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## Congenital Cytomegalovirus Infection: Review of the Epidemiology and Outcome

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**Cytomegalovirus (CMV) is one of the most common viral causes of congenital infection. A future decision to lower its incidence by vaccination will depend on epidemiological conditions within a country and on the safety of the vaccine to be used, because a live vaccine may cause latency and subsequent reactivation that still may harm the fetus. The aim was to review the epidemiological studies published so far, with respect to factors that affect the incidence of congenital CMV infection, and factors that may influence its outcome, such as preexisting maternal immunity. The study included the data of 19 studies that were retrieved from a MEDLINE search during the period 1977 to 1997. The incidence of congenital CMV infection varied between 0.15% and 2.0% and seemed to correlate with the level of preexisting immunity in the population. Although preexisting maternal immunity was reported to strongly reduce transmission, the severity of congenital CMV infection (symptoms at birth and or sequelae later in life) was not significantly greater after virus transmission due to a primary infection of the mother as compared with recurrence or reinfection. The data indicate that preexisting immunity of the mother does not significantly mitigate the outcome of congenital infection. Moreover, live vaccines may bear a serious risk when transmissible to the fetus.**

**Target Audience:** Obstetricians and Gynecologists, Family Physicians

**Learning Objectives:** After completion of this article, the reader will be able to describe the natural course of a CMV infection, to list the potential sequelae of a congenital CMV infection, to outline potential strategies to prevent transmission of CMV, and to summarize the diagnostic work up of a patient with a potential CMV infection.

### INTRODUCTION

Cytomegalovirus (CMV) infects people of all ages, races, and socioeconomic classes, throughout both

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the modernized and developing parts of the world (1). Infection is mainly asymptomatic in healthy individuals, but immunosuppressed individuals and fetuses may suffer from serious infection (2). CMV is the most common virus known to be transmitted *in utero*. The only option to lower its incidence is prevention, either by vaccination or by hygienic measures. An effective and safe vaccine is not yet avail-

able, but when it is, a decision has to be made whether an expensive screening and vaccination program should be implemented. Such a decision will depend on epidemiological conditions that appear to vary from country to country and for different classes of the population within a country. Such a decision will also depend on the safety of a vaccine since a live attenuated vaccine may cause latency and subsequent reactivation that may harm the fetus (3, 4).

The aim of this article is to review the worldwide epidemiological studies published so far, with respect to the incidences of congenital CMV infection that have been reported worldwide. Special emphasis was on the differences in the reported incidences, and the outcome of congenital infection with regard to the type of maternal infection, being primary or recurrent.

### CYTOMEGALOVIRUS

Cytomegalovirus (CMV) is the largest known member of the human herpes virus family, which further includes the herpes simplex viruses types 1 and 2, varicella zoster virus, Epstein-Barr virus, and the more recently discovered human herpes viruses types 6, 7, and 8 (3, 5). Herpes viruses are large enveloped DNA viruses, sharing the biologic properties of latency and reactivation. Herpes viruses have close structural similarity, some of them sharing also DNA homology and antigenic cross-reactivity (5).

Several different types of CMV exist which are host-specific. Humans and higher primates are the only known reservoir for the human subtype of CMV, designated here as CMV (6–8). The genome of human CMV is made up of a single large molecule of double-stranded DNA of 200 kilobase pairs and codes for more than 200 open reading frames (ORFs). Although CMV consists of a single genotype, individual isolates are characterized by subtle genomic heterogeneity. The genomic heterogeneity can be used to characterize individual strains based on restriction fragment length polymorphism (RFLP) (9–14). Individuals may be infected with more than one strain (4, 6).

Recently it has been stated that CMV can be subdivided into four subtypes based on variation in glycoprotein B (gB). The subdivision seemed to correlate with viral tropism *in vivo*, and some evidence exists that the variation in gB may influence the virulence of CMV (15). The virus can be cultured *in vitro* in human fibroblasts. In contrast, *in vivo* CMV primarily infects mononuclear cells of the hemato-

poietic system, endothelial and epithelial cells but not fibroblasts.

### NATURAL COURSE OF CMV INFECTION

#### CMV in Healthy People

As immunity develops after initial (primary) infection the virus turns into a latent state, from which it can be reactivated. This is designated as recurrent infection (i.e., in the presence of immunity). In healthy individuals, a primary CMV infection usually is clinically inapparent. About 10% of primary infections result in a mononucleosis similar to that caused by Epstein-Barr virus, with symptoms like malaise, persistent fever, myalgia and cervical lymphadenopathy and less common pneumonia and hepatitis (3). Laboratory findings include atypical lymphocytes, mild thrombocytopenia and elevated liver enzymes (16–22). CMV infection is self-limited but viral excretion can continue for extended periods of time and the virus persists throughout life. Because mononucleosis syndromes caused by Epstein-Barr virus and CMV cannot accurately be differentiated on clinical grounds, the diagnosis needs to be confirmed by appropriate laboratory testing (3).

Recurrent infection, which is defined as intermittent excretion of virus from single or multiple sites in the presence of host immunity, may either be due to reactivation of an endogenous virus or exposure to a new virus strain from an exogenous source. Distinction between these two kinds of recurrent infection can only be made by molecular analysis of virus isolates (3, 23). Several mechanisms may explain recurrence. After a primary infection, a low-grade chronic infection may be established with virus excretion that only periodically reaches detectable levels. Alternatively, CMV may become latent and be repeatedly reactivated during later life in response to different stimuli such as pregnancy (24). Molecular studies have shown that reactivation of a persisting virus is more common than reinfection with a new strain (25). However, in sexually active populations coinfection with multiple strains of CMV has been detected (26, 27).

#### CMV in the Fetus

Congenital infections are the result of transplacental transmission of CMV. Transmission may occur as a consequence of both primary and recurrent infection. Various ways of transmitting the virus from mother to fetus exist, e.g., hematogenous spread of

infected leukocytes across the placenta and infection of placental tissue and amniotic cells, which are subsequently swallowed by the fetus. The virus replicates in the oropharynx and is subsequently carried through the fetal circulation (4).

Earlier publications showed that 30% to 40% of primary infections during pregnancy result in a congenital infection (4). Most of the congenitally infected infants (85%–90%) have no signs or symptoms at birth, but 5% to 15% will develop sequelae, such as sensorineural hearing loss, delay of psychomotor development, and optic atrophy. Of the 10% to 15% with symptoms at birth, 20% to 30% will die, mostly of disseminated intravascular coagulation, hepatic dysfunction or bacterial superinfection. According to earlier publications, less than 1% of recurrent infections occurring during pregnancy result in a congenital infection, 99% of which will be asymptomatic at birth. Five percent to 10% of these asymptomatic children develop sequelae later in life (4). However, a more recent study indicates that the severity of congenital infection following recurrent maternal infection is rather underestimated. The clinical and laboratory findings in 106 infants with congenital CMV infection who were symptomatic at birth have been reviewed by Boppana et al. (28). Microcephaly was the most prominent finding. Other frequent clinical findings were petechiae, small for gestational age, and hepatosplenomegaly. Frequent laboratory findings were elevated alanine aminotransferase, elevated serum bilirubin, and thrombocytopenia.

Infants with asymptomatic congenital CMV infection have a better prognosis than those who are symptomatic at birth. Only 5% to 15% of the asymptomatic infants have an abnormal development, which usually becomes manifest within the first 2 years of life. Nevertheless, they are at risk for an abnormal development, mostly uni- or bilateral sensorineural hearing loss (4, 29, 30). In approximately 40%, the bilateral hearing impairment is so severe (50–100 dB) that communication and learning are disturbed. In most of these cases (80%), hearing impairment becomes manifest after the first year of life. Depending on the incidence, an active screening program should be considered, to prevent the consequences of hearing impairment.

## DIAGNOSIS OF CONGENITAL CMV INFECTION

### Virus Detection

Virus isolation must be attempted in the first 2 to 3 weeks of life because viral excretion after that time

may be due to an infection acquired either at birth from exposure to an infected birth canal or postnatally through breast-feeding or, less frequently blood transfusion (6). The most specific and sensitive test is virus isolation from urine or saliva (31). For rapid viral diagnosis, a combination is used of tissue culture and detection of CMV early antigens by means of immunofluorescence with monoclonal antibodies (Detection of Early Antigen Fluorescent Foci, DEAFF) (32–37). Also, polymerase chain reaction (PCR) has been applied successfully to detect the DNA of CMV in urine or saliva of newborn infants (38, 39). The sensitivity and specificity of PCR were found to be 89.2% and 95.8%, respectively, compared with classical tissue culture (39).

Congenital CMV infection can be diagnosed prenatally by investigation of amniotic fluid using PCR. Revello et al. (40) reported a sensitivity of 77% for a nested PCR (nPCR) and 69% for virus isolation. Even with a sensitive nPCR protocol not all cases of congenital infection could be diagnosed (41). Lazzarotto et al. (42) have also compared PCR and virus isolation from amniotic fluid of pregnant women at risk of transmitting CMV. PCR gave a sensitivity and specificity of 100% and 83%, respectively, and positive and negative predictive values of 40% and 100%, respectively. Virus isolation gave a sensitivity and specificity of 50% and 100%, respectively, and positive and negative predictive values of 100% and 95%, respectively. From this study it can be derived that PCR alone cannot be used for prenatal diagnosis but should be complemented with virus isolation. However, Liesnard et al. (43) reported in a prospective study of 237 pregnancies with suspected or confirmed primary CMV infection, using PCR and culture of amniotic fluid, a sensitivity and specificity of 84% and 100%, respectively. PCR on amniotic fluid was reliable for prenatal diagnosis of congenital CMV infection, but only after 21 weeks of pregnancy.

### Serology

The production of antibodies starts *in utero* and is continued throughout life (6). Serological tests measuring IgG antibodies are hampered, however, by the presence of maternal IgG antibodies (39). In theory, detection of specific IgM antibodies in the fetus or newborn is the most practical way to diagnose a congenital infection. Because IgM antibodies do not pass the placenta, their presence indicates fetal infection. Infected fetuses produce their own specific IgM antibody, although not always, which hampers diagnostic sensitivity of IgM serology (33, 44, 45). False-negative results may also derive from competition

between high levels of maternal IgG and relatively low levels of fetal IgM antibodies. Conversely, false-positive results derive at least in part from the occurrence of rheumatoid factors that are commonly produced during infection (45). Earlier studies from our laboratory have shown a limited sensitivity of IgM antibody testing but a much better performance of CMV-specific IgE responses (46). However, IgE testing has not become a diagnostic routine, thus far. In conclusion, serologic testing alone is not reliable enough to diagnose or to exclude the diagnosis of CMV infection in the fetus, the newborn, and in the pregnant mother.

## EPIDEMIOLOGY

### Postnatal Infection

Cytomegalovirus infection is endemic and the prevalence of antibody to CMV increases with age (6–8, 47). In general, the prevalence of CMV is lowest in developed countries and in high socioeconomic classes and high in poor countries and people with a low socioeconomic status (SES). The spread of infection requires intimate contact with infected excretions such as saliva, urine, cervical and vaginal excretions, semen, breast milk, and blood (3, 49–51). Factors, presumably accounting for increased expo-

TABLE 1 Reported seroprevalences of CMV antibodies and incidences of congenital CMV infection between 1977–1997

| Geography and Date of Publication | Ref. No. | Numbers Included in Study | Socio-economic Status | CMV Sero-prevalence (%) | Congenital CMV Infection (%) | Method for Diagnosis  |
|-----------------------------------|----------|---------------------------|-----------------------|-------------------------|------------------------------|---|
| <b>Europe</b>                     |          |                           |                       |                         |                              |   |
| 1. Helsinki, Finland, 1977        | 73       | 148                       | NA                    | 84                      | 2.0                          | Positive urine culture  |
| 2. Manchester, England, 1978      | 74       | 6,051                     | NA                    | NA                      | 0.4                          | Positive urine or saliva culture                              |
| 3. Aarhus-Viborg, Denmark, 1979   | 75       | 3,060                     | NA                    | 52                      | 0.4                          | Positive urine culture  |
| 4. London, England, 1984          | 54       | 10,847                    | NA                    | 58                      | 0.15                         | Positive urine culture  |
| 5. Malmö, Sweden, 1984            | 76       | 10,328                    | Middle                | 72                      | 0.5                          | Positive urine culture  |
| 6. London, England, 1991          | 77       | 2,737                     | Low, middle and high  | 60                      | 0.3                          | Positive urine culture  |
| 7. Louvain, Belgium, 1992         | 78       | 1,771                     | NA                    | 51                      | 0.54                         | Antenatal screening of saliva, urine, and cervical secretions |
| 8. Parma, Italy, 1997             | 79       | 1,045                     | NA                    | 70                      | 0.57                         | Specific anti-CMV antibodies and virus detection              |
| <b>United States and Canada</b>   |          |                           |                       |                         |                              |   |
| 9. Houston, Texas, 1980           | 80       | 461                       | Upper                 | 50                      | 0.6                          | Positive urine culture  |
|                                   |          | 493                       | Low                   | 83                      | 1.2                          |   |
| 10. Hamilton, Canada, 1980        | 81       | 15,212                    | NA                    | 44                      | 0.42                         | Positive urine culture  |
| 11. Birmingham, Alabama, 1986     | 65       | 2,579                     | Low                   | 77                      | 1.4                          | Positive urine culture  |
|                                   |          | 8,545                     | Middle/high           | 54                      | 0.54                         | Positive urine culture  |
| 12. Iowa City, Iowa, 1997         | 82       | 7,229                     | Middle                | 40                      | 0.48                         | Positive urine culture  |
| <b>Southern America</b>           |          |                           |                       |                         |                              |   |
| 13. Santiago, Chile, 1982         | 83       | 118                       | Low                   | 98                      | 1.7                          | Positive urine culture  |
| 14. Santiago, Chile, 1996         | 84       | 218                       | Middle/high           | NA                      | 1.8                          | Positive urine or saliva culture                              |
|                                   |          | 471                       | Low                   | NA                      | 1.7                          |   |
| <b>Africa</b>                     |          |                           |                       |                         |                              |   |
| 15. Abidjan, Ivory Coast, 1978    | 85       | 2,032                     | NA                    | 100                     | 1.38                         | Positive urine culture  |
| <b>Asia</b>                       |          |                           |                       |                         |                              |   |
| 16. Sapporo, Japan, 1983          | 86       | 2,070                     | NA                    | 94                      | 0.5                          | Positive urine culture  |
| 17. Seoul, Korea, 1992            | 87       | 514                       | NA                    | 96                      | 1.2                          | Positive urine culture  |
| 18. Taichung, Taiwan, 1996        | 88       | 1,000                     | NA                    | 90                      | 1.8                          | Positive urine culture  |
| <b>Australia</b>                  |          |                           |                       |                         |                              |   |
| 19. Melbourne, 1985               | 89       | 47,320                    | NA*                   | 58–71†                  | 0.03                         | Positive urine or saliva culture                              |

\* Different study design, see text.

† 58% among private pregnant women, and 71% among nonprivate pregnant women.

NA, information not available.

sure to CMV, are breast-feeding, crowding, increased contact with infants and toddlers, poor hygiene, and promiscuity (6, 48). High rates of seroprevalence have been observed among people with multiple sex partners and a history of sexually transmitted diseases. In the United States and Western Europe, seroprevalence rates in young women of childbearing age range from 40% for women of middle- to upper SES to 83% for women of lower SES (52–58). The seroprevalence rate among pregnant women in The Netherlands totals 40% in a semirural environment, but 70% in the cities of Amsterdam and Rotterdam. In these cities almost half of the pregnant population consists of women of foreign origin (e.g., Mediterranean, Caribbean, Middle East), with a seroprevalence rate of 90% (58). In several areas of Africa, Southern America and Asia infection rates of 90% to 100% have been recorded (59–61). In the United States, black, and native Americans appear to acquire CMV infection earlier in life than do white middle-income people (62).

#### *Acquisition of CMV During Pregnancy*

Because primary infection during pregnancy is supposed to be the major risk factor for congenital infection, many studies have focused on its incidence. The reported incidence during pregnancy varies from 0.75% to 4% and is higher in people with a low SES as compared with people with middle- or high SES (54, 56, 63–66). In developed countries, infants and young children with subclinical infection represent an important source of primary CMV infection in pregnant women (66–68). Particularly day-care centers where women are in frequent contact with young children facilitate the acquisition of primary infection (69–72).

#### *Incidence of Congenital CMV Infection*

Several prospective studies on the incidence of congenital CMV infection have been carried out. These studies vary widely in their study design, composition of the population that was investigated, number of pregnant women included, as well as their SES. There are also wide variations in the way the outcome has been assessed concerning the clinical condition of the congenitally infected infants at birth and during follow-up, as well as with regard to the type of maternal infection, which may affect disease severity in the child. Table 1 summarizes the data of 19 studies that were retrieved from a search in MEDLINE (1977–1997). In Europe, the reported inci-

dence of congenital CMV varied from 0.15% to 2.0% (54, 73–79). However, several of the European studies have limited value because of either a small number of pregnant women included (73), by having excluded women with preexisting immunity to CMV (54, 78), or by assessing only children that were symptomatic at birth (Italy, 1997). In studies reported from North America, the incidence varied from 0.42 to 1.4% and the incidence in South America was around 1.8% (65, 80–84). These figures are significantly higher than those in Europe. All of the American studies provided information on SES and its relationship to maternal seroprevalence and incidence of congenital infection. A low SES corresponded with a high maternal seroprevalence as well as with a high incidence of congenital infection.

Studies from Africa and Asia reported a very high maternal seroprevalence from 90% to 100% with incidences of congenital CMV varying from 0.5% to 1.8% (85–88). From a single but very large study among 47,320 pregnant women in Australia, an incidence of congenital CMV has been reported of only 0.03% (12 of 47,320) (89). This study, however, included only children who were symptomatic at birth. The children who were asymptomatic at birth were missed. Because 80% to 90% of infected children are asymptomatic at birth, extrapolation of the reported incidence of 0.03% provides an estimated total incidence of 0.2% to 0.3%, which is rather similar to that found in Europe. Primary infection in pregnancy is supposed to be the main risk factor for congenital infection.

However, from the literature it seemed that a high seroprevalence is associated with a high incidence of congenital infection. This is illustrated in Figure 1, which shows the correlation between the seroprevalence of CMV antibodies and the corresponding in-

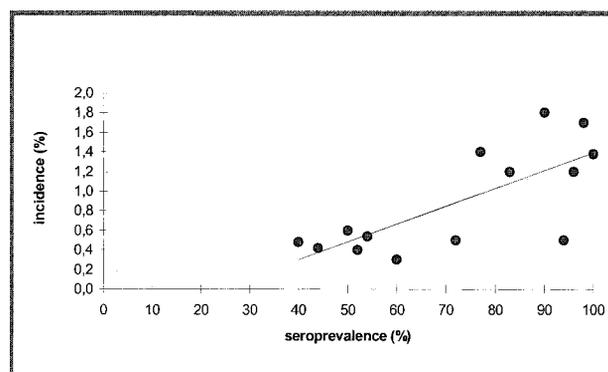


Fig. 1. Correlation between seroprevalence of CMV antibodies and incidence of congenital CMV infections.

idence of congenital CMV. Data were used from only 14 of the 19 studies, which presented adequate data for the analysis. The data from these 14 studies, plotted in Figure 1, shows a linear regression ( $R^2 = 0.55$ ,  $P = .0022$ ; SAS Institute Inc., 1996, Cary, NC). This means that there is a distinct relationship between the seroprevalence of CMV antibodies and the incidence of congenital CMV infections. A possible nonlinear regression was also investigated, but not found to be significant. To what extent reactivation or reinfection is responsible for congenital infection in the offspring of seropositive women is not known. The factors responsible for intrauterine transmission of CMV are not well understood as is the protective role of preexisting immunity. Knowledge of such factors is also crucial for an understanding of immunity to be acquired by vaccination. In a recent study, Boppana et al. (90) have determined whether acquisition of one strain of CMV in women with preexisting immunity against another strain results in intrauterine transmission of CMV. They found that 62% of the mothers of infants with congenital CMV infection had acquired antibodies with new specificities, as compared with 13% of the mothers whose infants were not infected. This finding suggests that acquisition of a new strain of CMV is responsible for the intrauterine transmission but the investigators did not exclude alternative explanations, such as boosting of the immune system by the endogenous CMV strain. It is not known whether more different strains circulate in populations with a high seroprevalence of CMV antibodies than among those with low seroprevalences, but the results as shown in Figure 1 suggest that this might indeed be the case.

#### SYMPTOMS AT BIRTH AND AT FOLLOW-UP

Aspects, as the type of maternal infection and the symptoms at birth, are indicative for the prognosis of the congenital infection. These aspects have been systematically analyzed in the 19 studies. However, not all studies gave sufficient information. Eighteen of the 19 studies presented information on symptoms present at birth (a total of 420 children). Of these 420 children, 326 (78%) were asymptomatic and 94 (22%) symptomatic at birth. The children with symptoms presented with a spectrum of symptoms that varied both in severity and outcome in relation to the type of maternal infection (Table 2). The most frequently reported symptoms at birth were jaundice, hepatomegaly, splenomegaly, and thrombocytopenia, i.e., a congenital syndrome. Also frequently

mentioned were symptoms of the central nervous system such as microcephaly, intracerebral calcifications, and chorioretinitis.

Symptoms in later life are divided into minor and major symptoms or handicaps. Minor symptoms are, for example, moderate psychomotor retardation, behavioral problems, and clumsiness, whereas severe mental retardation and hearing loss are designated as major symptoms.

Only six studies presented information on the type of maternal infection in relation to the outcome of congenital infection (Table 2, studies no 4, 5, 6, 8, 11, and 16). These studies reported a total of 164 infants, of which 144 (88%) were asymptomatic and 20 (12%) symptomatic at birth. For 136 of these 164 infants, information was available on the type of maternal infection. Eighty-six were infected because of a primary maternal infection and 50 because of a recurrent one. As shown in Table 3, 71 of 86 (83%) infants born to mothers with a primary infection were asymptomatic at birth. Three of these 71 asymptomatic infants (4%) developed minor symptoms, and 5 (7%) developed major symptoms. In contrast, 4 of 15 (27%) infants who were symptomatic at birth developed major symptoms.

After recurrent infection, 45 of 50 infected infants (90%) were asymptomatic at birth. One (2%) developed minor symptoms, and 4 (9%) developed major symptoms. Of the five infants who were symptomatic at birth, two (40%) developed major symptoms. These figures show both the incidence and the kind of symptoms to be quite similar in infants, infected after a primary or a recurrent maternal infection.

#### TREATMENT

No standard treatment of children with symptomatic congenital CMV infection is available as yet. Ganciclovir is used incidentally but has limited efficacy and may cause bone marrow suppression and gonadal toxicity (91). In infants with symptomatic congenital CMV infection, Nigro et al. (92) reported encouraging results of ganciclovir treatment, but the number of children included (12 infants), was too low to draw any conclusion about treatment efficacy. Whitley et al. (93) have studied 42 children with symptomatic congenital CMV infection during 6 weeks of treatment with ganciclovir. Excretion of CMV in the urine decreased, but returned to pretreatment levels after cessation of therapy. Improvement or stabilization of hearing impairment occurred in 16% after 6 months. Unfortunately, only infants with

TABLE 2 Survey of symptoms at birth and during follow-up (all figures are absolute numbers)

| Geography and Date of Publication              | Ref. No. | Infants With Congenital CMV | No Symptoms at Birth | Symptoms at Birth | Type of Maternal Infection               | Length of Follow-up (years) | Normal Development | Symptoms |       |
|--|----------|-----------------------------|----------------------|-------------------|--|-----------------------------|--------------------|----------|-------|
|  |          |                             |                      |                   |  |                             |                    | Minor    | Major |
| Europe   |          |                             |                      |                   |  |                             |                    |          |       |
| 1. Helsinki, Finland, 1977                     | 73       | 3                           | 3                    |                   | Unknown                                  | 1                           | 2                  |          |       |
| 2. Manchester, England, 1978                   | 74       | 84                          | 31                   | 53                | Unknown                                  | 1-5                         | 42                 | 14       | 20    |
| 3. Aarhus-Viborg, Denmark, 1979                | 75       | 11                          | 11                   |                   | Unknown                                  | 8 months                    | 9                  | 1        | 1     |
| 4. London, England, 1984                       | 54       | 9                           | 9                    |                   | 9 primary                                | 5                           | 7                  | 2        |       |
| 5. Malmö, Sweden, 1984                         | 76       | 47                          | 38                   | 9                 | 21 primary<br>15 recurrent<br>11 unknown | 4                           | 37                 | 1        | 5     |
| 6. London, England, 1991                       | 77       | 9                           | 7                    | 2                 | 4 primary<br>5 recurrent                 | 3                           | 5                  | 1        | 2     |
| 7. Louvain, Belgium, 1992                      | 78       | 7                           | 2                    | 5 (TOP*)          | 7 primary                                |                             |                    |          |       |
| 8. Parma, Italy, 1997                          | 79       | 6                           |                      | 6                 | 5 primary<br>1 recurrent                 | 1                           | 6                  |          |       |
| United States and Canada                       |          |                             |                      |                   |  |                             |                    |          |       |
| 9. Houston, Texas, 1980                        | 80       | 9                           | 9                    |                   | Unknown                                  | ?                           | 2                  | 3        | 6     |
| 10. Hamilton, Canada, 1980                     | 81       | 64                          | 60                   | 4                 | Unknown                                  |                             |                    |          |       |
| 11. Birmingham, Alabama, 1986                  | 65       | 82                          | 79                   | 3                 | 39 primary<br>26 recurrent<br>17 unknown | 8                           | 74                 |          | 8     |
| 12. Iowa City, Iowa, 1997                      | 82       | 35                          | ?                    | ?                 | Unknown                                  |                             |                    |          |       |
| South America                                  |          |                             |                      |                   |  |                             |                    |          |       |
| 13. Santiago, Chile, 1982                      | 83       | 2                           | 2                    |                   | 2 recurrent                              |                             |                    |          |       |
| 14. Santiago, Chile, 1996                      | 84       | 12                          | 11                   | 1                 | Unknown                                  |                             |                    |          |       |
| Africa   |          |                             |                      |                   |  |                             |                    |          |       |
| 15. Abidjan, Ivory Coast, 1978                 | 85       | 28                          | 28                   |                   | 28 recurrent                             |                             |                    |          |       |
| Asia   |          |                             |                      |                   |  |                             |                    |          |       |
| 16. Sapporo, Japan, 1983                       | 86       | 11                          | 11                   |                   | 3 primary<br>8 recurrent                 | 2                           | 10                 | 1        |       |
| 17. Seoul, Korea, 1992                         | 87       | 6                           | 6                    |                   | Unknown                                  | 1                           | 6                  |          |       |
| 18. Taichung, Taiwan, 1996                     | 88       | 18                          | 18                   |                   | Unknown                                  |                             |                    |          |       |
| Australia                                      |          |                             |                      |                   |  |                             |                    |          |       |
| 19. Melbourne, 1985                            | 89       | 12                          |                      | 12                | 2 primary<br>10 unknown                  |                             |                    |          |       |
| Total with follow-up (see table 3 for details) |          | 164                         | 144                  | 20                |  |                             |                    |          |       |
| Overall total (study 12 excluded)              |          | 420                         | 326                  | 94                |  |                             |                    |          |       |
|  |          |                             | (78%)                | (22%)             |  |                             |                    |          |       |

\* Termination of pregnancy.

clinical evidence of central nervous system (CNS) disease were enrolled, whereas symptomatic infants not having CNS involvement or treated with other antiviral drugs were excluded, causing unacceptable selection bias. Hence, it is still not known, whether treatment is beneficial in either infants that are symptomatic at birth or those asymptomatic at birth but acquiring symptoms later in life.

## PREVENTION

No CMV vaccine is currently available. Since the 1970s, two live attenuated vaccines have been developed which are still experimental (AD-169 and Towne 125) (94, 95). In preliminary testing, the Towne 125 vaccine has shown to be safe. It induces both, humoral and cellular immunity and provides

TABLE 3 Outcome of congenital infection in relation to the type of maternal infection, symptoms at birth and during follow-up (based on Ref. 54, 65, 76, 77, 79, and 86)

| Type of Maternal Infection          | Primary<br>(N = 86) | Recurrent<br>(N = 50) |
|-------------------------------------|---------------------|-----------------------|
| Symptomatic at birth (at follow-up) |                     |                       |
| Major                               | 15 (17%)            | 5 (10%)               |
| Minor                               | 4 (27%)             | 2 (40%)               |
| None*                               | 11 (73%)            | 3 (60%)               |
| No symptoms at birth (at follow-up) | 71 (83%)            | 45 (90%)              |
| Major                               | 5 (7%)              | 4 (9%)                |
| Minor                               | 3 (4%)              | 1 (2%)                |
| None*                               | †                   | †                     |

\* No follow-up of six infants.

† The type of maternal infection (primary or recurrent) was not indicated.

protection against CMV disease. It is not yet known, however, whether the vaccine will prevent infection by wild strains of CMV and whether vaccine-induced immunity will protect the fetus from intrauterine infection and disease. The attenuated vaccine strain might be reactivated in pregnancy with the risk of being transmitted to the infants (96).

Meanwhile, the development of CMV vaccines based on newer technology continues (97). The main candidate for a subunit vaccine is an envelope glycoprotein known as gB, which in purified form has been shown to induce neutralizing antibodies and lymphocyte sensitization in both animals and humans (98–100). Other possible approaches to CMV vaccines include synthesis of peptides that mimic key epitopes, production of anti-idiotypic antibodies, and genetic manipulation of the Towne live attenuated vaccine to augment its immunogenicity (97). Adler et al. (101) compared vaccination with the Towne 125 vaccine with wild-type infection among parents of children in day care. The authors showed that when vaccine-induced immune responses were equal to those induced by wild-type infection, healthy women were protected from acquiring CMV from their children. However, the magnitude of the vaccine-induced CMV-specific immune response was 10-fold lower than that afforded by the wild-type virus infection.

As long as reliable vaccines are not available, preventive measures should focus on educating pregnant women about how to avoid infection. Adler et al. (102) assessed a randomized, controlled trial to find out if seronegative mothers of seropositive children (younger than 36 months) could be counseled to avoid intimate contact with their children during pregnancy. Counseling concentrated on frequent hand washing, use of gloves, especially when han-

dling diapers or respiratory secretions, and avoiding mouth to mouth contact. Their results suggested that counseling and intervention could be effective in pregnant women because of their improved motivation to adhere to recommendations, as compared with nonpregnant women. However, it is doubtful whether parents will comply with these measures in nonstudy settings.

## DISCUSSION

Maternal seroprevalences of CMV antibodies in Europe and North America are quite similar, varying from 40% to 60% in populations with middle and high SES to 80% in those with low SES. In Europe, incidences of congenital CMV infection, derived from the most solid studies, varied from 0.15% to 0.5% (Table 1, no. 4, 5, and 6), whereas those in North America varied from 0.42% to 1.4%.

In Africa and Asia, the reported incidences vary from 0.5% in Japan, 1.38% in Ivory Coast, and 1.8% in Taiwan, in the presence of a very high rate of preexisting maternal immunity (90%–100%). The latter suggests that the majority of congenital CMV infections will be because of recurrent infections. Actually, all studies showed a distinct relationship between the incidence of congenital CMV infection and the rate of preexisting maternal immunity. Therefore, it seems probable that preexisting maternal immunity is unable to completely prevent transmission of the virus to the fetus, which explains why the incidence of congenital infections is higher in populations with a high percentage of carriers (24, 61, 91).

Eighty percent to 90% of the infants with congenital CMV infection are asymptomatic at birth. The chance of being symptomatic at birth was not greater when the congenital infection resulted from primary as compared with a recurrent infection of the mother. Neither were differences found for sequelae later in life. Regarding the infants who were asymptomatic at birth, low percentages of minor (2, respectively, 4%) and major symptoms (7, respectively, 9%) were seen. As for the infants who were symptomatic at birth, far more severe symptoms occurred during follow-up. This was observed for both groups, after primary and after recurrent infection (27% and 40%, respectively, Table 3). The higher frequency of severe symptoms in the group with recurrent infection is remarkable, as is the fact that even infants who were asymptomatic at birth developed major symptoms. It should be noted, however, that the number of infants in these groups was small.

Earlier studies have reported the type of maternal CMV infection to be a major determinant of outcome of congenital CMV infection (61, 65, 103). Preexisting maternal immunity should protect the fetus and newborn from serious damage. In contrast, the data from our review indicate that congenital CMV infection because of a recurrent infection bears similar consequences as that due to a primary infection during pregnancy. This conclusion was already drawn by Boppana et al. (104) for infants that were symptomatic at birth. In a retrospective comparison among infants with symptomatic congenital CMV infection as a result of primary versus recurrent maternal CMV infection, they observed that both the range of severity and the frequency of clinical and laboratory abnormalities of infants born to mothers with preexisting immunity were similar to those of infants born after a primary maternal infection. Furthermore, there were no significant differences in the number of children with one, two and three or more abnormalities in the two groups of children. Their follow-up data showed that the incidence of sequelae in children born to mothers with preexisting immunity was not different from that observed in children born after a primary maternal CMV infection. However, they did not investigate children that were asymptomatic at birth.

A number of case reports have been published describing newborns with symptomatic congenital CMV infection born to mothers with immunity to CMV (63, 65, 76, 79, 83, 84, 105, 106). The extent to which maternal immunity mitigates CMV-induced congenital damage is not known. However, the transmission rate of the virus from mother to fetus is reduced from 30% to 40% after primary, to less than 1% after recurrent infection (4). Fowler et al. (103) stated that determination of the effectiveness of maternal immunity in preventing the damaging consequences of congenital CMV infection is of major importance in assessing the potential benefit of a vaccine to prevent congenital infection. They reported that a vaccine that could be provided to all susceptible women of childbearing age could prevent congenital CMV infections. However, such a policy does not prevent congenital CMV infections after recurrent infection. Thus, the control of intrauterine CMV infection by using a live vaccine (such as in rubella-vaccination programs) is difficult (61).

Griffiths et al. (77) mentioned another problem concerning the groups that have to be immunized. They stated that women have to be immunized as infants to prevent them from acquiring infection in infancy or in childhood. Furthermore, they stated that

because of increasing opportunities for acquiring CMV infection during adolescence, immunization of male infants would be sensible, to prevent them from infecting adolescent girls later in life. Plotkin (107) argued that, in case of life-long lasting immunity after vaccination, a vaccine could be administered in the first year of life. If immunity is short-lived, however, vaccination before pregnancy or at the beginning of the childbearing years could be an option.

Griffiths et al. (77) proposed to prevent pediatric disease after intrauterine infection by identification at birth of the infants with the worst prognosis and to treat them with antiviral agents to suppress CMV replication. Unfortunately, such a treatment is not yet available. Moreover, infants who are asymptomatic at birth may still develop severe sequelae but would be missed in the policy suggested by Griffiths et al. (77).

Because there is no perspective on a quick development of a safe and effective vaccine, the only option that remains is only to educate women (irrespective of their CMV antibody status) to regard measures to prevent CMV acquisition. Pregnant and nonpregnant mothers of young children, health-care workers, day-care workers, and elementary-school teachers should, therefore, be advised to take care of simple infection control measures such as handwashing and proper cleansing of environmental surfaces (108). This should be effective and realistic (102). Furthermore, pregnant women should be aware that CMV infection can be sexually transmitted and that sexual promiscuity significantly increases the risk of acquiring the infection. These measures will stay the cornerstones of prevention as long as vaccines are not available.

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