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(See the Brief Report Mussi-Pinhata et al, on pages 1200–4.)

The human cytomegalovirus (CMV) is the most prevalent worldwide cause of congenital abnormalities. Whereas, rubella once claimed that superlative, and Zika is more topical these days, CMV produces fetal infections year after year and all over the world. Although deafness is the most common sequel to congenitally acquired CMV, and it is the cause of approximately 25% of all congenital hearing loss, more serious defects include microcephaly, retinitis, and mental retardation [1, 2].

Not surprisingly, efforts to develop antiviral treatments and vaccine prevention of congenital CMV infection have been going on since the 1970s [3, 4]. The former have had good success in treating infections acquired during immunosuppression incident to transplantation, but they have limited success in treating congenital infection, whereas vaccine development has progressed slowly but with increasing evidence for efficacy. There are now at least 10 vaccines in development, including one now in Phase II trials. Accumulated data from vaccine studies thus far show low to moderate efficacy against acquisition of CMV by seronegative women [5, 6] and impressive efficacy in preventing disease in solid organ transplant recipients [4, 7]. The newer vaccines on trial aim for higher efficacy.

Cytomegalovirus is ubiquitous in all populations, but there is an important difference between its epidemiology in developed versus developing countries. In the former, approximately half of women of childbearing age are CMV-seronegative and therefore susceptible to primary infection, whereas in the latter, almost all women have been infected in childhood and are thus seropositive during pregnancies later in life [8]. The indication for a vaccine in seronegative women is clear, but the situation in seropositive women raises controversy, because evidence has accrued that seropositive women can be infected during pregnancy and pass the virus to their fetuses with resultant defects, indicating that natural immunity is not necessarily protective [9]. Therefore, the concern has been raised that if natural immunity is imperfect, how can a vaccine be expected to work? Moreover, modeling estimations suggest that from a worldwide viewpoint, the population of seropositive women who transmit CMV to their fetuses is much larger than that of seronegative women [10].

This controversy has been well described [11], and it acts as a disincentive to investment in a CMV vaccine by manufacturers, although it can be argued that a vaccine that is immunogenic in both seronegative and seropositive women of childbearing age would be indicated everywhere throughout the world.

However, to justify the feasibility of a CMV vaccine, the potency of natural immunity with regard to prevention of acquisition and transmission to the fetus is a key issue. With regard to CMV acquisition by pregnant women, the issues of frequency of exposure and challenge dose loom large. Epidemiologic studies suggest that children, particularly toddlers, are often excreting high levels of CMV and are probably the main sources of infection for mothers [12]. Moreover, in countries with high seroprevalence, the frequency of exposure of pregnant women to others carrying CMV is likely high, resulting in many challenges to immunity. That being the case, the important question is how often is maternal immunity to CMV imperfect, or to put it another way, how often are fetuses of CMV seropositive women congenitally infected?

With regard to CMV infection in those women, Brazilian studies led by Dr. Maria Mussi-Pinhata have been paramount. In those studies, 35% of women excreted CMV during pregnancy, as the result of reinfection or reactivation [13]. However, the more important questions have been (1) what proportion of those women transmitted CMV to the fetus, and (2) how does that compare to infections in seronegative women? The study by Mussi-Pinhata et al [14] in this issue of the Journal of Infectious Diseases gives some of the first answers to these questions. In this Brazilian population, few women were seronegative when tested...
early in pregnancy, but 14% of those seronegative women were infected, suggesting a high risk of exposure, in line with previous studies. Of 36 seronegative women, 5 were infected during pregnancy, and 1 of those 5 transmitted CMV to her infant. These small numbers do not permit much interpretation, but it is of interest that in studies in populations with higher levels of seronegativity, approximately 30% to 40% of maternal infections are transmitted to the fetuses.

If we extrapolate from the 14% of seronegative women who were infected during pregnancy, it would suggest that 259 of the seropositive women were also exposed to CMV, 8 of whom, or 3%, were shown to transmit the virus to their fetuses. If these numbers are correct, the conclusion must be drawn that maternal immunity is largely protective against CMV fetal transmission. Of course, this conclusion can be correctly criticized as premature and based on presumptions, but it is striking that 2 other studies of CMV infections in pregnant women, one conducted in France and the other in Italy, also drew the conclusion that maternal-fetal transmission in seropositive women occurs at a rate that is between 0.2% and 3% [15, 16]. In the French study, fetal transmission from infected seropositive women occurred at one quarter of the rate seen in seronegative women. The implication is that if maternal immunity after natural infection can be duplicated by vaccination, a high degree of protection against transmission to the fetus will result. Although serious abnormalities have been reported from transplacental CMV infection in seropositive women, more data are needed to know whether primary and nonprimary infections of mothers lead to similar consequences.

CONCLUSIONS

The study by Mussi-Pinhata et al [14] provides us with important data on a congenital infection that is ubiquitous. The next crucial step is to compare humoral and cellular immunity in seropositive women who do or do not transmit CMV to their infants. Is transmission simply a chance phenomenon or one related to the size of the challenge dose, or is transmission the result of a low magnitude of specific immune functions? Data from vaccine studies in solid organ transplant patients show the importance of antibody to the glycoprotein B surface glycoprotein in protection against CMV [17], whereas studies of infected seronegative women stress the importance of neutralizing antibodies to a complex pentamer protein also on the viral surface [18]. In addition, data in a rhesus monkey model of CMV indicate the need for CD4+ T-cell functions in protection [7]. The Institute of Medicine (now the National Academy of Medicine) put CMV vaccine in its highest priority for vaccine development [19]. Mussi-Pinhata et al [14] are well poised to compare immune functions in seropositive women who do or do not transmit CMV to their newborn infants. In view of the worldwide incidence of intrauterine CMV infection, and the size of the current efforts to develop a vaccine against CMV that will replicate or surpass natural immunity, the public health implications of such studies are great.

Notes

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References


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