Immunotherapy for Congenital Cytomegalovirus Infection

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Cytomegalovirus (CMV) is an extremely important perinatal pathogen. Each year, approximately 1 percent of susceptible women seroconvert during pregnancy. Although sexual transmission of CMV can occur, most pregnant women acquire CMV infection through exposure to children in their own home or from occupational exposure to children in day care or elementary school. Exposure typically occurs as a result of contact with contaminated saliva, urine, or fomites such as toys. Approximately 40 percent of pregnant women with a primary infection transmit CMV to their fetuses. Rates of transmission are highest when maternal infection occurs in the third trimester; however, the risk of serious fetal injury is greatest when maternal infection occurs in the first trimester or early in the second trimester. Ten to 20 percent of congenitally infected infants have acute symptoms at birth. Of these, up to 20 percent die and the remainder typically have moderate-to-severe complications. Clinical manifestations of severe congenital CMV infection include growth restriction, microcephaly, ventriculomegaly, chorioretinitis, hepatosplenomegaly, hepatitis, thrombocytopenia, and a purpuric skin eruption (“blueberry-muffin baby”).

Until now, no consistently effective therapy for congenital CMV infection has been available. Accordingly, obstetricians have focused their attention on screening selected women considered at high risk for CMV infection and performing amniocentesis to identify infected fetuses. Targeted ultrasonography is then used to identify the severely injured fetus, and pregnancy termination is offered as a management option.

The report by Nigro et al. in this issue of the Journal is remarkable and provocative because it offers the promise of a means to treat and prevent congenital CMV infection. These authors performed a prospective cohort study at eight Italian medical centers of 157 pregnant women with confirmed primary CMV infection. Of these women, 148 were asymptomatic and were identified by routine serologic screening, 8 had a symptomatic viral infection consistent with CMV infection, and 1 was identified because her fetus had abnormal findings on ultrasonography. Forty-five women had a primary infection more than six weeks before enrollment, underwent amniocentesis, and had CMV detected in amniotic fluid by the polymerase chain reaction (PCR) or culture. Thirty-one of these women elected to receive intravenous treatment with CMV-specific hyperimmune globulin (200 U per kilogram of the mother’s body weight). Nine of the 31 received one or two additional infusions into either the amniotic fluid or umbilical cord because of persistent fetal abnormalities on ultrasonography. Fourteen women declined treatment with hyperimmune globulin; seven of them had infants who were symptomatic at delivery. In contrast, only 1 of the 31 treated women had an infant with clinical CMV disease at birth (adjusted odds ratio, 0.02; P<0.001), although 15 were carrying fetuses with unmistakable ultrasonographic evidence of CMV disease.

Eighty-four additional women did not undergo amniocentesis, because their infection occurred within 6 weeks before enrollment, their gestational age was less than 20 weeks, or they declined the procedure. Thirty-seven of these women received 100 U of hyperimmune globulin per kilogram every month until delivery (range of infusions, four to six), and 47 declined such treatment. Among the treated women, 6 delivered infected infants, as
compared with 19 of the untreated women (adjusted odds ratio, 0.32; \( P=0.04 \)). No adverse effects of hyperimmune globulin were noted in either group receiving immunotherapy.

These results are impressive, and there are reasons to believe that they are biologically plausible. For example, hyperimmune globulin has proved effective in preventing horizontal and vertical transmission of hepatitis B and in preventing or ameliorating neonatal varicella infection.\(^6\) A previous case report by Nigro et al.\(^7\) described successful antenatal treatment of congenital CMV infection in a twin fetus. Snydman and coworkers\(^8\) reported that treatment with hyperimmune globulin reduced the rate of CMV infection among preterm infants who received multiple blood transfusions.

However, before we fully embrace the present observations, several caveats should be considered. First, the design of this study was not optimal. Although prospective, the study was not randomized and controlled. The ethics committees did not approve a randomized, prospective, blinded trial because of the “likely safety of hyperimmune globulin, the efficacy of immune globulin in animal models, and the off-protocol availability of hyperimmune globulin.” In my opinion, the very safety of hyperimmune globulin, combined with the lack of prior substantive evidence of its effectiveness for the prevention or treatment of congenital CMV infection, is a compelling argument in favor of conducting a randomized, prospective, placebo-controlled trial. In such a study, all women with documented seroconversion should undergo amniocentesis to detect CMV by either culture or PCR. Those with positive tests then should be randomly assigned to receive hyperimmune globulin or placebo. Patients should be stratified according to the gestational age of the fetus at the time of treatment, the presence or absence of abnormal findings on fetal ultrasonography, and the severity of any such abnormalities.

The lack of a strict, prospective, randomized protocol resulted in a curious blend of two cohorts—a treatment group and a prevention group. The regimens of hyperimmune globulin were quite different in the two groups. Although most women in the treatment group received only one injection of hyperimmune globulin, some received additional injections directly into the amniotic cavity or fetal umbilical cord. Women in the prevention group received multiple injections of a different dose, and I question why more intensive therapy was necessary for prophylaxis than for the treatment of obviously affected fetuses. Moreover, the 40 percent rate of symptomatic infection at birth among the infants of the untreated women in the prevention group was unexpectedly high, as compared with rates of 10 to 20 percent in other reports.\(^1,9\)

The second caveat is that there are biologic reasons to question the remarkable success rates with hyperimmune globulin reported by Nigro et al. For example, women with antibodies against herpes simplex virus are not fully protected from recurrent symptomatic infection, particularly if they are immunosuppressed. Similarly, the presence of antibody against varicella–zoster virus does not fully protect a person from future outbreaks of herpes zoster infection, some of which can be quite severe. Administration of hyperimmune globulin against human immunodeficiency virus (HIV) has not protected neonates against perinatal transmission of HIV.\(^10\) Moreover, the presence of antibody against CMV does not fully protect a mother or her fetus against reactivation and subsequent perinatal transmission of CMV infection.\(^11,12\) This latter observation is of particular importance in assessing the authors’ observation that major abnormalities identified on ultrasonography, such as ascites, ventriculomegaly, intracerebral and intraabdominal echodensities, and intrauterine growth retardation, apparently resolved completely in 14 fetuses after maternal treatment with hyperimmune globulin.

Finally, the authors did not address the financial and logistic issues associated with screening large obstetrical populations for CMV infection, triaging patients with the inevitable false positive test results, offering amniocentesis and targeted ultrasonographic examination of the fetuses of women who seroconvert, and then treating at-risk women and fetuses with hyperimmune globulin. Each year in the United States alone, approximately 4 million women have ongoing pregnancies. Given a seroconversion rate of 1 percent, approximately 40,000 of these women would need intensive follow-up, which is quite a daunting task, in terms of both physical and financial resources.

Without question, the report by Nigro et al.\(^4\) is interesting and provocative. However, before the authors’ conclusions can be fully accepted, we should await the results of a better-designed clinical trial and the development of a practical, cost-effective algorithm for the identification and treatment of exposed and infected fetuses. In the interim, practitioners should focus on simple preventive measures, such as using CMV-negative blood products.
when transfusing pregnant women and encouraging pregnant women to use careful handwashing techniques after handling infants’ diapers and toys.

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