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EDITORIAL COMMENTARY

The Value of Hyperimmune Globulin in Pregnancies Complicated by Cytomegalovirus Infection: A Continuing Saga

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(See the Major Article by Nigro et al on pages 1491–8.)

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Human cytomegalovirus (HCMV) is the most common vertically transmitted infectious agent and occurs in the United States with an estimated prevalence of 0.65% [1]. The birth prevalence of congenital CMV (cCMV) is higher in developing countries [2] than in developed countries. Although most CMV-infected newborns are asymptomatic, cCMV can be a major cause of neurodevelopmental delay and infant brain damage and is the leading cause of nongenetic sensorineural hearing loss worldwide [3, 4]. The risk of transplacental transmission is highest (upwards of 40%) in the setting of a primary maternal infection during pregnancy, and the greatest risk of sequelae is associated with fetal infections that occur during the first trimester [5]. Although fetal infections occurring later in pregnancy are less likely to cause sequelae, some experts have recommended that all infants with cCMV should undergo routine audiologic and neurodevelopmental screening assessment [6].

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Most women have no symptoms associated with the acquisition of HCMV infection during pregnancy, and routine screening of women for HCMV antibodies is not typically performed by obstetricians. Thus, the precise timing of both maternal and fetal infection is very difficult to ascertain. There is interest in offering therapeutic interventions to women, particularly in the setting of documented first-trimester HCMV infections, toward the goal of minimizing the risk of adverse sequelae for the infected fetus. Because of the recognized importance of virus-neutralizing antibodies in convalescence and control of HCMV infection, and the beneficial effect of therapeutic HCMV hyperimmune globulin (HIG) in control of disease in immunosuppressed transplant patients [7], studies were commenced approximately 20 years ago to examine whether HIG could modify the risk of fetal infection and/or disease if administered to a pregnant woman with a primary HCMV infection. What has followed over the years is a saga of seemingly conflicting reports with very different conclusions.

In an early study conducted by Nigro and colleagues [8], women whose amniotic fluid contained either HCMV or HCMV DNA (indicating that fetal infection was already present) were offered intravenous HIG at a dose of 200 U per kilogram of maternal weight (treatment group). In parallel, a study was conducted in women with a recent primary infection before 21 weeks' gestation, at a monthly HIG dose of 100 U per kilogram intravenously every 4 weeks, toward the goal of preventing transplacental transmission (prevention group). The results were remarkable and encouraging. HIG therapy was associated with a significantly lower risk of congenital HCMV disease. Among 31 women receiving HIG in the therapy group (15 of whom were carrying a fetus with ultrasonographic evidence of HCMV infection), only 1 delivered an infant with HCMV disease, whereas 7 of 14 women who did not receive HIG had affected infants. HIG also appeared to be beneficial in the prevention group. Among 37 women who received HIG, 16% delivered infants with cCMV, as compared with 19 of 47 women (40%) who did not receive HIG. Additional studies suggested that HIG improved overall placental health and function [9] and was associated with regression of neurological injury [10].

Based in large part on these findings, HIG therapy was subsequently utilized by many obstetricians and infectious diseases physicians for over a decade, both for treatment of the HCMV-infected fetus and for prevention of HCMV transmission in the setting of a documented primary maternal HCMV infection. However, the uncontrolled nature

of the Nigro et al study [8] has been a source of ongoing controversy, since HIG therapy is expensive, typically requires at least a short-stay hospital admission for the patient, and carries some potential risks (including anaphylaxis). To help resolve these uncertainties, a placebo-controlled study of HIG for the prevention of congenital HCMV transmission, using the same dose as in the Nigro et al study (100 U/kg), was reported [11]. In this study (known as the Congenital HCMV Infection Prevention or "CHIP" study), 124 pregnant women with primary HCMV infection at 5 to 26 weeks of gestation were randomly assigned within 6 weeks after the infection onset to receive HIG or placebo every 4 weeks until 36 weeks of gestation or until detection of HCMV in amniotic fluid. The primary endpoint was congenital infection diagnosed at birth or by means of amniocentesis. This study—in contrast to the uncontrolled report from Nigro and colleagues [8] from 2005—failed to demonstrate any statistically significant benefit of HIG on cCMV transmission. The rate of congenital infection was 30% in the HIG group and 44% in the placebo group ($P = .13$). Moreover, although the clinical outcome of congenital infection at birth was similar in the 2 groups, more obstetrical adverse events were noted in the HIG group than in the placebo group (13% vs 2%). Surprisingly, this study furthermore demonstrated no effect of HIG on the activity of neutralizing antibodies in maternal plasma post-infusion. Hyperimmune globulin did not significantly modify the magnitude or duration of maternal DNAemia, nor did it significantly modify DNA levels in placentas. A subsequent study further demonstrated that HIG did not have any impact on placental histology [12].

Against the backdrop of these conflicting reports, what does the paper by Nigro and Adler [13] in the current issue of *Clinical Infectious Diseases* add to the story? This study analyzed a database of 304 Italian pregnant women with a primary HCMV infection who were identified between 2010 and 2017. The decision to be treated with HIG to prevent fetal HCMV infection or disease was determined by each woman and her physician; and multiple data points, including maternal DNAemia, timing and frequency of HIG infusions, and the infection status/clinical outcomes of infants, were collected. Primary maternal infection was defined as seroconversion, with or without symptomatic HCMV disease in the mother. Data on maternal HCMV immunoglobulin (Ig) G, IgM, avidity, and DNAemia were available; and for women with a primary infection in the first trimester, amniotic fluid was obtained for polymerase chain reaction at 19–21 weeks of gestation with follow-up fetal magnetic resonance imaging for all positive results. A dose of 200 IU of HIG monthly was typically used, based on the reasoning that, in many cases, it was difficult to rule out fetal infection if maternal infection was present, and hence the HIG regimen should be dosed at the higher dose, with the goal of potential in utero therapy of the infected fetus in mind. In the final logistic regression analysis, 4 factors stood out as key predictors of fetal infection: (1) the diagnosis of primary maternal infection via HCMV IgG seroconversion rather than by avidity index determination, (2) an abnormal prenatal ultrasound, (3) the presence of maternal DNAemia prior to HIG administration, and (4) the lack of HIG administration, which was associated with a 1.8-fold increase in infection ($P < .0001$). Thus, this current study—although not a double-blinded, prospective analysis—supports the use of HIG as an intervention to prevent cCMV transmission in the setting of maternal primary HCMV infection, particularly if such infections are documented by maternal seroversion and are associated with DNAemia.

Although the work from Adler and Nigro provides some encouraging and useful data, other recent (and conflicting) studies further add to the uncertainty about the value of HIG. On the positive side, a recently published study supporting the use of HIG performed in Tübingen, Germany [14], reported that biweekly HIG treatment until 20 weeks' gestation (at a dose of 200 IU/kg) reduced cCMV transmission in women with first-trimester infections when therapy was commenced prior to 14 weeks estimated gestational age. The authors argued that the frequency of dose administration (biweekly) is a critical component of effective therapy. Unfortunately, these results were compared with historical controls, not contemporaneous placebo controls. In contrast, negative data from another, as-yet unpublished study [15], a multicenter placebo-controlled trial of HIG, were recently presented. Conducted through the National Institute of Child Health and Human Development (https://clinicaltrials.gov/ct2/show/NCT01376778?term=anderson&cond=cytomegalovirus&rank=7), this study enrolled women with a primary HCMV infection (defined by the presence of either HCMV IgM and IgG with low avidity, or IgG seroconversion), who then received either monthly infusions of HIG (at a dose of 100 U/kg) or placebo until delivery. An interim analysis of outcome data for 394 participants revealed a 22.7% cCMV rate in the HIG group and a (perhaps unexpectedly low) 19.4% rate in placebo recipients ($P = .42$), and the trial was stopped at the recommendation of the study's Data and Safety Monitoring Committee, based on the conclusion that continuation of the study would not be likely to demonstrate a benefit of HIG in decreasing the risk of cCMV infection.

What, then, should obstetricians, perinatologists, and infectious diseases physicians recommend at this point, when studies seem to report conflicting information about the benefit of HIG in the context of primary maternal HCMV infection? Important observations from the current study in *Clinical Infectious Diseases* include the importance of monitoring for maternal DNAemia when primary infection is suspected, as well as the importance of documenting primary HCMV infection by demonstration of seroconversion. In particular,

the presence of sustained, high-grade DNAemia is a factor clinicians should take into consideration in counseling women about HIG prophylaxis, and diagnostic PCR testing should probably be included in the routine monitoring of women being evaluated for possible HCMV infections during pregnancy. It remains unresolved whether HIG is effective for prophylaxis against HCMV transplacental transmission: although evidence from controlled trials [11, 15] does not suggest efficacy for prophylaxis, differences in study design, enrollment criteria, gestational age at the time of HIG administration, and the dose interval of HIG infusions may be factors contributing to conflicting observations among the various studies performed to date. In contrast to prophylaxis, for in utero therapy for fetuses in the setting where HCMV transmission has been confirmed (based on fetal ultrasonographic abnormalities, or infection documented by amniocentesis) HIG should probably be offered, and third party payers should cover the cost of this therapy.

Thus, this saga continues, and more trials are needed to definitively resolve the question of the benefit of HIG in the setting of primary maternal HCMV infection. It is imperative that future trials be conducted with rigorous pharmacokinetic analyses and crucial that all trials be placebo controlled. Better biomarkers for diagnosis of primary maternal infection, particularly early in pregnancy, are needed. Since maternal reinfections can also lead to disabling cCMV transmission, future studies should consider strategies for therapeutic intervention in this setting as well, although currently such reinfections are not easily identifiable outside of the research laboratory setting. The role of nucleoside therapy also deserves more attention, given the observations that high-dose valacyclovir (8 g/day) has been suggested to be beneficial when administered during pregnancy in improving the outcome of moderately symptomatic infected fetuses [16]. Such oral antiviral studies could be extended to prophylaxis of primary infection [17], again with the caveat that placebo controls are necessary. Although not recommended by any official obstetrical organizations, it has been pointed out that HCMV serological screening during pregnancy has become a de facto practice in many European countries [18], and the question of intervention strategies for HCMV infections identified during pregnancy is only going to become more commonly posed to infectious diseases practitioners. It is premature to conclude that HIG has no role in managing pregnancies complicated by primary HCMV infection. Clinical trials of more potent monoclonal antibodies targeting key neutralization epitopes expressed on the viral envelope [19] are needed, and this strategy may represent a substantially more effective approach than currently available formulations of HIG for both prophylaxis and therapy in the setting of HCMV infections that occur during pregnancy.

Notes

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