Symptomatic Congenital Cytomegalovirus Infection in Infants Born to Mothers With Preexisting Immunity to Cytomegalovirus

Suresh B. Boppana, MD*; Karen B. Fowler, DrPH*‡; William J. Britt, MD*§; Sergio Stagno, MD*§; and Robert F. Pass, MD*§

ABSTRACT. *Objectives.* **To determine the frequency of symptomatic congenital cytomegalovirus (CMV) infection in the offspring of women with a recurrent maternal CMV infection and to characterize the demographic and newborn findings.**

Methods. **Study subjects consisted of infants with symptomatic congenital CMV infection identified by a newborn virologic screening program at the University of Alabama Hospital between 1991 and 1997 and were enrolled in a long-term follow-up study. Maternal infections were categorized by an analysis of archival serum specimens collected before pregnancy and at the time of delivery. Demographic data and clinical findings at birth were collected from maternal and newborn hospital records and from parents at the time of initial evaluation.**

Results. **Of the 47 infants with symptomatic congenital CMV infection identified during the study period, 8 were born to mothers with a confirmed nonprimary or recurrent CMV infection. The type of maternal infection could be ascertained in only ~43% (20/47) of the children with symptomatic congenital CMV infection born at the University of Alabama Hospital during the study period. There were no significant differences in demographic characteristics of the recurrent infection group and the infants who were born to mothers with either primary CMV infection during pregnancy or unclassified maternal infection. Similarly, the range of severity of clinical abnormalities during the newborn period did not differ in the two groups of children. Furthermore, there were no significant differences in the incidence of sequelae at long-term follow-up in the two groups of children.**

Conclusions. **Symptomatic congenital CMV infection can occur after a nonprimary or recurrent maternal infection. However, the exact incidence of symptomatic congenital CMV infection among children born to women with preexisting immunity remains to be defined.** ***Pediatrics* 1999;104:55–60; *cytomegalovirus, congenital infection, symptomatic, immunity, recurrent CMV infection.***

ABBREVIATIONS. CMV, cytomegalovirus; IgM, immunoglobulin M; IgG, immunoglobulin G.

From the Departments of *Pediatrics, ‡Epidemiology, and §Microbiology, University of Alabama at Birmingham, Birmingham, Alabama.
Received for publication Nov 25, 1998; accepted Feb 10, 1999.
Reprint requests to (S.B.B.) University of Alabama at Birmingham, 1600 7th Ave S, Suite 752, Birmingham, AL 35233. E-mail: sboppana@peds.uab.edu

Congenital cytomegalovirus (CMV) infection is the leading infectious cause of brain damage and hearing loss in children.[1–3] Only ~10% of the estimated 40 000 infants with congenital CMV infection born each year in the United States exhibit clinically apparent or symptomatic infection at birth, and the vast majority of infected newborns have no detectable clinical abnormalities (asymptomatic infection).[1–4] Most children with symptomatic congenital CMV infection develop one or more sequelae including sensorineural hearing loss, mental retardation, motor deficits, seizures, and chorioretinitis, whereas only ~10% to 15% of infants with asymptomatic congenital CMV infection develop sequelae.[1–3,5–7]

Preconceptional immunity to CMV provides substantial protection against intrauterine transmission and severe fetal infection.[1,5,8] However, this protection is incomplete, and congenital CMV infection has been shown to occur in infants of mothers who were seropositive before pregnancy.[5,8–10] Natural history studies of maternal and congenital CMV infection have demonstrated that symptomatic congenital CMV infection occurs almost exclusively after primary CMV infection during pregnancy.[5,8] Although the occurrence of symptomatic congenital CMV infection in children born to women who were seropositive before pregnancy has been described, most of the previous reports consisted of individual cases.[11–14] To determine the frequency of symptomatic congenital CMV infection in children born to women with preexisting immunity, we analyzed the data from screening of >20 000 infants born at the University of Alabama Hospital between 1991 and 1997 for congenital CMV infection.

METHODS

Study Population

Study subjects include 246 children with congenital CMV infection identified from newborn virologic screening at the University of Alabama Hospital between 1991 and 1997. Neonates born during the study period were screened for congenital CMV infection during the first 2 weeks of life by the detection of early antigen fluorescent foci in urine or saliva using a locally prepared monoclonal antibody to CMV immediate-early antigen as described previously.[15,16] Infants were classified as symptomatic if they shed CMV and exhibited any of the clinical findings suggestive of congenital infection in the newborn period including petechiae, jaundice with conjugated hyperbilirubinemia (direct bilirubin >2 mg/dL), hepatosplenomegaly, thrombocytopenia (<100 000/mm^3), microcephaly, seizures, and chorioretinitis.[4] Demographic data and clinical findings at birth were collected from maternal and newborn hospital records and from parents at the

time of initial evaluation of the patient. In addition, the presence of laboratory abnormalities in the neonatal period such as an elevated alanine aminotransferase (>80 IU/mL), and elevated cerebrospinal fluid protein (>120 mg/dL) was obtained from the newborn hospital records. The study subjects were monitored in an outpatient clinic as part of an ongoing long-term follow-up study; serial assessments of their neurologic, developmental, audiologic, and visual status were performed using standard methods that have been described previously.[5] The demographic data, newborn clinical findings, and outcome data were recorded on standardized case report forms and compiled into a SAS for Windows dataset (SAS Institute, Cary, NC). Informed consent was obtained from the parents or legal guardians of the study children.

Ascertainment of Maternal Immune Status

Maternal infections were categorized by analyzing the archival serum samples collected before pregnancy and before delivery.[5] In most cases, this categorization was accomplished by examining the serum specimens obtained during their previous pregnancy and those obtained at the time of delivery. Primary maternal infection was defined by evidence of de novo seroconversion or the presence of CMV-specific immunoglobulin M (IgM) antibodies during pregnancy. Women with detectable CMV-specific immunoglobulin G (IgG) antibodies before pregnancy were classified as having a confirmed recurrent maternal infection. When preconceptional serum samples were not available, maternal infection was presumed to be recurrent by the presence of CMV-specific IgG antibodies in the absence of CMV-IgM antibodies within the first 12 weeks of gestation. Serum IgG (IMx System; Abbott Laboratories, Abbott Park, IL) and IgM (CMV STAT M; BioWhittaker Inc, Walkersville, MD) antibody to CMV was detected using enzyme immunoassay. The IgM antibody assay was performed as recommended by the manufacturer except that an enzyme immunoassay value of 0.6 instead of 0.3 was used as the cut-off for the positive IgM result. Previous experience in our laboratory showed that this modification resulted in a reduced rate of false positive results with no significant change in sensitivity for the detection of primary infection.[17]

Statistical Analysis

Univariate analyses of the newborn findings and outcome data were performed to obtain frequencies, and the results were compared in the subgroups of infants born to women with confirmed recurrent infection and those who were born to mothers with primary CMV infection during pregnancy. In addition, the demographic characteristics were analyzed in children with congenital CMV infection who were born to mothers who were seropositive before pregnancy and compared with the groups of children with symptomatic and asymptomatic infection. Statistical significance was determined using χ^2, Fisher's exact test, and Wilcoxon's rank sum test as appropriate.

RESULTS

During the study period, we identified 246 children with congenital CMV infection from the screening of 20 885 infants born at the University of Alabama Hospital, a rate of 11.8/1000 live births. Of the 246 congenitally infected children, 47 infants had evidence of clinical abnormalities (symptomatic congenital CMV infection) and 8/47 (17%) of the symptomatic infants were born to mothers with a confirmed recurrent CMV infection. An additional 4 children with symptomatic congenital CMV infection were born to mothers who had CMV-IgG antibodies at the first prenatal visit without detectable CMV-IgM antibodies (presumed recurrent infection). Maternal infection was categorized as primary in 17% (8/47) of the mothers. However, classification of maternal infection was not possible in more than half of the children (27/47) with symptomatic congenital CMV infection because of the unavailability of preconceptional and prenatal serum specimens. We have also identified 28 children with asymptomatic congenital CMV infection during the study period who were born to mothers with preexisting immunity to CMV before pregnancy (confirmed recurrent infection).

The demographic characteristics of the groups of children with asymptomatic and symptomatic congenital CMV infection born to women with recurrent CMV infection were compared, and the results are shown in Table 1. All the symptomatic infants were black, compared with 93% (26/28) of the asymptomatic children. There were no significant differences between symptomatic and asymptomatic infants who were born to mothers with preexisting immunity to CMV with respect to maternal age, marital status, source of prenatal care, insurance status, and

TABLE 1. Demographic Characteristics of Children With Congenital CMV Infection Born to Mothers Who Were CMV-Seropositive Before Pregnancy

Finding	Asymptomatic Congenital CMV Infection (n = 28)	Symptomatic Congenital CMV Infection (n = 8)
	Positive/Total Examined (%)	
Sex		
Female	16 (57)	2 (25)
Male	12 (43)	6 (75)
Race		
Black	26 (93)	8 (100)
White	2 (7)	0
Single mothers	27 (96)	7 (88)
Maternal age ≤20 y	13 (46)	4/8 (50)
Source of prenatal care		
Private provider	0	0
Public health clinic	28 (100)	7 (88)
None	0	1 (12)
Insurance		
Private	0	0
Medicaid/no insurance	28 (100)	8 (100)
Previous pregnancies		
0	0	0
1	15 (54)	3 (38)
≤2	13 (46)	5 (62)

the number of previous pregnancies. Approximately half of the mothers in both groups were ≤20 years of age, and most were single, received prenatal care at public health clinics, and had at least one previous pregnancy.

Various newborn findings among children with symptomatic congenital CMV infection of the groups of children born to mothers with recurrent infection and children born to mothers with primary CMV infection during pregnancy were compared (Table 2). Approximately one third of infants in both groups were premature (<37 weeks' gestation) and small for gestational age. The frequency of various clinical findings at birth including jaundice, petechiae, hepatosplenomegaly, purpura, microcephaly, and seizures was similar in the two groups of children. Of the 2 infants in the recurrent infection group, 1 failed a newborn hearing screen compared with 1/4 in the primary infection group. Of the 11 children who had an ophthalmologic examination in the neonatal period (3 in the recurrent infection group and 8 in the primary infection group), 1 child in each group had an abnormal evaluation. In addition, the number of children with one clinical abnormality and those with two and three or more abnormalities was not different in the two groups of children. The presence of laboratory abnormalities in the neonatal period such as an elevated alanine aminotransferase, thrombocytopenia, conjugated hyperbilirubinemia, and elevated cerebrospinal fluid protein did not differ in the two groups of subjects (Table 3). Similar with the results of the clinical findings, we did not observe significant differences in the two groups with respect to the number of children with one, two, and three or more laboratory abnormalities (Table 3). When the 4 children who were born to mothers with presumed recurrent infection were included in the analysis, there were no significant differences in the two groups (data not shown). Similarly, the clinical and laboratory findings of the recurrent infection group and the group of 27 children in whom the type of maternal CMV infection could not be ascertained were not significantly different (data not shown).

The incidence of various sequelae in children with symptomatic congenital CMV infection at follow-up is shown in Table 4. The mean age at the time of their last clinic visit was 43.1 ± 19.5 months for the group of children born to mothers with recurrent CMV infection, compared with 38.5 ± 30.1 months for the primary infection group. As presented in Table 4, none of the 8 children in the recurrent infection group had sensorineural hearing loss, compared with 2/7 children who were born to mothers with primary CMV infection. Of the 7 children in the recurrent infection group who were tested, 4 had an IQ <70, whereas all 4 children in the primary infection group who were tested had IQ >70. These differences were not statistically significant. However, 3/8 children in the primary infection group were younger than 1 year of age at their last follow-up visit, and thus, the results of psychometric testing were not available in these children. There were no differences in the two groups in the incidence of sequelae such as motor abnormalities, seizures, and chorioretinitis. Although a majority of children in the recurrent infection group (6/8) had at least one sequelae compared with only approximately one third (3/8) of children who were born to women with a primary CMV infection, this difference is not statistically significant. There were no significant differences in the two groups even after the inclusion of 4 children who were born to mothers with presumed recurrent CMV infection in the analysis (data not shown). Similarly, the incidence of sequelae was not different in the recurrent infection group and the group of 27 children in whom the type of maternal infection could not be categorized (data not shown).

DISCUSSION

Several previous reports have documented the occurrence of symptomatic congenital CMV infection in children born to women with preexisting immunity, and most of these publications consisted of either reports of individual cases or infants born to immunocompromised mothers.[11–14,18–20] Ahlfors et al[13] published the results of a follow-up study of a large number of women who received obstetric care at a hospital in Malmö, Sweden, and screened their

TABLE 2. Clinical Abnormalities in Newborns With Symptomatic Congenital CMV Infection Born at the University of Alabama Hospital Between 1991 and 1997

Finding	Children Born to Women With Recurrent Infection (N = 12)	Children Born to Women With Either Primary or Unclassified Maternal Infection (N = 35)
	Positive/Total Examined (%)	
Prematurity (<37 wk GA)	2/8 (25)	3/8 (38)
Small GA	3/8 (37.5)	1/8 (13)
Jaundice	4/8 (50)	3/8 (38)
Petechiae	4/8 (50)	5/8 (63)
Hepatosplenomegaly	2/8 (25)	2/8 (25)
Purpura	0/8	0/8
Microcephaly	3/8 (37.5)	3/8 (38)
Seizures	0/8	0/8
Chorioretinitis	1/3 (33)	1/8 (17)
Abnormal hearing screen	1/2 (50)	1/4 (25)
One abnormality	3/8 (37.5)	4/8 (50)
Two abnormalities	3/8 (37.5)	2/8 (25)
Three or more abnormalities	2/8 (25)	2/8 (25)

TABLE 3. Laboratory and Imaging Abnormalities in 47 Children With Symptomatic Congenital CMV Infection Born at the University of Alabama Hospital Between 1991 and 1997

Finding	Children Born to Women With Recurrent Infection (N = 8)	Children Born to Women With Primary Maternal CMV Infection (N = 8)
	Positive/Total Examined (%)	
Elevated alanine aminotransferase (>80 IU/mL)	3/4 (75)	1/3 (33)
Thrombocytopenia (<100 000/mm^3)	3/3 (100)	0/1
Conjugated hyperbilirubinemia (>2 mg/dL)	3/4 (75)	0/2
Elevated CSF protein (>120 mg/dL)	1/4 (25)	1/2 (50)
Cranial CT scan abnormalities	2/3 (67)	1/3 (33)
One abnormality	0/4	1/3 (33)
Two abnormalities	3/4 (75)	2/3 (67)
Three or more abnormal findings	1/4 (25)	0/3

TABLE 4. Comparison of Sequelae in Children With Symptomatic Congenital CMV Infection Born to Women With Recurrent CMV Infection, Primary Infection and Those Born to Women With Unclassified Maternal Infection

Sequela	Recurrent Infection Group (N = 8)	Primary Infection Group	Unclassified Infection Group (N = 27)
	Positive/Total Examined (%)		
Sensorineural hearing loss	0/8	2/7 (29)	7/27 (26)
Progressive hearing loss	0	1/2	2/7
Delayed hearing loss	0	1/2	3/7
Mental retardation			
IQ <70	4/7 (57)	0/4	2/10 (20)
IQ <50	0/7	0/4	0/9
Motor abnormalities	1/8 (13)	1/8 (13)	4/26 (15)
Chorioretinitis	1/8 (13)	0/8	3/25 (12)
Seizures	0/8	0/8	2/25 (8)
At least one sequela	6/8 (75)	3/8 (38)	13/26 (50)

newborns for congenital CMV infection. They screened 10 328 neonates born at the study hospital for CMV viruria and identified 47 infants with congenital CMV infection. Among the 9 children with symptomatic congenital CMV infection, 2 infants were born to women with a nonprimary or recurrent CMV infection, and the type of maternal infection could be categorized as confirmed recurrent infection in 1 of the mothers.[13] In addition to this report, individual cases of symptomatic congenital CMV infection in children born to women with recurrent maternal infection have been reported, including infants born to mothers after transplantation and to 1 mother with HIV infection.[11,14,18–20]

A previous study from this laboratory has thoroughly investigated the association between maternal antibody status and outcome in 197 children with congenital CMV infection born between 1972 and 1990.[5] None of the 64 congenitally infected children who were born to women with recurrent CMV infection and were included in the study had clinical abnormalities at birth, and all 24 infants with symptomatic infection were born after a primary maternal infection. An earlier publication from this laboratory by Stagno et al[8] also reported that none of the congenitally infected children born to women with preexisting immunity had symptomatic infection. Based on these findings, it has been believed widely that symptomatic congenital CMV infection almost always occurs after a primary maternal infection. However, the results of the present study clearly document that symptomatic congenital CMV infection after a recurrent maternal infection occurs more frequently than has been thought previously. Although we do not have a clear explanation for the discrepancy between the results of the present study and those from our previous reports, several possibilities may account for this phenomenon. One obvious explanation is our improved ability to categorize maternal infections, especially in women receiving obstetric care at the study hospital with a newborn virologic screening program. We have focused our recent studies on infants with congenital CMV infection who were identified by newborn virologic screening at the University of Alabama Hospital. The presence of a well organized serum bank at this laboratory containing the cord and the maternal delivery serum samples from the University of Alabama Hospital has enabled us to analyze prepregnancy samples from a greater proportion of mothers, thus allowing identification of more cases of congenital CMV infection in offspring of women who were proven to be immune at the time of previous pregnancy. This is evidenced by the finding that categorization of maternal infection was possible in approximately half (20/47) of the women who delivered infants with symptomatic congenital CMV infection at the University of Alabama Hospital during the study period.

It is possible that women with primary CMV infection at, or shortly before, conception have been classified mistakenly to the group with recurrent infection, because CMV-specific IgM antibodies become undetectable in most cases within a few

months of primary CMV infection.[21] To avoid the possibility of misclassification of maternal infection, only those children of mothers with confirmed recurrent CMV infection were included and the 4 children who were born to women with presumed recurrent infection were not included in the data analysis. Because the occurrence of symptomatic congenital CMV infection in children of mothers with recurrent CMV infection has been observed only in our studies of children born after 1990, it is possible that a change in the characteristics of the virus accounts for this phenomenon. We believe that this is unlikely, because the rate of congenital CMV infection in infants born at the University of Alabama Hospital during the study period (11.8/1000) was similar to the rate for the period between 1980 and 1990, which was reported as 12.5/1000 live births.[22] We did observe an increase in the proportion of children with symptomatic congenital CMV infection (47/246, 19%) during the study period, compared with ~12% of children with congenital CMV infection who were born before 1991.[16] However, the criteria for classification of an infant with congenital CMV infection as symptomatic or asymptomatic have remained the same. Furthermore, there were no significant changes in the characteristics of our patient population during the study period, compared with the patient populations of our previous studies.[5,22]

Additional factors that may affect the transmission of CMV with subsequent disseminated fetal infection in women with preexisting immunity include viral strain variation and strain-dependent immune responses. Previous studies from this laboratory have demonstrated that maternal age <20 years, measures of sexual activity, and a history of sexually transmitted diseases were identified as significant risk factors for CMV infection in our study population.[22–24] Another recent study from this laboratory suggested that increased exposure to young children in our population of urban, low income, young women was associated with maternal CMV infection.[25] It is possible that an increase in exposure to CMV in our study population could potentially result in reinfection with a different strain of CMV with subsequent intrauterine transmission and severe fetal infection. The possibility of maternal HIV infection as a predisposing factor for disseminated fetal infection was excluded, because none of 12 women with recurrent CMV infection were infected with HIV-1.

To determine whether children with symptomatic congenital CMV infection born to immune mothers have a milder disease, we have examined the incidence of various clinical and laboratory abnormalities in infants with symptomatic congenital CMV infection. The results of this comparison showed that the range of severity of clinical and laboratory abnormalities of the group of infants born to mothers with recurrent CMV infection was similar with the group of infants born after a primary maternal infection (Table 2). In addition, there were no significant differences in the number of children with one, two, and three or more abnormalities in the two groups of children. Furthermore, the frequency of clinical and laboratory abnormalities of the recurrent infection group is similar with the group of children born to women with primary CMV infection (Tables 2 and 3). The follow-up data show that the incidence of sequelae in children born to mothers with preexisting immunity is not different from that observed in children born after a primary maternal CMV infection and from those children born to women with uncategorized maternal infection (Table 4). The finding that 4/7 children in the recurrent infection group have developed mentally retardation (IQ <70), compared with none of the 4 children in the primary infection group who were tested should be interpreted with caution because 3/8 children born to women with primary infection were too young to obain reliable results from psychometric testing. A comparison of the newborn findings and the incidence of sequelae in the recurrent and primary infection groups show that children with symptomatic congenital CMV infection who were born to immune mothers do not have milder disease in the newborn period and these children do not seem to have better long-term outcomes than those children who were born after primary maternal CMV infection.

The true impact of recurrent maternal infection on both the incidence of congenital CMV infection and the long-term neurologic deficits in children with this intrauterine infection is not known, and prospective population-based studies are needed to define this issue. A major limitation of the present study is our inability to categorize the type of maternal infection in more than half of the children with symptomatic congenital CMV infection born during the study period. It is possible, and perhaps likely, that the vast majority of symptomatic infections occur after a primary CMV infection during pregnancy. It is also possible that categorization of most maternal infections will lead to identification of an increased proportion of children who were born to mothers with preexisting immunity among infants with symptomatic congenital CMV infection. The definition of the importance of recurrent maternal infection in neonatal morbidity and long-term outcome is crucial because of the considerable interest in the development of a safe and effective vaccine for the prevention of sequelae associated with congenital CMV infection. Knowledge of the mechanisms of transplacental transmission of CMV in women with preexisting immunity could provide important information about the protective role of virus-specific immune responses. Furthermore, studies in this population could shed more light on the issue of reinfection and strain-specific immune responses against CMV.

ACKNOWLEDGMENTS

This work was supported in part by the National Institutes of Health, National Institute of Child Health and Human Development Grant P01 HD10699, National Institute of Deafness and Other Communication Disorders Grant K08 DC00079-05, and the General Clinical Research Center Grant RR-032.

REFERENCES

1. Stagno S. Cytomegalovirus. In: Remington JS, Klein JO, eds. *Infectious Diseases of the Fetus and Newborn Infant*. 4th ed. Philadelphia, PA: WB Saunders; 1995:312–353
2. Demmler GJ. Infectious Diseases Society of America and Centers for

Disease Control. Summary of a workshop on surveillance for congenital cytomegalovirus disease. *Rev Infect Dis*. 1991;13:315–329
3. Britt WJ, Alford CA. Cytomegalovirus. In: Fields BN, Knipe DM, Howley PM, eds. *Virology*. 3rd ed. New York, NY: Raven Press; 1996: 2493–2523
4. Boppana SB, Pass RF, Britt WJ, Stagno S, Alford CA. Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. *Pediatr Infect Dis J*. 1992;11:93–99
5. Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. *N Engl J Med*. 1992;326:663–667
6. Pass RF, Stagno S, Myers GJ, Alford CA. Outcome of symptomatic congenital CMV infection: results of long-term longitudinal follow-up. *Pediatrics*. 1980;66:758–762
7. Conboy TJ, Pass RF, Stagno S, et al. Intellectual development in school-aged children with asymptomatic congenital cytomegalovirus infection. *Pediatrics*. 1986;77:801–806
8. Stagno S, Pass RF, Dworsky ME, et al. Congenital cytomegalovirus infection: the relative importance of primary and recurrent maternal infection. *N Engl J Med*. 1982;306:945–949
9. Stagno S, Reynolds DW, Huang ES, Thames SD, Smith RJ, Alford CA. Congenital cytomegalovirus infection: occurrence in an immune population. *N Engl J Med*. 1977;296:1254–1258
10. Schopfer K, Lauber E, Krech U. Congenital cytomegalovirus infection in newborn infants of mothers infected before pregnancy. *Arch Dis Child*. 1978;53:536–539
11. Rutter D, Griffiths P, Trompeter RS. Cytomegalic inclusion disease after recurrent maternal infection. *Lancet*. 1985;2:1182
12. Ahlfors K, Harris S, Ivarsson S, Svanberg L. Secondary maternal cytomegalovirus infection causing symptomatic congenital infection. *N Engl J Med*. 1981;305:284
13. Ahlfors K, Ivarsson SA, Harris S, et al. Congenital cytomegalovirus infection and disease in Sweden and the relative importance of primary and secondary maternal infections. *Scand J Infect Dis*. 1984; 16:129–137
14. Morris DJ, Sims D, Chiswick M, Das VK, Newton VE. Symptomatic congenital cytomegalovirus infection after maternal recurrent infection. *Pediatr Infect Dis J*. 1994;13:61–64
15. Balcarek KB, Warren W, Smith RJ, Lyon MD, Pass RF. Neonatal screening for congenital cytomegalovirus infection by detection of virus in saliva. *J Infect Dis*. 1993;167:1433–1436
16. Boppana SB, Smith R, Stagno S, Britt WJ. Evaluation of a microtiter plate fluorescent antibody assay for rapid detection of human cytomegalovirus infections. *J Clin Microbiol*. 1992;30:721–723
17. Stagno S, Tinker MK, Elrod C, Fuccillo D, Cloud G, O'Beirne AJ. Immunoglobulin M antibodies detected by enzyme-linked immunosorbent assay and radioimmunoassay in the diagnosis of cytomegalovirus infections in pregnant women and newborn infants. *J Clin Microbiol*. 1985;21:930–935
18. Schwebke K, Henry K, Balfour HH, Olson D, Crane RT, Jordan MC. Congenital cytomegalovirus infection as a result of nonprimary cytomegalovirus disease in a mother with acquired immunodeficiency syndrome. *J Pediatr*. 1995;126:293–295
19. Laifer SA, Ehrlich GD, Huff DS, Balsan MJ, Scantlebury VP. Congenital cytomegalovirus infection in offspring of liver transplant recipients. *Clin Infect Dis*. 1995;20:52–55
20. Hayes K, Symington GRM. Maternal immunosuppression and cytomegalovirus infection of the fetus. *Aust N Z Med J*. 1979;9:430–433
21. Griffiths PD, Stagno S, Pass RF, Smith RJ, Alford CA. Infection with cytomegalovirus during pregnancy: specific IgM antibodies as a marker of recent primary infection. *J Infect Dis*. 1982;145:647–653
22. Fowler KB, Stagno S, Pass RF. Maternal age and congenital cytomegalovirus infection: screening of two diverse newborn populations, 1980–1990. *J Infect Dis*. 1993;168:552–556
23. Fowler KB, Pass RF. Sexually transmitted diseases in mothers of neonates with congenital cytomegalovirus infection. *J Infect Dis*. 1991;164: 259–264
24. Sohn YM, Oh MK, Balcarek KB, Cloud GA, Pass RF. Cytomegalovirus infection in sexually active adolescents. *J Infect Dis*. 1991;163:460–463
25. Fowler KB, Pass RF, Stagno S. Young children as a source of maternal cytomegalovirus infection in young nonwhite urban women. Presented at the Society for Pediatric Epidemiological Research 10th Annual Meeting; 1997; Edmonton, Alberta, Canada

RUNAWAY SUBSCRIPTION COSTS

Trying to keep up with the newest advances in microbiology? . . . A year's subscription to the academic journal *FEMS Microbiology Letters* now costs $5005.

Journal of Microbiology, a sister publication, goes for $4190.

These are the two most expensive journals cited in a report released last week by a Cornell University faculty committee that has been studying runaway subscription prices for biological or agricultural research journals. But they are a long way from being the most expensive journals on the market.

Comparative Biochemistry and Physiology, a journal not included in the study, carries an annual subscription price of $8835. . . . Journals published by corporations, as opposed to universities or nonprofit societies, are the most likely to have raised subscription prices substantially in recent years. In 1994, the report states, 26 of the 30 most highly priced biological journals and, 24 of the 25 most expensive agricultural journals, were published by commercial companies. . . .

http://adam.mannlib.cornell.edu/jps/jps.htm. *New York Times,* March 3, 1999

Symptomatic Congenital Cytomegalovirus Infection in Infants Born to Mothers With Preexisting Immunity to Cytomegalovirus

Suresh B. Boppana, Karen B. Fowler, William J. Britt, Sergio Stagno and Robert F. Pass

Pediatrics 1999;104;55
DOI: 10.1542/peds.104.1.55

Symptomatic Congenital Cytomegalovirus Infection in Infants Born to Mothers With Preexisting Immunity to Cytomegalovirus

Suresh B. Boppana, Karen B. Fowler, William J. Britt, Sergio Stagno and Robert F. Pass

Pediatrics 1999;104;55
DOI: 10.1542/peds.104.1.55