Congenital Cytomegalovirus Infection: Update on Treatment

1. Introduction

Cytomegalovirus (CMV), a member of the human herpesvirus family, is the most common viral cause of congenital infection, affecting 0.5–1% of all live births.\(^1\) It is responsible for significant morbidity, especially in infants, who are symptomatic in the neonatal period. It is the leading non-genetic cause of sensorineural hearing loss (SNHL) and a major cause of neurological disability. Around 13% of neonates with congenital CMV will be symptomatic at birth, with a similar proportion developing problems later in childhood.\(^4\)

This Scientific Impact Paper will summarise the issues around screening, diagnosis and treatment of CMV in pregnancy, utilising the best available evidence and highlighting recent advances.

2. Epidemiology

CMV infection may be acquired for the first time during pregnancy (primary infection) or women may experience secondary CMV infection, either by reactivation of prior CMV infection or by a new infection with a different strain of the virus. Transmission of the virus to the fetus can occur antenatally by the transplacental route, during labour and delivery through contact with cervicovaginal secretions and blood, or postnatally through breast milk. Transmission is more likely following maternal primary infection in pregnancy than following reactivation or recurrent infection with a different strain.\(^5,6\) Infants born to mothers with primary infection have a risk of congenital infection of the order of 30–40%, and 13% of these will be symptomatic at birth.\(^7\) Following recurrent CMV infection in pregnancy, the risk of congenital infection is of the order of 1–2%.\(^7\)–\(^11\) The risk of congenital infection appears to vary according to the time during gestation at which primary infection occurs, increasing from around 30% in the first trimester to 47% in the third trimester.\(^12,13\) While the risk of viral transmission is lower in early pregnancy, the proportion of cases with a prenatal diagnosis of severe fetal infection is higher when infection occurs in the first compared with the third trimester of pregnancy.\(^14,15\)

The majority of women who acquire CMV infection for the first time (primary infection) will remain asymptomatic.\(^16\) However, a minority do experience symptoms similar to those of infectious mononucleosis (glandular fever), including fever, malaise, myalgia, cervical lymphadenopathy and, less commonly, hepatitis and pneumonia, but few suffer long-term sequelae. Just as with other herpesviruses, CMV can remain dormant lifelong at particular sites, primarily in the salivary glands, and the virus can be reactivated at any time, including during pregnancy.

3. Detection of and screening for congenital CMV

The clinical features of congenital CMV at birth include jaundice, petechial rash, hepatosplenomegaly, microcephaly and infants born small for gestational age. As mentioned, 13% of babies born with congenital CMV infection will be symptomatic at birth. The other 87% will be asymptomatic or have subclinical manifestations of the disease; in fact, many of these will go undiagnosed in the absence of routine antenatal or neonatal screening programmes. However, 15% of these asymptomatic neonates will later develop some degree of hearing loss.\(^17\)
Since routine CMV screening does not meet several of the criteria for an effective screening test, not least the fact that until now there has been no effective treatment, routine prenatal screening is not recommended outside the research setting.\textsuperscript{16,19} Consequently, serological testing for CMV is offered only to women who have developed influenza-like symptoms during pregnancy or in whom routine ultrasound detects fetal abnormalities suggestive of possible CMV infection, such as ventriculomegaly, microcephaly, calcifications, intraventricular synechiae, intracranial haemorrhage, periventricular cysts, cerebellar hypoplasia, cortical abnormalities, echogenic bowel, small for gestational age, pericardial effusion, ascites and fetal hydrops.

Prenatal diagnosis of CMV infection is challenging and options for prevention and treatment are limited. In general, the options with congenital CMV infection are either conservative management, in other words continuation of the pregnancy, or termination. More recently, medical therapies aimed at reducing the risk of transmission, and likelihood and/or severity of neonatal infection have been investigated including antiviral drugs and CMV hyperimmune globulin (HIG).\textsuperscript{20–22}

4. Prenatal therapy

4.1 Antiviral drugs

Valaciclovir

In immunocompromised (nonpregnant) women, three antiviral drugs are licensed for use for CMV infection, namely ganciclovir, cidofovir and foscarnet, but their teratogenic and toxic effects preclude their use in pregnancy. However, two studies have investigated the use of another antiviral agent, valaciclovir (valacyclovir) in CMV-infected pregnancies\textsuperscript{20,21}. Valaciclovir is a prodrug that is converted in vivo by esterases into the active drug aciclovir in the liver during first pass metabolism. Valaciclovir is favoured because it has greater oral bioavailability than aciclovir (55% versus 10–20%).\textsuperscript{24,25} Aciclovir has an excellent safety profile in pregnancy. It is not genotoxic (it does not cause damage to genes) in vitro, and in animal studies no drug-related neoplasia has been observed.\textsuperscript{26} There is considerable evidence that its use in humans in the first trimester is not associated with any increase in the rate of birth defects.\textsuperscript{27,28}

Jacquemard et al.\textsuperscript{20} treated pregnant women with primary CMV in pregnancy with oral valaciclovir 8 g/day in a pilot study of 21 cases. Twenty pregnancies with 21 fetuses were treated at 28 weeks of gestation (range 22–34 weeks) for 7 weeks (range 1–12 weeks). Therapeutic concentrations of the drug were achieved in both maternal and fetal blood, and the viral load in the fetal blood decreased significantly after 1–12 weeks of treatment. In terms of outcome, six out of seven cases had evidence of in utero progression of the disease with worsening cerebral lesions, resulting in termination of pregnancy or intrauterine fetal death. A further two infants had severe isolated unilateral deafness. One child had microcephaly with severe deafness and was also diagnosed with incontinentia pigmenti. The remaining ten infants were developing normally at follow-up, having reached between 1 and 5 years of age. By comparison, of 24 untreated symptomatic CMV-infected fetuses the outcome for 14 (58%) was termination of pregnancy, intrauterine fetal death or severe neonatal infection. The remaining ten infants were healthy at follow-up.

Oral valaciclovir 8 g/day was subsequently studied in a phase II open label trial entitled ‘In Utero Treatment of Cytomegalovirus Congenital Infection with Valacyclovir (CYMEVAL)’.\textsuperscript{21} High dose valaciclovir was given for a median of 89 days to pregnant women carrying a moderately-infected fetus presenting with non-severe ultrasound features (extracerebral ultrasound abnormalities and/or mild ultrasound brain abnormalities). Valaciclovir was associated with a significantly greater proportion of neonates born asymptomatic with treatment (82% with treatment versus 43% without
treatment). This study also provided reassuring safety data for the use of valaciclovir in pregnancy: maternal clinical and laboratory tolerances to this high dosage regimen were excellent, and no adverse neonatal effects were observed. Moreover, adherence to treatment exceeded 90%, despite the requirement to take 16 tablets every day. A randomised controlled trial would be the ideal method to confirm whether valaciclovir should be recommended routinely to pregnant women carrying a fetus with mild congenital CMV infection in order to reduce the risk of symptomatic congenital CMV disease.

4.2 Hyperimmune globulin

The other therapeutic agent that has been investigated is CMV HIG. Nigro et al. conducted a nonrandomised clinical trial using CMV HIG in two separate groups:

1. Women with primary CMV infection whose amniotic fluid was positive for CMV; these women were offered CMV HIG 200 U/kg of maternal weight (the ‘therapy group’).
2. Women with a recent primary CMV infection and unknown fetal status before 21 weeks of gestation who declined amniocentesis; these women were offered monthly HIG 100 U/kg (the ‘prevention group’).

In the therapy group, only 1/31 (3%) of neonates had symptomatic CMV disease compared with 7/14 (50%) of women who did not receive the treatment. In the prevention group, 6/37 (16%) women who received HIG had neonates with congenital CMV infection compared with 19/47 (40%) of women who did not receive HIG. The authors concluded that HIG therapy was associated with a significantly lower risk of congenital CMV infection, especially symptomatic infection.

Unfortunately, the efficacy of this preventative strategy with CMV HIG was not borne out in a phase II randomised placebo-controlled double-blind study. This study included a total of 124 pregnant women diagnosed with primary CMV infection at 5–26 weeks of gestation (median 13 weeks) following systematic screening. These women were randomly assigned within 6 weeks after the presumed primary infection to receive either intravenous HIG (100 U/kg of maternal weight) or placebo (0.9% saline solution) every 4 weeks until 36 weeks of gestation or until the detection of CMV in the amniotic fluid. The primary endpoint was congenital infection diagnosed at birth or amniocentesis positive for CMV. The rate of congenital infection was 30% in the HIG group compared to 44% in the placebo group (a nonsignificant difference; \( P = 0.13 \)). This study found no significant difference between the two groups in the risk of transmission, the levels of virus specific antibodies, T-cell mediated immune response or viral DNA in the blood. The clinical outcome of congenital infection at birth was similar in the two groups. However, the number of adverse obstetric events, including preterm birth, pre-eclampsia and fetal growth restriction, was higher in the HIG group compared with the placebo group (13% versus 2%; \( P = 0.06 \)). The power calculation for this trial was based on the findings of the observational study of Nigro et al., nevertheless it may still have been underpowered.

Given these conflicting findings, HIG is not routinely recommended for the treatment of women with primary CMV infection in pregnancy, and should currently be reserved for use in the research setting. Another trial assessing HIG in pregnancy is currently underway (clinicaltrials.gov: NCT01376778).

5. Management and prevention

A proposal for management of CMV fetal infection is presented in Figure 1.
In neonates with symptomatic congenital CMV infection, postnatal valaciclovir/ganciclovir treatment should be considered and commenced within the first 4 weeks of life. There is evidence that treatment can reduce or prevent progression of SNHL and improve long-term neurodevelopmental outcomes in some infants.\textsuperscript{30} The diagnosis and management of congenital CMV in the neonate is beyond the scope of this document and is outlined in other guidance.\textsuperscript{31}

Figure 1: Proposed management of congenital CMV infection (adapted from Benoist et al.\textsuperscript{29})

Prevention using vaccination

There is no licensed vaccine for CMV, and while candidate vaccines are progressing through clinical trials, a vaccine for use in routine clinical practice remains a distant prospect.

6. Opinion

- When fetal CMV infection has been confirmed by amniocentesis, serial ultrasound examination of the fetus should be performed every 2–3 weeks until delivery. During these examinations, a detailed assessment of the fetal brain is essential.
- In infected fetuses, cerebral MRI is indicated at 28–32 weeks of gestation (and sometimes repeated 3–4 weeks later) using T1, T2 and diffusion sequences; its role in the assessment of the fetal brain should be considered complementary to that of ultrasound.
- In infected fetuses, primarily those with intermediate prognosis, that is non-cerebral fetal ultrasound abnormalities, the role of fetal blood sampling to check platelet count should be discussed with the parents.
- Infected fetuses may be classified into one of three prognostic categories:
1. **Asymptomatic fetuses**: defined as those with no ultrasound abnormalities, normal cerebral MRI and normal biological parameters, in particular platelet count in fetal blood. The prognosis is generally good for these fetuses but with a residual risk of hearing loss.

2. **Severely symptomatic fetuses**: defined as those with severe cerebral ultrasound abnormalities (e.g. microcephaly, ventriculomegaly, white matter abnormalities and cavitations, intracerebral haemorrhage, delayed cortical development) associated with thrombocytopenia. The prognosis for this group is poor and counselling regarding the option of termination of pregnancy should take place.

3. **Mild or moderately symptomatic fetuses**: defined as those with isolated biological abnormalities (on fetal blood sampling) either without brain abnormalities on ultrasound or with isolated ultrasound abnormalities such as hyperechogenic bowel, mild ventriculomegaly or isolated calcifications. In this group the prognosis is uncertain and further follow-up (with ultrasound and possibly MRI) may help to refine the prognosis. Therapeutic options, such as antiviral therapy, are being evaluated but their use is still limited to the research setting. The option of termination of pregnancy should also be discussed.

**References**


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