Hyperimmunoglobulin for Prevention of Congenital Cytomegalovirus Disease

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Primary cytomegalovirus (CMV) infection during the first half of pregnancy is responsible for the majority of symptomatic congenital infections. Between one-third and one-half of fetuses become infected, and up to one-half of infected fetuses will have neurologic or sensorineural sequelae at birth or later in life. Following favorable results obtained in animal experiments, observational studies have shown beneficial effects after administration of high-titer CMV hyperimmunoglobulin to pregnant women with fetal infection or disease subsequent to primary CMV infection. The mechanisms of action of hyperimmunoglobulin are multiple and not yet fully understood. However, they could reside in 2 major properties: (1) antiviral activities due to high-avidity neutralizing antibodies and (2) immunomodulating activities mostly including downregulation of cytokine-mediated cellular immune responses. A decreased viral pathogenicity occurs as an immediate consequence, whereas reduced placental inflammation and restored function are the long-term effects.

Keywords. congenital cytomegalovirus disease; primary cytomegalovirus in pregnancy; hyperimmunoglobulin; immunoglobulin; ventriculomegaly; bowel hyperechogenicity; placentomegaly.

Fetal cytomegalovirus (CMV) infection following maternal primary infection may be extremely severe. Children with congenital CMV infection can develop a variety of immediate or long-term disabilities, such as spastic or convulsive syndromes, cerebral palsy, mental retardation, learning disabilities, epilepsy, deafness or hearing impairment, and visual deficit or blindness. Clinical manifestations can also occur in any other organ or system. Although diagnosis may be reliably obtained by viral DNA detection in the amniotic fluid, prenatal therapy is still far from becoming routine. Major obstacles include a lack of public awareness of CMV, universal serologic screening for CMV during pregnancy, and proven therapeutic options. However, a few therapeutic attempts of fetal CMV infection have been performed. In spite of possible teratogenic fetal effects, 2 antiviral drugs have been used. Valacyclovir appeared to not be clinically efficient, and ganciclovir efficacy was related to only anecdotal case reports. Hyperimmunoglobulin (HIG) appeared to be the only potentially efficient therapeutic approach to fetal CMV infection or disease [1].

RATIONALE FOR HIG THERAPY

In fetal infections, maternal immunity and placenta are the key points to inhibit or decrease CMV pathogenicity. After a primary maternal infection, the severity of fetal infection decreases with gestational age despite the increasing rate of CMV transmission from 33% to 75% [2]. This correlates with the increasing protection given by maternal immunoglobulin G (IgG) antibodies because IgG transport increases with advancing gestation from 6 weeks’ gestation [3]. In fact, the occurrence of symptomatic congenital infections following recurrent maternal CMV infections is >2%, apart from higher rates reported in at-risk women [4]. Preexisting humoral immunity protects seropositive women against reinfection at a rate of 66%–93% [1]. CMV-specific neutralizing
titers and IgG avidity are both inversely associated with fetal transmission, whereas cellular immunity modulates viral transmission and pathogenicity in pregnancy [5]. Women with impaired cellular immune responses to CMV are more likely to transmit CMV to the fetus and deliver symptomatic infants [1].

Primary maternal CMV infection during pregnancy leads to placental enlargement due to viral placentitis and neovascularization, and subsequent impaired support of oxygen and nutrients to the developing fetus [6]. Although not completely elucidated, placental tissue damage is due to direct tissue injury by persistent CMV replication, ischemic tissue damage subsequent to CMV endothelitis, and tissue damage by immune complex deposition. In fact, CMV damages the fetus not only directly but also by modifying maternal immunity through an inflammatory process leading to abortion or immune-mediated disease, most commonly in the brain resulting from neurotoxicity of overexpressed cytokines [7]. Therefore, HIG appears to be the preferable therapeutic approach to fetal CMV infection, since it has both antiviral and immunomodulatory activities that are essential to regulation of the innate and adaptive immune responses in the interplay between infection control and immunopathological processes. Antiviral neutralizing properties mostly include blocking of CMV glycoproteins, elevated anti-CMV IgG titers, and high IgG avidity, which were predominantly identified in the antibodies directed against the gH/gL/UL128/UL130/UL131 complex [8]. Prominent immunomodulatory properties of HIG include downregulation of interleukin synthesis, blockade of Fc receptors, and specific antibodies to T-cell receptors [1].

**CMV HIG in Animal Models**

The protective role of antibodies was shown by several randomized experiments in animals. The guinea pig CMV (GPCMV) was used frequently because GPCMV crosses the guinea pig placenta, causing infection in utero. Pregnant guinea pigs were challenged with GPCMV before or after passive administration of immune serum, resulting in markedly reduced amounts of virus and inflammatory lesions in the brain [11].

**CMV HIG for Treatment of Fetal Infection in Humans**

Besides several case reports and case series, there are 3 large studies on the possible efficacy of HIG in treating fetal infection or disease. The first was a multicentre prospective cohort study of 157 pregnant women with confirmed primary CMV infection, including 45 women who had CMV DNA or virus in the amniotic fluid [12]. Only 1 of 31 women who received HIG delivered a diseased infant, contrary to 7 of 14 nontreated women, who had fetal or neonatal abnormalities (P < .001). Immunological investigations, including antibody titers and avidity, T-cell subpopulations, and NK cytotoxic activity, supported HIG efficacy. HIG was also associated with a reduction or disappearance of placental enlargement, ventriculomegaly, and hyperechogenic bowel associated with fetal CMV infection [13–15]. Immunohistochemical investigations showed that antibody treatment promotes compensation in placentas with CMV-induced damages, including improvement of placental blood flow and decreased hypoxia and syncytiotrophoblastic nodules [6]. The favorable results of HIG treatment were supported by a case-control study with 64 congenitally infected children [16]. Cases were 32 children with either hearing deficit and/or psychomotor retardation and whose mothers had a confirmed or probable primary CMV infection at <20 weeks’ gestation. Controls were 32 congenitally infected children who were normal but whose mothers had a confirmed primary infection at <20 weeks’ gestation. Of the 32 cases, only 4 mothers received CMV immunoglobulin compared to 27 of the 32 mothers of control infants. The only risk factor for an affected child was the mother not receiving immunoglobulin (P = .001). Furthermore, the longer the interval between maternal infection and the receipt of immunoglobulin, the poorer the outcome. The third study included 92 fetal infections following maternal primary infection before 17 weeks’gestation [17]. Twenty-four women chose termination of pregnancy; of the remaining 68 women, 16 of 37 untreated mothers (43%) had children who developed disabilities by 1 year of age, contrary to 4 of 31 HIG-treated mothers (13%; P < .01). A meta-analysis using logistic regression that accounts for study assignment finds that the odds ratios (ORs) for the 3 treatment studies all favor treatment with ORs of 30 (95% confidence interval [CI], 3.1–285), 35 (95% CI, 9.9–124), and 5.1 (95% CI, 1.5–17.7), with a combined OR of 17.6 (95% CI, 7.9–43.3).

**Conclusions**

Randomized experimental and observational clinical studies showed a statistically significant efficacy of HIG therapy for decreasing both the rate and severity of the disabilities caused by CMV after a primary maternal infection in the first half of
pregnancy. Although HIG is expensive, the financial impact of severe disabilities caused by congenital CMV infection is far more costly. A cost-benefit analysis found that universal serologic screening at 20 weeks’ gestation, when compared to screening of only high-risk women or those with abnormal ultrasound findings, was the preferred and most cost-effective approach when used with 1 HIG infusion to mothers with fetal CMV infection confirmed by amniocentesis [18]. This approach, which could miss primary infections in the early gestational months, would be cost effective if HIG was at least 47% protective against severe disabilities.

Off-label use of HIG during pregnancy should be considered as a possible alternative to pregnancy termination, particularly if there are fetal abnormalities diagnosed via ultrasound. The rationale for this is the availability of HIG, its lack of known toxicity, and its modest cost when compared to the cost of caring for a mentally disabled or deaf child, particularly in the United States because of insurance reimbursement in nearly all cases. A limitation of the published studies 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 cost-benefit analyses. However, although the use of HIG for CMV-infected fetuses would be strongly supported by the results of a randomized prospective study, this will probably be never available [1]. Barriers to such a study include nonacceptance of placebo when the study drug appears to be well tolerated and readily available off label, the need of testing approximately 100 000 pregnant women to identify a hundred fetal infections, the extremely high cost for a large multicenter trial, and the lack of enthusiasm for funding such a study both by industry and government.

In conclusion, there are 4 main reasons to consider passive immunization for treating or preventing fetal CMV infection: (1) HIG has been shown to be efficacious in animal models; (2) HIG is the most purified blood derivative and can be pasteurized, and is thereby deemed safe in terms of its capacity to transmit blood-derived pathogens; (3) HIG displays immunomodulatory effects that amplify the capacity of viral antigen binding; (4) HIG commercial preparations are widely available.

Notes

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