

Managing primary CMV infection in pregnancy

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The cytomegalovirus (CMV) is the most common cause of congenital infection and a common cause of sensorineural hearing loss and neurodevelopmental delay. The birth prevalence of congenital CMV is 0.64% (95% CI 0.60–0.69), while that of symptomatic infection at birth is 0.07%.¹ CMV is the largest of the human herpesvirus family. The virus is species specific, and humans are the only natural host for human CMV infection. It is transmitted by close contact, through contamination from urine, saliva, blood, semen and cervical secretions.² Vertical infection can occur antenatally through the placenta, during delivery through cervical secretions and blood and postnatally through breast milk. CMV is endemic and most adults will be infected during their lifetime. Adult seroprevalence in developed countries is around 50%, but in developing countries it may be as high as 90–100%. Primary infection in immunocompetent adults is usually asymptomatic, and viral shedding continues for some months before the infection is brought to its latent phase. In children, viral shedding may persist for years after a primary infection and toddlers in day care constitute an important infectious source. In common with other herpesviruses, CMV remains lifelong at specific sites (mainly the salivary glands) and the viral replication cycle can be reactivated. Secondary infection can occur due to such reactivation of the residing virus or due to infection with a different strain (reinfection).³ Primary CMV infection during pregnancy carries a greater risk for congenital infection than secondary infection; in infants born to women with primary infection during pregnancy, the risk of vertical transmission is 30–40%, while it is 1–2% for secondary infection. The difficulty in detecting secondary maternal infection means that much research concentrates on primary infection.

The nature of primary maternal CMV infection makes prenatal counselling of women complicated. While the risk of fetal infection following maternal seroconversion in pregnancy is 30–40%,⁴ about 80–90% of infected infants will be asymptomatic at birth, with only 10–20% having symptomatic

infection (Table 1). Thus, fetal infection does not equate to an affected fetus. The prognosis of those affected fetuses (i.e. symptomatic infants) is very poor, with the vast majority suffering severe mental impairment and/or hearing loss. Fetal infection can be established by an amniocentesis carried out after 6 weeks of maternal seroconversion, which can detect presence of CMV DNA in the amniotic fluid. Questions that remain unanswered are whether it is possible to predict which of the infected fetuses will also be symptomatic (affected) and whether the implications of fetal infection depend on the gestation at which the fetus acquired the infection. Two papers^{6,7} in this issue attempt to fill these gaps in our knowledge and help clinicians to advise pregnant women.

Is the timing of fetal infection related to the likelihood of an affected fetus?

Gindes *et al.*⁶ report on 28 women with primary CMV infection acquired at a median gestational age of 30 weeks (range 26–37 weeks). Vertical transmission was detected in 21/28 pregnancies (75%). This rate is higher than the generally quoted risk of fetal transmission following maternal infection and that *in utero* transmission rate is higher at later gestation is not universally accepted. Infant follow up in the study ranged from 6 to 36 months (median 36 months) and was available in all cases. None of the infants, including those infected with CMV, showed evidence of symptomatic CMV disease. The paper therefore indicates that fetal CMV infection acquired later in pregnancy may be benign as far as the risk of an affected fetus is concerned. Other authors also suggest that infection in the first half of pregnancy may carry a higher risk of an affected fetus than infection in later pregnancy.³ The findings by Gindes *et al.* are reassuring for women with late seroconversion, but it is important to realise that there may also be a selection bias: cases were selected due

Table 1. Proportion of clinical findings in infants with symptomatic congenital CMV infection (modified from Ross and Boppana)⁵

Finding	%
Petechiae	76
Jaundice	67
Hepatosplenomegaly	60
Microcephaly	53
Intrauterine growth retardation	50
Chorioretinitis/optic atrophy	20
Purpura	13
Seizures	7

either to maternal symptoms or seroconversion on routine monthly serology; none of the women underwent testing due to detection of ultrasound abnormalities. It is therefore possible that cases with ultrasound abnormalities (and the ones most likely to result in an affected fetus) were not included. Therefore, these results will not be applicable when CMV-related fetal damage is suspected on ultrasound.

What is the outlook with confirmed fetal CMV infection?

The paper by Benoist *et al.*⁷ reports on 73 fetuses with documented fetal CMV infection and attempts to identify cases destined for an affected fetus. None of the fetuses included in this study was infected in the third trimester. Cases came to light due to maternal symptoms, seroconversion on random testing or identification of ultrasound abnormalities. Thirty-eight fetuses (52%) showed some ultrasound abnormality. It is not surprising that the presence of an ultrasound abnormality was highly correlated with the likelihood of fetal affection (sensitivity 85.7% and specificity 78.9%).

Thirty-four pregnancies (47%) ended due to termination or intrauterine death, while 39 (53%) pregnancies continued. Of these 39 pregnancies, 36 infants (92%) showed no abnormalities on follow up. Overall, there were 35 (48%) fetuses with a poor outcome, defined as an abnormal clinical examination at the age of 6 months (including hearing loss) or termination for fetal abnormalities confirmed postmortem. Importantly, there were five infants with poor outcome that had no antenatal ultrasound findings, meaning that in confirmed fetal infection the risk of poor outcome despite normal ultrasound examination is 14%. In a smaller study, Lipitz *et al.*⁸ reported 18 fetuses with confirmed fetal infection, where the pregnancy was not terminated: 16 fetuses had no prenatal ultrasound features. Three of the 16 (19%) had postnatal neurological abnormalities. This figure compares well with the present study, suggesting that in cases of confirmed fetal infection, the risk of an affected

fetus in the absence of ultrasound abnormalities is about 1 in 5 to 1 in 7.

Predicting symptomatic fetal infection after maternal seroconversion with ultrasound alone

Theoretically, the risk of fetal infection following maternal seroconversion is 30–40%. In these infected fetuses, a large proportion showing abnormal ultrasound features are expected to result in an affected fetus. The chance of an affected fetus following maternal seroconversion with unknown fetal status and normal ultrasound findings would be $1/3 \times 1/5$ to $1/7 = 1/15$ to $1/20$ (approximately 5–7%). However, another recent publication tells a very different story: Guerra *et al.* studied 600 women with primary CMV infection and follow up. It is unclear why women underwent serological testing for CMV infection. The median duration of follow up was 42 months (range 6–72 months). Fetal infection occurred in 154 (26%) pregnancies, of which 84 (56%) were affected. This unusual high rate may be due to a degree of selection bias, as the study was performed in a tertiary centre for CMV infection in pregnancy. Although ultrasound of 51 fetuses was reported as abnormal, only 18 (35%) of these were infected and symptomatic, with the remaining 33 abnormal scans occurring in noninfected fetuses ($n = 28$), or infected but asymptomatic fetuses ($n = 5$). This meant that the sensitivity of an abnormal ultrasound finding in predicting symptomatic newborn was only 21%. Possible reasons for the differences between this study and that by Benoist *et al.* include differences in recruitment and protocols for ultrasound follow up. Nevertheless, the study by Guerra *et al.*⁹ has cast a significant doubt on the general view that serial prenatal ultrasound is very valuable in predicting or excluding symptomatic fetal infection. So are there any other useful markers?

Fetal blood sampling in confirmed fetal infection

Fetal blood sampling (FBS) has the potential value of providing information on the platelet count and liver enzyme levels in suspected fetal CMV infection. Benoist *et al.* showed that the platelet count was low (as defined as $<120\,000/\text{mm}^3$) in 20/33 (66%) cases with abnormal outcome and gamma-glutamyl transferase (GGT) was elevated in 17/29 (58.6%) cases with abnormal outcome. Of course, many of these fetuses also had ultrasound abnormalities. The most important question is this: are the platelet count and liver enzyme levels of any *additional* value in predicting an affected fetus over and above the ultrasound scan? Benoist *et al.* report that of the five affected fetuses with no

ultrasound abnormalities, two had a low platelet count and three had elevated GGT (sensitivity of 40 and 60%, respectively). Moreover, of all the fetuses with a normal outcome, 27 fetuses had a normal platelet count and 13 had normal GGT (specificity of 95 and 55%, respectively). The logistic regression analysis supports an independent prognostic value of a low platelet count for prediction of a poor outcome. It will be fair to say that a normal platelet count and absence of ultrasound abnormalities do not exclude symptomatic fetal infection but make it less likely (85% negative predictive value). However, we must not forget that FBS is associated with a risk of pregnancy loss. In this study, both the cases that underwent an intrauterine demise had undergone a FBS, although loss might have occurred regardless of intervention.

Both these papers have made important contributions to the debate on how to best manage primary maternal CMV infection in pregnancy. If fetal infection has been established, careful examination for ultrasound features characteristic of the infection should be carried out. If these are present, the risk of an affected fetus is high. FBS may be a useful additional test for those women without such features who wish to gain additional reassurance. ■

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