

# The Role of the Placenta in the Pathogenesis of Congenital Cytomegalovirus Infection: Is the Benefit of Cytomegalovirus Immune Globulin for the Newborn Mediated through Improved Placental Health and Function?

**Mark R. Schleiss**

Center for Infectious Diseases and Microbiology Translational Research, Department of Pediatrics, University of Minnesota Medical School, Minneapolis

(See the article by La Torre et al. on pages 994–1000)

Congenital infection with human cytomegalovirus (CMV) is common and underrecognized. In the United States and Europe, estimates regarding the frequency of congenital CMV infection range from 0.5% to 1% of all newborns [1]. Although the majority of infants with congenital CMV infection appear healthy at birth, many go on to experience serious neurodevelopmental sequelae. These sequelae include cerebral palsy, seizures, microcephaly, mental retardation, developmental delay, and sensorineural hearing loss, which may occur, to varying degree, in up to 15% of all infected infants [2–6]. The magnitude of the disability caused by congenital CMV infection is immense, and the attendant financial costs are high. It is estimated that ~40,000 infants per year have congenital CMV infection in the United States and that 8000 of these infants will require complex medical and surgical care as a result of the consequences of this infection. In the 1990s, the

estimated costs associated with congenital CMV infection were estimated to be ~\$1.9 billion annually [7]. Children with congenital CMV-induced sequelae have a wide range of special needs, and they often require extensive interventions from health care providers, such as cochlear implantation, speech therapy, neurodevelopmental assessments, and, in severe cases, lifelong custodial care. Thus, the benefit of any successful intervention that could target prevention of in utero transmission of CMV would be substantial.

The optimal strategy for prevention of congenital CMV infection has not yet been defined. Much attention has been focused on the potential for CMV vaccines to prevent transmission of CMV to the fetus. The potential utility of this strategy is supported by epidemiological observations indicating that preconceptual immunity to CMV provides protection against both infection and disease in the newborn [8]. Further evidence of the protective effect of preconceptual CMV immunity was noted in a study that demonstrated that prior immunity protected young women of childbearing age against reinfection following intense exposure to the virus in the secretions of young children attending group day care [9]. In another study, preconceptual immunity was estimated to

have an efficacy of ~70% in preventing congenital CMV infection in subsequent pregnancies [10]. The Institute of Medicine, in its 1999 assessment of the cost-effectiveness of potential new vaccine priorities for the new millennium, identified a hypothetical CMV vaccine (modeled on the assumption that it would be given to adolescents) as the highest-level priority for any new vaccine for the 21st century [11]. A report from the National Vaccine Advisory Committee reinforced the Institute of Medicine recommendations, further emphasizing the significant toll that CMV infections exert on newborns [7]. In spite of the theoretical value of a CMV vaccine, there are no vaccines currently licensed for clinical use [12]. The barriers to implementation of vaccination against CMV include uncertainty regarding the optimal vaccine strategy (should it be a live-attenuated vaccine or a protein subunit vaccine? If a subunit vaccine, which viral proteins should be employed? What is the optimal expression strategy?), uncertainty about the optimal population to be vaccinated (should the target population be young women of childbearing age or adolescents? Should universal vaccination of infants be considered?), and unanswered regulatory questions (what are the barriers to moving vaccine candidates

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Reprints or correspondence: Dr. Mark R. Schleiss, University of Minnesota Medical School, Center for Infectious Diseases and Microbiology Translational Research, 2001 6th Ave. SE, Minneapolis, Minnesota, 55455 (schleiss@umn.edu).

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forward in clinical trials? What would be required of a clinical trial to achieve licensure of a CMV vaccine?). Among the candidate CMV vaccines, a subunit vaccine based on the immunodominant envelope glycoprotein B is currently being evaluated in an efficacy study involving young women [13], and studies from animal models suggest that the antibody response to this protein may be sufficient to protect against congenital CMV-associated infection and disease [14].

Until a CMV vaccine is available, other strategies need to be deployed to prevent the disabling effects of congenital infection. One global strategy that has merit is that of prenatal screening of women for CMV infection. Obstetrical monitoring could identify women with primary or active infection who are at risk for transmission, and identification of such "high-risk" pregnancies could allow development of interventional approaches designed to prevent transmission to the fetus or to treat the fetus in utero. In the article by La Torre et al. [15], published in the current issue of *Clinical Infectious Diseases*, this team of investigators describes the ultrasonographic findings present for a group of 92 pregnant women with primary CMV infection and compares these findings with those observed for 73 control patients with evidence of preconceptual immunity to CMV. In the women with evidence of primary infection, at each measurement between 16 and 36 weeks of gestation, CMV infection was associated with significant increases in placental thickness, compared with control subjects. Moreover, placental thickness was further increased in a subgroup of women in the primary infection group who eventually gave birth to an infant with CMV disease. The administration of CMV hyperimmunoglobulin (HIG) to women in the primary infection group was associated with significant reductions in placental thickness. These observations build on the results of an important interventional trial of HIG conducted by Nigro and col-

leagues at the Department of Gynecological Services at La Sapienza University in Rome, Italy [16]. In that study, pregnant women with primary CMV infection (whose amniotic fluid contained either CMV or CMV DNA) were offered HIG. In the therapy group, receipt of HIG was associated with a significantly lower risk of congenital CMV infection and disease [16]. Although this was not a controlled study, the data strongly suggest that HIG therapy should be offered to women with evidence of primary CMV infection during pregnancy and that more aggressive prenatal monitoring of women for CMV infection could lead to better pregnancy outcomes.

In the current study [15], the data presented by La Torre and colleagues suggest that a major target of primary CMV infection is the placenta and that the beneficial effect of HIG may be mediated through improved placental health. These observations underscore the importance of studies aimed at understanding the mechanisms of CMV transmission at the placental level. An elegant series of studies conducted by Lenore Pereira, in collaboration with Susan Fisher, at the University of California, San Francisco, have begun to elucidate, at the cellular level, the impact of CMV infection on the developing placental trophoblast [17, 18]. The impact of CMV on placental function and homeostasis may be to impair delivery of oxygen, substrate, and nutritional factors to the fetus. Moreover, the inflammatory milieu induced by CMV infection of the placenta could, via induction of proinflammatory cytokines and modulation of normal trophoblast gene expression, be a contributing factor in the pathogenesis of intrauterine growth retardation and fetal injury [19–21]. Indeed, much of the injury that CMV produces in the newborn may be caused by placental insufficiency and injury and not by viral infection of the fetus, per se. The findings of La Torre et al. [15], showing increased placental thickness in pregnant women with primary CMV infection, may represent edema and

inflammation induced by CMV. It remains to be determined what impact CMV infection has on solute, substrate, and oxygen transport to the fetus. Further study of events at the virus-placental interface should also help to clarify the role of immune globulin in preventing placental injury and subsequent fetal infection. Recent observations by Maidji et al. [22] suggest that the mechanism of transcytosis of CMV virions across the surface of the trophoblast to the fetus is via the neonatal Fc receptor. This observation highlights the potential importance of virus-neutralizing antibody in prevention of transmission to the fetus and provides a potential mechanism for the salutary effect of HIG.

What are the implications of these observations for clinicians who care for women of childbearing age? As La Torre et al. [15] point out, although screening for maternal CMV infection is (unfortunately) not standard practice in most countries, ultrasound evaluation is commonly used to monitor most pregnancies. The establishment of ultrasonographic parameters that suggest placental CMV infection should aid obstetricians and radiologists who routinely perform such examinations and underscore the importance of careful examination of not only the fetus but also the placenta during the course of such studies [23, 24]. It can be hoped that these studies suggesting the potential value of in utero immunotherapy will promote greater awareness of the importance of prenatal CMV screening. Only with increased awareness of the risks of this virus can clinicians begin to have an impact on the epidemic of disabling congenital CMV infection in the United States. Women of childbearing age should be encouraged to ascertain their CMV serostatus, and health care personnel who care for pregnant patients should screen more aggressively for CMV infection, using serological methods and, when warranted, amniocentesis [25]. Although antiviral interventions are by no means "standard of care" for women with evidence of primary CMV infection, immune

globulin can be offered to women with the highest-risk pregnancies, and women can be empowered by knowledge of their CMV status in making reproductive choices. More importantly, identification of CMV status provides a window of opportunity for clinicians to educate women about prevention measures, including behavioral modifications and the importance of careful hygienic practices, which, in turn, have been shown to decrease the risk of primary infection and subsequent fetal transmission [26, 27]. Finally, additional clinical research, preferably based on multicenter controlled studies, is greatly needed in this area. Although there is a suggestion of benefit provided by HIG in the studies done to date, these observations must be confirmed by blinded, controlled studies, and regulatory bodies need to enable the conduct of such trials. The key viral targets of the protective antibodies present in HIG should be identified, and this information should be used, in turn, to direct clinical trials of CMV subunit vaccines. In addition to future controlled trials of HIG, there is also a rationale for study of antiviral drugs targeting prevention of CMV transmission to the fetus [28], and clinical trials should examine the potential usefulness of these agents, either alone or in combination with immune globulin, for the protection of the fetus. Within ~10 years of the discovery of the etiologic agent of AIDS, it was demonstrated, via a randomized, double-blinded, placebo-controlled trial, that an antiviral intervention could prevent vertical transmission of HIV during pregnancy [29]. Prevention of vertical transmission of CMV should be assigned the same priority and should be studied using the same rigorous, well-controlled experimental approach. Increased public awareness of the magnitude of the problem of congenital CMV infection should help mold the social and political forces necessary to drive the study of innovative approaches to protect the newborn from this potentially devastating infection.

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