IUGR and Congenital Cytomegalovirus Infection

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Intrauterine growth restriction (IUGR), a condition in which the fetus is pathologically growth restricted in utero, remains a serious problem. Although the term is often used interchangeably with small for gestational age (SGA), it is important for studies to differentiate these conditions. The latter term refers to all infants in whom the birth weight is below the 10th percentile for the gestational age, which for a full-term infant corresponds to a weight <2500 g. Infants may be constitutionally SGA simply because of their heredity. Pathological IUGR also is not a single entity and has multiple causes, including poor maternal nutrition, chronic hypertension, diabetes, genetic abnormalities, smoking, substance abuse, preclampsia, and intrauterine infections such as cytomegalovirus, rubella, syphilis, or toxoplasmosis. The etiology of IUGR can be extrinsic to the fetus, as when uteroplacental insufficiency causes diminished transport of nutrients and oxygen, or intrinsic to the fetus, as when growth restriction results from chromosomal abnormalities or fetal infection. The origin of the IUGR can also be both intrinsic and extrinsic to the fetus, as when maternal infection results in both placental insufficiency and fetal infection. In approximately half of IUGR cases, however, there may be no identifiable cause, and such cases are classified as idiopathic.

It has been known for >50 years that intrauterine infection with human cytomegalovirus (CMV), a member of the herpesvirus group, could damage the central nervous system of the fetus [1, 2]. In fact, CMV is the major viral cause of birth defects. Between 0.5% and 2.5% of all newborns are infected with CMV, and of the 5%–10% who are symptomatic at birth, sequelae develop in most; these include microcephaly, sensorineural hearing loss, optic atrophy, and chorioretinitis, and motor disabilities. Even in the asymptomatic group, approximately 15% will later show progressive hearing loss, visual impairment, or cognitive disabilities. Infection of the fetus can occur in CMV-seronegative women because of primary infection, or in women with preexisting immunity because of reactivation of endogenous virus from a prior infection or reinfection with a new virus. However, the risk of transmission to the fetus is higher during primary infection (approximately 40%) than in CMV-seropositive women (1%). Although it was previously believed that only congenitally infected children born to women who had a primary infection had sequelae leading to permanent disability, it is now appreciated that hearing loss and other neurological disabilities occur in 10%–20% of congenitally infected children born to women with preexisting immunity [3–6]. In both situations, sensorineural hearing loss is the most common outcome.

In the past when more sensitive assays were not available, IUGR was one indicator of congenital CMV disease. Although it has been established that congenital CMV infection resulting from primary infection of the mother has severe outcomes, including placental damage and IUGR, it has been difficult to show a definitive association of IUGR with congenital CMV infection in infants who had no other clinical manifestations. One of the earliest studies suggesting a link was by Starr and Gold [7], who in 1969 reported that 93% of >1000 infants born at the Cleveland Metropolitan General Hospital were tested for CMV infection. This was before polymerase chain reaction and DNA-based diagnostic assays, and identification of congenital CMV infection required inoculation of urine samples from 1–2-day-old infants into tissue culture and observation for evidence of CMV cytopathic effect. CMV infection was confirmed in 1.5% of the infants, and none had clinical manifestations of cytomegalic inclusion disease. The only abnormal finding was that the birth weights of the infected infants were significantly lower than those of the uninfected infants, and this difference was not due to premature delivery.
Subsequent studies have confirmed these observations, but the differences are small, and the reciprocal finding has not been observed; that is, studies of SGA infants have shown that infection with CMV is infrequent (2%) and most CMV-infected infants are not SGA [8–10].

There is little information regarding the pathological mechanism of CMV infection of the placenta in seropositive women who have reactivated virus from prior infection and how this affects infection of the fetus and IUGR. The article by Pereira et al [11] in this issue looks at placental disease, anti-CMV antibodies, hypoxia-related factors, and CMV infection in cases of idiopathic IUGR. The sample was small and included placentas from 7 patients who delivered infants showing IUGR but no other clinical manifestations of congenital infection. Based on CMV serological testing, 1 woman was seronegative, 2 had primary infection that was not diagnosed during pregnancy, 3 had recurrent infection, and 1 had evidence of long-past infection (>6 months previously). For comparison, placentas from 9 normal deliveries were examined. In this group, there were 2 seronegative women, 5 women with recurrent infection, and 2 women with long-past infection. For comparison, 3 women with preeclampsia were included; 2 were seronegative, and 1 had long-past infection. Although the serological results for both maternal blood and cord blood are presented for all patients, the results of in-depth analysis of the placentas are only presented for 4 of the 9 control patients (1 seronegative and 3 with recurrent infection) and 5 of the 7 patients in the IUGR group (3 with recurrent infection and 2 with primary infection). However, for the 9 placentas analyzed, not only were the pathological findings described, but they were also quantified, providing a level of information that goes beyond most studies on placental pathology.

As expected, the placentas from the patients in the IUGR group who had a primary infection during pregnancy showed the most severe disease, with large fibrinoids, necrotic avascular villi, leukocyte infiltration at the basal plate, and dilated blood vessels. Two placentas from patients in the IUGR group with recurrent infection also had significant, albeit less severe, disease with fibrinoids, necrotic villi, and an enhanced number of edematous villi. Unexpectedly, the third placenta from the patient with recurrent infection in the IUGR group displayed no significant disease and was comparable to the placenta from the seronegative control patient. Also surprising was the detection of a low level of fibrinoids, necrotic avascular villi, and edematous villi in the 3 placentas from the patients in the asymptomatic control group with recurrent infection. Two of these control placentas also showed evidence of inflammation, as indicated by variable infiltration of leukocytes.

The placentas were also analyzed for evidence of CMV infection by polymerase chain reaction for viral DNA and immunohistochemistry for viral proteins. Viral DNA was detected in only 3 placentas in the IUGR group; 1 from a patient with primary infection and 2 from patients with recurrent infection and significant placental disease. Viral proteins, however, could be detected in all 5 placentas from the IUGR group. Most surprising, however, were the results of the immunohistochemical analysis of the amniotic membrane polarized epithelial cells facing the fetal compartment. As expected, viral proteins were detected in the samples from the patients with primary infection. However, they were also detected in the samples from the 3 asymptomatic control patients with recurrent infection, indicating fetal infection. In contrast, regardless of whether there was placental disease, viral proteins were not detected in the amniotic membrane epithelial cells of the IUGR group with recurrent infection. Unfortunately, it was not possible to test urine from the newborns for the presence of viral DNA, and thus we do not know whether these 3 normal-weight infants of the control patients were infected. If they were, this would represent an unusually high level of transmission (>40%) from CMV-seropositive women with asymptomatic infants.

During the last 15 years, Pereira and her colleagues have contributed significantly to our understanding of the molecular and cell biology of placental infection with CMV and the mechanistic basis of the pathogenesis through studies on the pattern on infection, the types of cells infected both in vivo and in vitro, and the effects of infection on cell maturation and function. One of the most surprising findings from her group was the high incidence of CMV DNA (63%) at the uterine-placental interface in first-trimester placentas, which increased to 74% in second-trimester placentas, and was 62% at term [12–14]. The placenta still presents a significant barrier to fetal infection, but transmission in women with primary infection is significantly higher than in women who have reactivated virus from prior infection. Work from the same laboratory showed that this was related in part to the avidity of the CMV-specific antibody [15]. After primary CMV infection, the immunoglobulin G (IgG) is of low avidity, and avidity increases as the immune response matures. The neonatal Fc receptors of the placental sycnyctiotrophoblasts are important for transcytosis of IgG from the maternal blood to the fetus, thereby protecting the fetus by passive immunization. This same process, however, could facilitate the transcytosis of CMV-specific IgG bound to CMV virions. Thus, in pregnant women with primary infection and low-avidity antibodies, virions attached to IgG could be transcytosed without neutralization, resulting in spread of infection to the fetal compartment. In contrast, virions bound to high-avidity IgG could still be transcytosed, but infection would not spread. These findings provided the rationale for treating pregnant women who have primary infection with CMV-specific hyperimmune globulin to
of maternal primary infection by routinely obtaining a baseline serum sample at the earliest prenatal visit and monitoring seronegative women throughout the pregnancy for CMV seroconversion.

Note

Potential Conflicts of interest. Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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