The consequences of primary cytomegalovirus infection in pregnancy

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SUMMARY Altogether 54 children exposed prenatally to maternal cytomegalovirus (CMV) infection were followed up in a prospective study. Nine had congenital infection with CMV and 37 escaped congenital infection; in 8 congenital CMV could not be confirmed. The birthweight of children with congenital CMV was significantly lower than that of both controls and those who escaped congenital infection. Intrauterine infection was not clinically suspected in any of the children with congenital CMV, although two had head circumferences less than the third centile. Subsequently one child with congenital CMV developed marked psychomotor retardation, and one, in whom congenital CMV was not confirmed, showed mild developmental delay. Speech and language ability was significantly impaired in children with congenital CMV compared with controls and those who escaped congenital infection, suggesting that subtle damage may have occurred.

The incidence of intrauterine transmission of CMV after exposure to infection in the first trimester was 20% and in the third trimester 40%, but no congenital infections resulted from exposure in the second trimester. The severity of congenital infection was not related to the time of exposure in utero. Our findings suggest that the risk to an individual fetus from maternal infection in early gestation is so low that termination of pregnancy cannot be recommended; screening of women for primary CMV infection in pregnancy seems therefore to have limited value.

Cytomegalovirus (CMV) is the most common viral infection known to be transmitted in utero.¹ Although most infants with congenital CMV infection are normal at birth, with fewer than 5% showing neurological signs in the neonatal period, a further 10-20% may develop neurological sequelae such as mental handicap or sensorineural deafness in the first years of life.²⁻⁵ Screening of mothers to identify primary CMV infection in pregnancy has been advocated to reduce the number of infants handicapped by CMV.⁶ There are, however, inadequate data as yet on which to recommend termination of pregnancy.

In this study we attempted to estimate the incidence of intrauterine transmission of CMV after primary maternal infection at different stages of pregnancy, and to determine whether the adverse sequelae of congenital CMV are related to the stage of pregnancy at which infection occurs. In addition to following up those children with congenital infection we also followed up those who escaped

congenital infection to determine whether adverse sequelae can result from maternal infection that is not transmitted in utero.

Patients and methods

Between 25 July 1975 and 31 July 1982, 10 847 women were screened at St Bartholomew's Hospital for primary CMV infection during pregnancy. Women who lacked CMV specific complement fixing antibodies at the time of their first antenatal visit had serial blood samples taken throughout pregnancy to determine whether seroconversion occurred.⁷ The initial blood samples of 2486 unselected women who already possessed complement fixing antibodies at their first visit were tested retrospectively for the presence of CMV specific IgM antibodies by solid phase radioimmunoassay as a marker of recent primary infection.⁸ In addition, we studied 10 women who had been seronegative in a previous pregnancy and who possessed CMV specific IgG and IgM antibodies when presenting for further

antenatal care. The stage of pregnancy at which maternal infection developed was calculated from the time of seroconversion and the persistence of IgM antibodies, because this class of antibodies has been shown to persist for up to 16 weeks after primary CMV infection in pregnancy.⁹

We defined three possible periods for maternal infection during pregnancy. Maternal infection during the 'first trimester' was defined as occurring when CMV specific IgM antibody was present within 14 weeks of the last menstrual period—that is, roughly 12 weeks after conception. 'Second trimester' infection was defined as seroconversion between 14 and 28 weeks of amenorrhoea or between 14 weeks and term but with no CMV specific IgM antibody detectable at the time of delivery. This group also included women in whom IgM antibody was present in the first antenatal blood specimen collected between 14 and 28 weeks. 'Third trimester' infection was defined as seroconversion after 28 weeks or seroconversion between 14 weeks and term with CMV specific IgM detectable at delivery.

Congenital infection was diagnosed either by isolating CMV from a urine sample collected from the infant within three weeks of birth⁷ or by showing CMV specific IgM antibodies in cord serum by radioimmunoassay.¹⁰ Each pregnant woman who had developed primary CMV infection was matched with a control. The controls were seronegative pregnant women attending the same hospital who were of similar age (± 2 years), social class, race, and marital status.

From July 1980 to 31 December 1982 the children of all mothers who had developed primary CMV infection during pregnancy, including those born before 1980, were contacted irrespective of whether intrauterine transmission of virus had taken place. Each child and his or her control was examined, where possible, at 9 months, 18 months, three years, and five years of age. At each visit a physical, developmental, and audiological examination was performed. The developmental examination was based on the Stycar sequences.¹¹ Audiological ability was assessed by distraction testing at 9 months, cooperative and Kendal toy tests at 18 months, and Kendal toy test together with pure tone audiometry at 3 and 5 years. At each visit an impedance test was performed to assess middle ear function. At 3 and 5 years speech and language development was assessed using the Reynell Developmental Language Scale.

Results

Primary CMV infection was identified in 58 pregnant

women. Infection was diagnosed by seroconversion in 32 and by the presence of CMV specific IgM in the first antenatal blood sample in 26. In the latter group two pregnancies aborted spontaneously and there were two stillbirths.⁸ The remaining 54 pregnancies resulted in the birth of live infants and are the subject of the present paper.

In 46 of the 54 cases of primary maternal infections appropriate specimens were collected from the neonates to diagnose or exclude congenital infection. Nine of the 46 (20%) were congenitally infected (Table 1). In a further 8 infants no cord blood or early urine samples were available so it was not possible to establish whether intrauterine transmission had occurred.

Table 2 relates transmission of virus in utero to the stage of pregnancy at which CMV infection developed. Two of 10 (20%) maternal infections in the first trimester resulted in congenital infection whereas none of 20 in the second trimester and 6 of 15 (40%) in the third trimester did. There was a significant increase ($P = 0.003$) in the rate of transmission between the second and third trimesters, but no significant difference between the first and second trimesters or the first and third. Intrauterine transmission of CMV was not related to maternal age, social class, or marital status.

Clinical findings in infants at birth

Birthweight

The mean birthweights and standard deviations of

Table 1 Incidence of intrauterine transmission of virus after primary maternal infection with cytomegalovirus

Specimens collected from each child	Congenital infections		
	Yes	No	Total
Urine and cord blood (n=18)	3	15	18
Urine only (n=9)	4	5	9
Cord blood only (n=19)	2	17	19
Total (n=46)	9	37	46

Table 2 Relation between intrauterine transmission of cytomegalovirus (CMV) and timing of maternal infection

Trimester	Total No of maternal infections	Intrauterine transmission of CMV		
		Yes	No	Transmission (%)
First	10	2	8	20
Second	20		20	0*
Third	15	6	9	40*
Not known	1	1		
Total	46	9	37	20

*Difference in transmission rate between second and third trimesters $P = 0.003$ by Fischer's exact test.

control children and those who escaped transmission of CMV in utero were 3350 g (SD 420) and 3360 g (550) respectively (Fig. 1). The mean birthweight of infants with congenital CMV was 3100 g (410), which is significantly lower than that of controls ($t = 1.69$, $P < 0.05$, one tailed).

Abnormalities noted at birth

None of the 9 congenitally infected infants was clinically suspected of having congenital CMV. Two children had microcephaly—namely, occipitofrontal circumference of less than the third centile. One of these was also small for gestational age, but none had hepatosplenomegaly, thrombocytopenia, or respiratory distress. In all but one of the 37 infants who escaped intrauterine infection the neonatal period was uncomplicated and no abnormalities were detected. One child, however, was small for gestational age (birthweight 2400 g at 39 weeks' gestation) and had eventration of the diaphragm and congenital heart disease. The diaphragm was operated on within 24 hours of birth, but the child then developed congestive cardiac failure and died

at 13 days. At necropsy the left side of the heart was hypoplastic with ventricular and atrial septal defects, a patent ductus arteriosus, and common atrio-ventricular canal. There was also a cystic right kidney. Histological examination showed no evidence of congenital CMV, and tests on both cord blood and urine samples taken before death excluded congenital infection. No neonatal abnormalities were noted in the controls.

Progress at follow up. Altogether, 39 children exposed to CMV in utero and 39 controls were over 9 months of age at follow up and therefore eligible for their first full examination. Of these, 29 cases (74%) and 27 controls (69%) were examined; Table 3 shows the clinical findings.

Of the 8 congenitally infected cases, one child, who was exposed to maternal infection at approximately 33 weeks' gestation and was asymptomatic at birth, subsequently showed definite global psychomotor delay. When assessed aged 3 years 8 months his developmental age was 2 years 9 months. He had retarded speech and language development and was attending a special nursery school for handicapped children. He had had secretory otitis media requiring surgical drainage, but there was no evidence of sensorineural deafness, failure to thrive, microcephaly, or specific central nervous system defect. One other child with congenital CMV, who was developing normally, was noted to have a large capillary haemangioma overlying the left buttock and subsequently showed slight shortening of the left leg. The two children with microcephaly at birth were both developing normally at follow up, although one still had a head circumference on the third centile. The remaining four congenitally infected children over 9 months of age were developing satisfactorily.

None of the 21 children who escaped congenital infection showed any impairment of psychomotor development. Two had suffered from uncomplicated febrile convulsions between 9 and 18 months, and

Fig. 1 Birthweight of infants exposed to maternal CMV infection. The mean is indicated (—).

Table 3 Subsequent progress of children exposed prenatally to cytomegalovirus (CMV) infection

Clinical findings	Congenital CMV		Controls
	Yes	No	
Psychomotor delay	1*		
Secretory otitis media, normal hearing	1*	2	1
Secretory otitis media with conductive hearing loss		5*	1
Other abnormalities	1	3*	
None	6	12	25
Total	8	21	27

*One child in each group with two abnormalities listed.

Fig. 2 Results on Reynell Development Language Scale in children exposed to maternal CMV infection. The mean is indicated (●).

one, aged 3 years, was clumsy and immature in his behaviour. None had sensorineural deafness, but 7 (33%) had secretory otitis media. In 5 (23%) this was associated with conductive hearing loss.

Two controls (7.3%) suffered from secretory otitis media, associated with conductive hearing loss in one. No other defects were shown in the controls.

Speech and language assessment. Reynell assessments were carried out in 24 children (five with congenital CMV, 10 who escaped congenital infection, and 9 controls). The standard scores were expressed as standard deviations from the mean (Fig. 2). The mean scores for the expressive scale were +0.27 for controls and +0.38 for those not infected with CMV. The mean of -1.08 for those with congenital CMV was significantly below both groups ($P < 0.05$ in both cases). When the child with psychomotor delay is excluded from this analysis the difference is still significant when compared with those who escaped congenital infection ($P < 0.05$) but not when compared with controls. A significant difference was also found in the verbal comprehension score in both comparisons ($P < 0.05$) even excluding the child with psychomotor delay.

Discussion

Maternal CMV infection has been shown to be associated with high fetal wastage⁸; placental infection without transmission to the fetus has also been reported.¹² Follow up of the infants who escaped congenital infection showed that their development had been normal. We conclude, therefore, that maternal infection that is not transmitted to the fetus has no harmful effects on that child's subsequent neurological development.

The overall incidence of intrauterine transmission

in this study was 20%. This contrasts with the findings of other workers who found a transmission rate in London of 45%,¹³ in Sweden of 43%,¹⁴ and in Scotland of 38%.¹⁵ All these previous studies used seroconversion to identify maternal infections and so were unable to detect primary infections before the first antenatal visit. We used a combination of seroconversion and detection of IgM antibody by solid phase radioimmunoassay and found that, though the incidence of CMV infection is the same throughout pregnancy, the incidence of intrauterine transmission in early pregnancy was 20% compared with 40% in late pregnancy. The rate after seroconversion in this study was 29% but in the IgM positive group it was only 8%. This may partly account for the differences in overall incidence of transmission between previous studies and our own. This trend of increased intrauterine transmission towards the end of pregnancy has also been reported for toxoplasmosis¹⁶ and rubella.¹⁷

In contradistinction to both toxoplasmosis and rubella, early intrauterine infection with CMV does not seem to be more damaging to the fetus. In the present study the two infants with congenital infection whose mothers developed primary CMV infection in the first trimester were both normal at 6 years and 3 months respectively. The only congenitally infected child in this study to show delay in psychomotor development was exposed to maternal infection at around 33 weeks' gestation. Overall, therefore, we can provide no evidence that early intrauterine infection is more likely than late infection to result in future handicap.

None of the infants in this study was clinically suspected of having congenital CMV infection. Although mean birthweight of congenitally infected infants was significantly lower than controls, only one was small for gestational age. The child, who subsequently developed psychomotor delay, had a birthweight of 3700 g and so did not give rise to concern at birth. Starr *et al.* have suggested that CMV is associated with low birthweight¹⁸ but this was not found by Reynolds *et al.*² The prognosis of congenitally infected infants with microcephaly at birth is reported to be poor,^{19 20} but neither of the children in the present study who had a head circumference below the third centile showed any neurological defect at birth and both showed normal intellectual development at ages 3 and 4 years respectively. The older child's head circumference at follow up was in the normal range, but the younger one, who was also small for gestational age remained small with height and weight on the tenth centile and head circumference on the third centile.

It is possible that congenital CMV infection may cause more subtle defects that are not apparent in routine physical examination.^{3 20} Evaluations using the Reynell Development Language Scale, a precise measurement of a child's speech and language ability, suggests that this may be so. Results in congenitally infected children showed a definite trend towards lower values even when the one child with known psychomotor delay was excluded. As the number of congenitally infected children was small, this observation needs cautious interpretation. The Reynell assessments should be repeated at 5 years of age and we will then be able to determine whether these interesting preliminary observations become more or less apparent.

None of the 9 congenitally infected children had sensorineural deafness, although this has been reported to develop in 8–50% of infected children.^{2 5} It is essential to follow all infected children to 5 years of age because, as in rubella, CMV deafness may be progressive.²¹ One unexpected finding was the high incidence of secretory otitis media in children who escaped intrauterine transmission despite maternal infection. This may be caused by CMV infection acquired either perinatally or in the postnatal period, ages at which upper respiratory infections and pneumonitis have been associated with CMV.^{22 23}

The findings in this study suggest that screening in pregnancy for primary CMV infection is of limited value. We identified primary maternal infection in 54 women; in 30, in whose babies it was possible to confirm or exclude congenital infection, it developed before the legal limit for termination of pregnancy. Only two of these infants were congenitally infected. One infant not infected died soon after birth, but the other 29 were progressing normally at follow up. This suggests that termination of early infection is not warranted. Furthermore, reactivation of latent maternal infection, which may be responsible for at least 15% of cases of congenital CMV in this country,²⁴ may not be identified by the serological methods currently available.

Screening for CMV infection in pregnancy may be useful in alerting paediatricians to infants with possible congenital infection with CMV but specimens of urine must be obtained from these babies within three weeks of birth if such a diagnosis is to be confirmed.²⁵ After this period children who acquire CMV perinatally will excrete CMV and distinction between congenital and acquired infection is not possible. This is illustrated by 8 children in this study from whom we were unable to collect samples for virus culture within the first three weeks; they were therefore excluded. One of two subsequently shown to be culture positive at 5 and 7

months respectively developed neurological impairment. This child was delivered at another hospital at 30 weeks' gestation, the mother having developed CMV infection late in the second trimester. The infant was moderately jaundiced (maximum bilirubin concentration 270 $\mu\text{mol/l}$ (16 mg/100 ml)) and treated with phototherapy. Subsequently he developed mild psychomotor delay and retrolental fibroplasia. This suggests that congenital infection may have occurred, but, as is often the case in clinical practice, by the time these symptoms were present definitive, retrospective diagnosis of congenital CMV was not possible.

We conclude that the model of intrauterine infection based on rubella is not appropriate for CMV and that screening in pregnancy cannot be advocated in routine practice. At present it is not possible to judge whether screening neonates for congenital CMV is warranted, but large prospective British studies are in progress to assess the value of this procedure.

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References

- 1 Weller TH. The cytomegaloviruses: ubiquitous agents with protean clinical manifestations. *N Engl J Med* 1971; **285**:203–14, 267–74.
- 2 Reynolds DW, Stagno S, Stubbs KG, *et al.* Inapparent congenital cytomegalovirus infection with elevated cord IgM levels: causal relation with auditory and mental deficiency. *N Engl J Med* 1974; **290**:291–6.
- 3 Hanshaw JB, Scheiner AP, Moxley AW, Gaev L, Abel V, Scheiner B. School failure and deafness after "silent" congenital cytomegalovirus infection. *N Engl J Med* 1976; **295**:468–70.
- 4 MacDonald H, Tobin JO'H. Congenital cytomegalovirus infection: a collaborative study on epidemiological, clinical and laboratory findings. *Dev Med Child Neurol* 1978; **20**:471–82.
- 5 Saigal S, Lunyk O, Larke RPB, Chernesky MA. The outcome of children with congenital cytomegalovirus infection. *Am J Dis Child* 1982; **136**:896–901.
- 6 Anonymous. Cytomegalovirus in adults. (Editorial). *Lancet* 1977; **ii**:541.
- 7 Griffiths PD, Campbell-Benzie A, Heath RB. A prospective study of primary cytomegalovirus infection in pregnant women. *Br J Obstet Gynaecol* 1980; **87**:308–14.
- 8 Griffiths PD. The presumptive diagnosis of primary cytomegalovirus infection in early pregnancy by means of a radioimmunoassay for specific-IgM antibodies. *Br J Obstet Gynaecol* 1981; **88**:582–7.
- 9 Kangro HO, Griffiths PD, Huber TJ, Heath RB. Specific IgM class antibody production following infection with cytomegalovirus. *J Med Virol* 1982; **10**:203–12.

- ¹⁰ Griffiths PD, Stagno S, Pass RF, Smith RJ, Alford CA, Jr. Congenital cytomegalovirus infection: diagnostic and prognostic significance of the detection of specific immunoglobulin M antibodies in cord serum. *Pediatrics* 1982;**69**:544-9.
- ¹¹ Sheridan MD. *Children's developmental progress from birth to five years: the Stycar sequences*. Windsor, UK: NFER Publishing Company, 1973.
- ¹² Hayes K, Gibas H. Placental cytomegalovirus infection without fetal involvement following primary infection in pregnancy. *J Pediatr* 1971;**79**:401-5.
- ¹³ Stern H, Tucker SM. Prospective study of cytomegalovirus infection in pregnancy. *Br Med J* 1973;**ii**:268-70.
- ¹⁴ Ahlfors K, Ivarsson SA, Johnsson T, Svanberg L. Primary and secondary maternal cytomegalovirus infections and their relation to congenital infections. Analysis of maternal sera. *Acta Paediatr Scand* 1982;**71**:109-13.
- ¹⁵ Grant S, Edmond E, Syme J. A prospective study of cytomegalovirus infection in pregnancy. *J Infect Dis* 1981;**3**:24-7.
- ¹⁶ Desmonts G, Couvreur J. Congenital toxoplasmosis: a prospective study of 378 pregnancies. *N Engl J Med* 1974;**290**:1110-6.
- ¹⁷ Miller E, Cradock-Watson JE, Pollock TM. Consequences of confirmed maternal rubella at successive stages of pregnancy. *Lancet* 1982;**ii**:781-4.
- ¹⁸ Starr JG, Jr. Cytomegalovirus infection in pregnancy. *N Engl J Med* 1970;**282**:1075-8.
- ¹⁹ Pass RF, Stagno S, Myers GJ, Alford CA. Outcome of symptomatic congenital cytomegalovirus infection: results of long-term longitudinal follow-up. *Pediatrics* 1980;**66**:758-62.
- ²⁰ Williamson WD, Desmond MM, LaFevers N, Taber LH, Catlin FI, Weaver TG. Symptomatic congenital cytomegalovirus: disorders of language, learning and hearing. *Am J Dis Child* 1982;**136**:902-5.
- ²¹ Dahle AJ, McCollister FP, Stagno S, Reynolds DW, Hoffman HE. Progressive hearing impairment in children with congenital cytomegalovirus infection. *Journal of Hearing and Speech Disorders* 1979;**44**:220-9.
- ²² Olson LC, Ketusin AR, Mansuwan P, Snitbhan R. Respiratory tract excretion of cytomegalovirus in Thai children. *J Pediatr* 1970;**77**:489-504.
- ²³ Stagno S, Brasfield DM, Brown MB *et al*. Infant pneumonia associated with cytomegalovirus, chlamydia, pneumocystis and ureaplasma: a prospective study. *Pediatrics* 1981;**68**:322-9.
- ²⁴ Peckham CS, Chin KS, Coleman JC, Henderson K, Hurley R, Preece PM. Cytomegalovirus infection in pregnancy: preliminary findings from a prospective study. *Lancet* 1983;**i**:1352-5.
- ²⁵ Reynolds DW, Stagno S, Hosty TS, Tiller M, Alford CA, Jr. Maternal cytomegalovirus excretion and perinatal infection. *N Engl J Med* 1973;**289**:1-5.

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