Prospective Study of Cytomegalovirus Infection in Pregnancy

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Summary
In a prospective study of cytomegalovirus infection in 1,040 pregnant women in London 319 (42%) of the white Englishwomen but only 28 (10%) of the immigrant Asian women were without antibodies at the onset of pregnancy. Out of 254 susceptible white women and 16 susceptible Asian women 8 (3%) and 3 (16%) respectively experienced primary infection during the course of pregnancy. The overall incidence of fetal infection after primary infection in the mother was almost 50%, and was higher in early pregnancy. One out of the five infected infants was found to be mentally retarded.

Reactivation of latent infection was recognized in 0.7-2.9% of pregnant women; this occurred without involving the fetus.

Introduction
Cytomegalovirus is one of the few agents known to damage the brain in utero. Infants who survive the classical syndrome of neonatal cytomegalic inclusion disease are usually mentally retarded and microcephalic (Weller and Hanshaw, 1962; Medearis, 1964). This severe illness, however, is comparatively
rare despite the fact that as many as 0.5-1% of all infants excrete cytomegalovirus at birth (Birnbaum et al., 1968; Cherry et al., 1968; Hanshaw et al., 1968; Stern, 1968; Starr et al., 1970; Walker and Tobin, 1970). Most congenitally infected infants are apparently healthy at birth or have relatively mild illnesses such as transient jaundice or purpura, respiratory illnesses with or without hepatosplenomegaly, hepatosplenomegaly alone, or simply feeding difficulties with failure to thrive (Stern et al., 1969). Nevertheless, a proportion of these infants, including some who are asymptomatic at birth, also become mentally retarded.

The present paper is a preliminary report from a continuing prospective study of cytomegalovirus infection in pregnancy. The object of the study is to establish the risk to the infected fetus of sustaining brain damage and also to determine the stage of pregnancy when primary infection is most harmful. This cannot be done by purely clinical methods, since unlike rubella cytomegalovirus infection in adults is almost invariably subclinical.

Methods

Women were recruited into the study on their first attendance at the antenatal clinics of the Hillingdon Hospital or St. George's Hospital in London, the only selection being that they were in the first trimester of pregnancy. About 90% of the women lived in the Borough of Hillingdon, which has a large immigrant Asian population. A blood specimen was taken at the initial attendance and again at intervals of two to three months until term, when blood and urine were collected from mother and baby. Further specimens were obtained from the infants whenever possible during the first year of life.

Urine was collected directly into transport medium and inoculated within 24 hours into diploid human embryonic lung fibroblasts. Serum specimens were examined for cytomegalovirus complement-fixing antibodies by the microtitre technique, with cell-associated antigen prepared from the Rawles and Ad169 strains of virus. The isolation and serological techniques have been described elsewhere (Stern and Eley, 1965; Stern et al., 1963).

Results

The frequency of cytomegalovirus antibody in the first 1,040 women examined on their first antenatal attendance is shown in Table I. Altogether 761 (73%) of the women were native white Englishwomen, and 442 (58%) of them possessed antibodies. On the other hand, of the 279 Asian women 251 (90%) had antibodies. Near maximum frequency of antibodies was already present in the youngest age groups.

The frequency of primary infection in those women who were followed to term is shown in table II. Out of 584 white women 254 were without antibodies at the start of pregnancy, and eight of these acquired antibodies during the course of pregnancy—that is, 3% of the seronegative women and 14% of the total group. Only 16 out of 136 Asian women were initially without antibodies but 3 (19%) developed them subsequently.

The number of women excreting cytomegalovirus in the urine at term and the relation between virus excretion and primary infection are given in Table III. Urine specimens suitable for virus culture were obtained from 566 white women, including the eight women who had undergone primary infection. Only three of the latter were found to be excreting virus at term, while a further four women, who already had antibody at the time of their first antenatal attendance and who showed no rise in the titre of antibody during the rest of pregnancy, were also excreting virus. Similarly, two of the three Asian women who had undergone primary infection were excreting virus at term, and there were four others excreting virus who already had antibody in the initial blood specimen. None of the babies born to the eight white and Asian women who were excreting virus at term but who already had antibody at the first antenatal visit was found to be excreting cytomegalovirus in the urine; all eight infants were apparently healthy at birth and after one year had made normal physical and mental progress. In contrast the five babies born to the women who were excreting virus at term but who had undergone primary infection, as shown by the acquisition of antibodies during the course of pregnancy, were also excreting virus in the urine at birth. The overall rate of virus excretion in the 720 newborn babies examined was 0.7%.

Details of the 11 women who experienced primary infection during pregnancy, including the trimester of pregnancy when seroconversion occurred, are given in Table IV. Cases 1 and 2 may have been first trimester infections. Both women, however, were first seen during the second month of pregnancy and not again until late in the fourth month, so that the infections could have taken place early in the second trimester. In case 7 the patient was probably infected shortly before term, since she had no antibody at term but acquired it two weeks later. Maternal viruria was found more often after primary infection during the first six months of pregnancy; four of the six women infected during the first or second trimester were excreting virus, as compared with only one out of five infected later. Also, only women who were themselves excreting virus at term produced infected babies. Consequently fetal infection occurred more commonly after maternal infection during the first or second trimester.
All 11 babies were apparently well at birth, and 10 of them, including four of the infected infants, remained healthy one year later. Only one infant, born to a mother infected during the second trimester, failed to make normal progress, and at 6 months of age showed generalized hypotonia and was mentally retarded though not microcephalic.

Discussion

The frequency of cytomegalovirus antibodies in the white women at the start of pregnancy was similar to that previously found for the same age groups in the general population of London (Stern and Elek, 1965). The much higher frequency in the immigrant Asian women was not unexpected, since cytomegalovirus infection is known to be much commoner and to occur at an earlier age in Asian and African populations than in most countries of Western Europe (Krech et al., 1971). On the other hand, what was unexpected was the finding that though few Asian women are susceptible to infection at the onset of pregnancy those that are seem to run a much greater risk of infection during the subsequent course of pregnancy than do susceptible white women, presumably because of the greater reservoir of infection in the immigrant population.

Only primary infection in the mother at some time during the course of pregnancy provides a significant risk of infection for the fetus. In the present study 11 women experienced primary infection, and five of their infants were born infected—that is, were excreting cytomegalovirus at birth. The risk of infection for the fetus after primary infection in the mother is therefore of the order of 50%, a greater overall risk than in the case of rubella. As with rubella, infection of the fetus seems to be more likely to occur when the mother is infected early, during the first or second trimester. Nevertheless, the fetus can be infected even very late in pregnancy, and Hayes and Gibas (1971) also showed that the fetus may escape infection during the second trimester even when this involves the placenta. In the same way early infection of the fetus is not necessarily followed by obvious brain damage. Though the one infant who had severe brain damage was born to a mother infected during the second trimester, two other infants infected during the first or very early second trimester remained perfectly healthy after one year. In a similar study in the United States (Monif et al., 1972) two infants infected during the second trimester were severely mentally retarded while two others infected in the third trimester remained well. Serious brain damage may, therefore, be more likely to follow maternal infection during the first six months of pregnancy.

In neither of these two investigations were there any cases of neonatal cytomegalic inclusion disease. This severe syndrome may well occur only after infection very early in pregnancy. Davis et al. (1971), however, reported a case of cytomegalovirus infection that occurred during the first few weeks of pregnancy and was recognized clinically because the woman developed typical cytomegalovirus mononucleosis; after therapeutic abortion at 22 weeks the fetus showed none of the classical features of neonatal cytomegalic inclusion disease despite the presence of cytomegalic cells in many internal organs.

Only one of the five infected infants in the present series became mentally retarded (20%). In Monif et al.'s study two out of four infants were retarded. Nevertheless, both series are still very small and available accumulated evidence suggests that a more reasonable figure for the risk to the infected fetus of sustaining severe brain damage is 10% (Hanshaw, 1971). Obviously much more work is needed to establish the role of cytomegalovirus in mental deficiency, but it is worth remembering that in England and Wales, with a birth rate of about 830,000 and an incidence of congenital cytomegalovirus infection of, say, 0.5%, about 4,000 cytomegalovirus-injected babies are born every year. If 10% of them are mentally retarded this means the birth each year of about 400 infants with severe brain damage caused by cytomegalovirus.

Cytomegalovirus behaves like other herpesviruses and persists in the body after infection in a latent form, probably for life. It is not yet known whether otherwise healthy persons carrying such latent infection suffer recurrent reactivations, such as occur with herpes simplex, though such reactivations could obviously play an important part in the spread of infection. Pregnancy, however, can certainly reactivate latent cytomegalovirus infection, perhaps because of the increased steroid levels, and excretion of virus in the throat and urine, on the cervix, and in the milk may persist for weeks or months after term (Numazaki et al., 1970; Montgomery et al., 1972; Hayes et al., 1972). The higher rate of reactivation in the Asian women (2.9%) as compared with the white women (0.7%) reflects the greater frequency of antibodies and thus of latent infection in the immigrant population. Since reactivating women possess pre-existing circulating antibody intrauterine infection of the fetus does not occur and the baby is born healthy and uninfected. Others have found that 2.3% of pregnant women excrete cytomegalovirus in the urine and on the cervix without infecting the fetus (Hildebrandt et al., 1967; Krech et al., 1968; Feldman, 1969; McCracken et al., 1969; Foy et al., 1970), though higher figures have been obtained for some Far Eastern countries (Alexander, 1967; Levinsohn et al., 1969). Continuing excretion of virus after term, however, perhaps in the throat and milk, provides a source of early infection for the infant once he has lost his maternal antibodies (Alexander, 1967; Stern, 1968; Levinsohn et al., 1969; Numazaki et al., 1970; Walker and Tobin, 1970); so far as is known these early postnatal infections are essentially benign.

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References