27 of 32 mothers of control infants (adjusted odds ratio, 14 [95% confidence interval {CI}, 1.7–110]). The only risk factor for affected children was nonreceipt of immunoglobulin by the mother (P = .001). Also reported in this study were an additional 20 infants who could not be matched. When these individuals were included, there were 4 diseased infants among 40 women who received immunoglobulin, compared with 35 diseased infants among 44 untreated mothers.

The study led by Vistentin and Manara in the current issue of Clinical Infectious Diseases is a very important additional study [12]. This study was again facilitated by the serologic screening for CMV among pregnant women in Italy. In this study, beginning in 2002 all women with a primary CMV infection at <17 weeks gestation were enrolled in prospective natural history study and did not receive an intervention. Starting in 2007, all newly enrolled women were offered treatment with Cytotect at 200 U/kg if the fetus was infected, on the basis of detection of CMV in the amniotic fluid after week 20 of gestation and at least 6 weeks after infection. These criteria were nearly identical to those used in the original Nigro study [3]. The core finding was that at 1 year of age a poor outcome occurred in 4 infants from 31 Cytotect-treated mothers, compared with 16 infants from 37 untreated mothers (P < .01).

A meta-analysis using logistic regression that accounted for study assignment found that the odds ratios for the 3 treatment studies all favored treatment, with odds ratios of 30 (95% CI, 3.1–285), 35 (95% CI, 9.9–124), and 51 (95% CI, 1.5–17.7) and a combined odds ratio of 17.6 (95% CI, 7.9–43.3).

A review of ClinicalTrials.gov revealed that no randomized trial of immunoglobulin therapy for CMV-infected fetuses is planned or ongoing.

Another potential use of CMV hyperimmunoglobulin is for the prevention of fetal infection after a primary maternal infection during pregnancy. In the initial study by Nigro and colleagues on the prevention of fetal infection, women who seroconverted in early pregnancy or did not undergo amniocentesis received monthly hyperimmunoglobulin (Cytotect 100 units/kg/infusion) as prophylaxis until delivery [3]. Six of the 37 women (16%) who chose this prophylaxis had infected infants, while 19 of the 47 women (40%) who did not agree to prophylaxis had infants who were infected at birth. This difference was statistically significant (P < .04).

Another double-blinded, randomized, placebo-controlled trial of Cytotect prophylaxis was recently completed in Italy [13]. The end point was congenital infection at birth or CMV-positive amniotic fluid. After 122 subjects were enrolled (61 received Cytotect and 61 received placebo), the trend was toward efficacy. Placebo recipients had a 44% infection rate. Those who received Cytotect had a 30% infection rate (95% CI, .19–.42). The P values (by the Fisher exact test) for the difference between treated and untreated groups was .13 (2 tailed) and .065 (1 tailed). The study by Nigro and colleagues [11] observed a an infection rate of 16% (95% confidence interval, 0.7–3) among treated women.

For a meta-analysis, if one combines the data from the 2 studies, which is justified by the overlapping CIs and uses a logistic regression model that accounts for study assignment, there is no evidence that the rates from the 2 studies are significantly different (likelihood ratio χ² statistic, 0.89; P = .3449). Combination of the observations from the 2 studies, however, finds that 46 fetuses (42%) from 108 women who had a primary infection and were not receiving Cytotect became infected, compared with 24 from 98 women (24%) treated with Cytotect (likelihood ratio χ² statistic, 8.04; P = .0046; odds ratio, 2.35 [95% CI, 1.30–4.34]).

Thus, for prevention of fetal infection, the best estimates to date indicate that passive immunization reduces the rate of fetal infection by one-half after a primary maternal infection during pregnancy.

The placenta of women with primary CMV infections during pregnancy is enlarged, compared with that of seronegative women and women seropositive before conception. The enlarged placenta decreases in size after hyperimmunoglobulin administration [14]. This led to the hypothesis that immunoglobulin acts by improving placental function [15] and that many symptoms of congenital CMV infection that are present at birth may not be due to a direct effect of the virus on the fetus but rather to a direct effect on the placenta. Immunohistological analysis of placental specimens from women with untreated congenital infection, women who received CMV-specific hyperimmunoglobulin treatment, and uninfected controls found that antibody treatment suppressed CMV replication and associated inflammation and indicated improvement in placental function and fetal outcome [15].

Immunoglobulin preparations are available. In the United States, the available product is Cytogam (CSL Behring), and in Europe, the product is Cytotect (Biotest AG). The Australian Red Cross blood services also produce an intravenous immunoglobulin preparation enriched for antibodies to CMV. We have tested the neutralizing activity of each preparation by measuring the titer of antibodies directed against CMV glycoprotein B, a CMV envelope protein that induces the majority of neutralizing activity directed against CMV entry into fibroblasts. Each product has an anti-glycoprotein B titer of 1:400 000. This is approximately 2–4-fold higher than that observed among individuals naturally seropositive for CMV. Cytogam and Cytotect also contain very high titers of antibodies that block viral entry into epithelial cells [16]. CMV immunoglobulins also
have a transient immunomodulatory effect in pregnant women [3].

The benefits of screening pregnant women for a primary CMV infection need reassessment. Although immunoglobulins are expensive, the cost of severe disabilities caused by congenital CMV infection are far more costly [17]. A cost–benefit analysis found that universal serologic screening at 20 weeks’ gestation, when compared with screening only high-risk women or women with abnormal ultrasonography findings, was the preferred and most cost effective approach when used with administration of 1 immunoglobulin infusion to mothers with fetal CMV infection confirmed by amniocentesis [18]. This approach would be cost-effective if immunoglobulin therapy was at least 47% protective against severe disabilities [18]. A limitation of the studies cited above is that they were not designed to detect subtle or long-term deficits in neurologic or cognitive function that may persist after immunoglobulin therapy, which may affect outcomes of cost–benefit analyses.

In summary, all of the available data indicate that passive immunization is effective for in utero treatment of fetal CMV infections.

Note

**Potential conflicts of interest.** S. P. A. certifies no potential conflicts of interest.

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