Cytomegalovirus and the National Health and Nutrition Examination Surveys

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(See the article by Bate et al, on pages 1439–1447.)

Bate et al [1] present stimulating work on the seroprevalence of cytomegalovirus (CMV) in the United States during 2 periods, 1988–1994 and 1999–2004, which showed that the prevalence of CMV infection remained stable between these 2 periods. Such studies are rare, and many countries clearly lack epidemiologic data. The past decade has seen numerous studies of the management and consequences of CMV infection during pregnancy, but most of these studies were heterogeneous and based on small numbers of patients. More recent studies have sought to evaluate prevention strategies [2, 3] and treatments [4, 5], whereas others have focused on vaccine development [6]. Both options are important and certainly not mutually exclusive.

Bate et al [1] remind us, “Compared with a maternal nonprimary infection (i.e., reinfection or reactivation), a maternal primary infection is more likely to transmit CMV from mother to fetus (1% vs. 32%)” (p. 1439). We must note, however, that 32% is a mother-to-fetus transmission rate, whereas 1% is an estimated incidence of the infected children born to mothers with preexisting immunity before pregnancy. These rates are therefore difficult to compare. Although a diagnosis of primary infection during pregnancy is reliable, the diagnosis of recurrent infection is much more questionable. Most studies base a diagnosis of recurrent infection on an increase of immunoglobulin (Ig) G (with high IgG avidity) or the presence of IgM antibodies or both. These findings can also be found in other clinical situations, such as nonspecific stimulation of the immune system, maternal autoimmune disorders, and other cross-reacting herpetic infections. In addition, in some studies, CMV detection in urine or cervical samples in women who were CMV seropositive before pregnancy is also defined as recurrent infection [7, 8].

Another unresolved question about recurrent infections is whether transplacental transmission of CMV in women with preexisting immunity is most often secondary to reactivation or to infection with a different CMV strain during pregnancy. Reactivation is the reappearance of the endogenous CMV strain acquired before pregnancy and would be mainly local: in the macrophages of the uterus [8], in the cervix, and in the kidneys, leading to maternal viruria. Such local reactivation is unlikely to be linked with maternal viremia. Unless reactivation occurs in the uterus, the risk of fetal infection appears highly improbable. Reinfection, on the other hand, is infection with a new viral strain. Reinfection is thought to lead to maternal viremia and eventually to fetal infection. In both cases (reactivation and reinfection), it is difficult to investigate the kinetics of humoral immune response.

Novak et al [9] developed a novel approach to diagnosis of reinfection based on the appearance of new antibody specificity against at least 1 of 4 polymorphic epitopes designed from 2 prototypic laboratory strains of CMV (AD169 and Towne). This procedure made it possible to show that reinfection with a different strain of CMV can lead to intrauterine transmission and symptomatic congenital infection [10]. Investigators estimate the annual incidence rate of reinfection at 10% in populations with a high CMV seroprevalence, which are thus at high risk of CMV infection during pregnancy [11, 12]. However, the recombinant antigens described herein failed to detect up to one-third of the CMV-seropositive individuals in their population, that is, up to one-third of CMV strains. Accordingly, they can give us only a general idea of the incidence of reinfections during pregnancy, but it is not...
known how many women will have a reactivation during pregnancy, how many will have infected infants, and what the consequences of this congenital infection will be. Before we can learn these things, the diagnosis of both reinfection and reactivation during pregnancy must be improved, along with our understanding of the mechanisms leading to intrauterine CMV transmission and congenital infection in infants born to women with pre-existing immunity.

Maternal antibodies to CMV before conception provide substantial protection to the fetus against congenital damage from maternal infection [13]: primary maternal infection during pregnancy is associated with more severe sequelae of congenital CMV infection, even though the frequency may not differ. A study of hearing loss, for example, found the prevalence in children born to mothers with non-primary infection (10%) was similar to that in those with primary infection (11%) but also that significantly more children in the primary infection group had progressive and severe or profound hearing loss compared with children in the non-primary group [14].

Child-to-mother CMV transmission in seronegative pregnant women with young children can probably be prevented by hygienic intervention [2, 3], and treatments are under evaluation for pregnant women who have acquired a primary CMV infection during pregnancy (CMV hyperimmune globulin, valacyclovir) [4, 5, 15]. What kind of prevention is possible for the population with a preconceptional CMV immunity? A vaccine is probably an effective solution. Again, Bate et al [1] have pertinent epidemiologic information. They describe the population at high risk of developing CMV infection during pregnancy, that is, nonwhite women with low socioeconomic statuses and low education levels. They report that nearly all non-Hispanic black women who are CMV seronegative during their teen years seroconvert by the time they are in their 30s—that is, still during the reproductive period. However, most congenital CMV infections in the United States result from recurrent infections among pregnant women. This proportion is likely to be even higher in countries with higher CMV seroprevalence. Therefore, all women would benefit from hygiene counseling throughout pregnancy.

Regardless of maternal immune status, CMV infection during pregnancy remains a global public health problem. All of the strategies discussed herein—hygiene counseling, new treatment, and vaccine development—must be developed in combination to decrease the burden of this infection.

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References