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Congenital Cytomegalovirus Infection: Update on Treatment

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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 0.2–2.2% of all live births.[1–3] 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 10–15% of neonates with congenital CMV will be symptomatic at birth, with a similar percentage 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] 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.[6] Following recurrent CMV infection in pregnancy, the risk of congenital infection is of the order of 1–2%.[1] 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.[7,8] 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.[9,10] Although CMV transmission is more likely in women with primary infection, at the population level, especially in populations with high CMV seroprevalence, the majority (around two-thirds) of infants with congenital CMV infection are born to women with pre-existing CMV immunity.[11]

The majority of women who acquire CMV infection for the first time (primary infection) will remain asymptomatic.[12] 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, but the virus can be reactivated at any time, including during pregnancy.

3. Detection of and screening for congenital cytomegalovirus (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, 6–23% of these asymptomatic neonates will later develop some degree of hearing loss.[13]

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.[14,15] Consequently, serological testing for CMV is offered only to women who have developed influenza-like symptoms, or symptoms of glandular fever (with negative test results for Epstein–Barr virus) or of hepatitis (with negative test results for hepatitis A, B and C) 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.[16]

For other viral infections, such as rubella, the presence of immunoglobulin (Ig) M is often diagnostic of recent primary infection. However, this is not the case for CMV for several reasons:

- IgM may persist for many months after the primary CMV infection.
- IgM may be detected during a secondary infection.
- There may be cross-reactivity with IgM due to another viral infection, e.g. Epstein–Barr virus.
- IgM may be detected as a result of nonspecific polyclonal stimulation of the immune system.

As a result, IgG avidity testing is often used in order to better define the timing of the infection (i.e. before or during pregnancy). Avidity levels are quantified by the avidity index, which describes the proportion of IgG bound to the antigen following treatment with denaturing agents.[17] In general, a high avidity index (greater than 60%) is highly suggestive of past (more than 3 months) or secondary infection, while a low avidity index (less than 30%) is highly suggestive of a recent primary infection (i.e. within the past 3 months).[18] It is important to recognise that there is little standardisation among the various CMV testing kits available, so the avidity index is dependent on the kit/technique used. For this reason, when comparing serial results, it is important to use the same technique for each test.

Diagnosis of secondary CMV infection can be difficult. A rise in IgG levels does not confirm secondary infection as this may be due to nonspecific polyclonal stimulation of the immune system. In practice, therefore, the only way of confirming secondary CMV infection (whether reinfection or reactivation) is by invasive testing.

The diagnosis of primary CMV infection in pregnancy can be made by one of the following findings:

1. The appearance of CMV-specific IgG in a woman who was previously seronegative.
2. The detection of CMV IgM antibody with low IgG avidity.

Maternal serology is still the mainstay for the diagnosis of maternal infection. Virological tests of maternal serum or urine are available, although these correlate poorly with the timing of infection or neonatal outcomes and are, therefore, less useful in the clinical setting.[12] The mainstay of diagnosis of fetal infection is by identification of the

virus or viral genome (DNA) in the amniotic fluid following amniocentesis. The most commonly used virological test is polymerase chain reaction (PCR), generally real-time PCR. The timing of amniocentesis is very important; the appearance of the virus in the amniotic fluid is dependent on excretion of the virus in fetal urine. It should be performed, therefore, after 20 weeks of gestation when fetal urination is well-established.

4. Prenatal prognostic indicators in congenital CMV infection

Accurate prenatal prediction of poor prognosis for affected infants has proved challenging; estimates are based largely on the timing of the infection, presence and type of fetal abnormalities and laboratory parameters. It appears that, in common with other viral infections, the risk of vertical transmission increases with gestation. The association between the timing of infection and *severity* of fetal/neonatal outcome is less well defined. Nevertheless, there is growing evidence that, in common with other viral infections in pregnancy, infection earlier in pregnancy is associated with greater risk of more severe harm to the fetus/neonate.[10,19] It appears that the main sonographic prognostic indicator is fetal cerebral abnormalities.[20] Ultrasound and magnetic resonance imaging (MRI) should be considered as complementary imaging modalities for the investigation of the fetal brain;[21] when both are performed in the third trimester in a fetus known to be infected with CMV, they have a 95% sensitivity for the identification of related central nervous system lesions. When both ultrasound and MRI of the fetal brain are normal prenatally, the neonatal outcome is generally good.[22] Prenatal fetal blood sampling has also been investigated for possible prognostic indicators; both virus-specific markers and nonspecific fetal blood parameters. It has been shown that the mean viral load in the blood of infected neonates is higher in symptomatic neonates compared with asymptomatic neonates ($P = 0.02$).[23] Fabbri et al.[24] examined viral and nonviral fetal blood sample markers in infected fetuses. They found that the best nonviral factors for differentiating symptomatic from asymptomatic congenital infection were beta-2-microglobulin and platelet count, and the best virological markers were fetal IgM and DNAemia.

Prenatal diagnosis of CMV infection is challenging and options for prevention and treatment are limited. In general, the options for 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).[25–28]

5. Prenatal therapy

5.1 Antiviral drugs

In immunocompromised (nonpregnant) women, the antiviral drugs which are licensed for use for CMV infection include ganciclovir, valganciclovir, cidofovir, foscarnet and valaciclovir, but, with the exception of valaciclovir, their teratogenic and toxic effects preclude their use in pregnancy. Two studies have investigated the use of valaciclovir (valacyclovir) in pregnancies with CMV-infected symptomatic fetuses.[25,26] 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%).[29,30] 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.[31] 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.[32,33] Both aciclovir and valaciclovir have limited antiviral activity against CMV.

Jacquemard et al.[25] 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 a decrease in the fetal blood viral load was associated with better outcome. Seven pregnancies resulted in termination, of which six had evidence of progressive disease, and one termination was performed on parental request. Of the 13 live births, ten babies had normal clinical examination at 6 months (with follow-up 6–39 months), two had isolated unilateral SNHL and one had hearing loss, microcephaly and incontinentia pigmenti. 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 pregnancies (10/24) resulted in healthy infants, compared with 71% of healthy infants in those pregnancies that were treated and did not undergo termination.

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)'.[26] 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; see Appendix I). Valaciclovir was associated with a significantly greater proportion of neonates born asymptomatic with treatment (82% with treatment versus 43% without treatment from a historical cohort). This study also provided reassuring safety data for the use of valaciclovir in pregnancy: maternal clinical and laboratory tolerances to this high-dose regimen were excellent, and no adverse neonatal effects were observed. Moreover, adherence to treatment exceeded 90%, despite the requirement to take 16 tablets daily. Nevertheless, these pregnancies should be monitored closely by a fetal medicine expert. 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.

5.2 Hyperimmune globulin (HIG)

The other therapeutic agent that has been investigated is CMV HIG. Nigro et al.[27] 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 (within 6 weeks before enrolment) primary CMV infection and unknown fetal status before 21 weeks of gestation who declined amniocentesis; these women were offered monthly HIG 100 U/kg of maternal weight (the 'prevention group').

In the therapy group, 1/31 (3%) of women who received HIG had neonates with symptomatic CMV disease compared with 7/14 (50%) of women who did not receive the treatment. In the prevention group, 6/37 (16%) of women who received HIG had neonates with congenital CMV infection compared with 19/47 (40%) of women who did not receive treatment. 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.[28] 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 by Nigro et al.,[27] 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 be reserved for use in the research setting. A trial assessing HIG in pregnancy is currently underway and is estimated to conclude at the end of 2018.[34]

6. Management and prevention

A proposal for management of CMV fetal infection is presented in Appendix II.[35]

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. An alternative strategy to reduce the risk of infection is behaviour modification in order to minimise CMV infection during pregnancy. Simple hygiene-based measures that have been shown to reduce the risk of CMV acquisition include handwashing after contact with urine or saliva, and avoiding sharing utensils, drinks or food with young children. However, most of the studies[36–39] which have investigated such measures in pregnancy have been underpowered or nonrandomised. It has been reported that such educational interventions are more likely to be effective during pregnancy than before, probably because pregnant women are more motivated to adhere to these recommendations.[37] In a study[37] of seronegative women with a child younger than 36 months who received preventative information in pregnancy, the seroconversion rate was 1.2% compared to 7.6% in a group of women who did not receive such advice ($P < 0.001$), providing evidence that risk reduction is possible. A study assessing the feasibility of educational intervention to reduce the risk of congenital CMV (Reducing Acquisition of CMV through antenatal Education; RACE-FIT) is currently underway in the UK.[40]

Congenital CMV should be confirmed at birth (e.g. urine or oral swab for CMV PCR within 3 weeks of birth). In neonates with symptomatic congenital CMV infection, postnatal valganciclovir/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.[41,42] The diagnosis and management of congenital CMV in the neonate is beyond the scope of this document and is outlined in other guidance.[43,44] Organisations, such as CMV Action (cmvaction.org.uk) and Antenatal Results and Choices (www.arc-uk.org), can be useful sources of emotional support and information for expectant parents.

7. 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 noncerebral 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.

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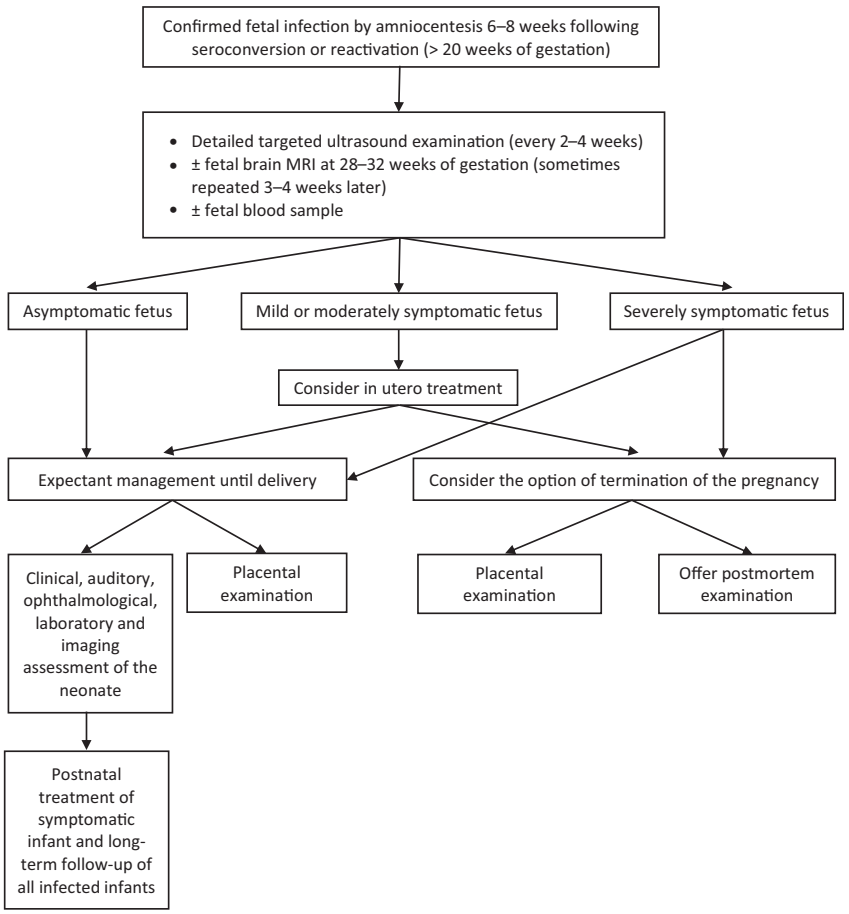
Appendix I: Criteria to define a moderately-infected fetus, according to the inclusion criteria in the study by Leruez-Ville et al.[26]

At least one extracerebral abnormality compatible with fetal CMV infection
Fetal growth restriction
Abnormal amniotic fluid volume
Ascites and/or pleural effusion
Skin oedema
Hydrops
Placentomegaly > 40 mm
Hyperechogenic bowel
Hepatomegaly > 40 mm
Splenomegaly > 30 mm
Liver calcifications
And/or one isolated cerebral abnormality
Moderate isolated ventriculomegaly (< 15 mm)
Isolated cerebral calcification
Isolated intraventricular adhesion
Lenticulostriate vasculopathy
And/or laboratory findings of generalised CMV infection in fetal blood
Fetal viraemia > 3000 copies/ml
Fetal platelet count < 100 000/mm^3

Appendix II: Proposed management of congenital CMV infection (adapted from Benoist et al.[35]).



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