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Scientific Impact Paper

Congenital Cytomegalovirus Infection: Update on Screening, Diagnosis and Treatment

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PLAIN LANGUAGE SUMMARY

Cytomegalovirus (CMV) is the most common cause of viral infection in newborn babies, and affects 1 in 200 of all live born infants in high-income countries; and 1 in 71 in low- and middle-income countries. It is a major cause of hearing loss and brain damage.

Women may get CMV infection for the first time during pregnancy (primary infection) or may experience 'non-primary' infection, either by reactivation of previous CMV infection or by a new infection with a different strain of the virus. The most common source of infection to pregnant women is the saliva and urine of young children. Therefore, all pregnant women, especially those in regular contact with young children, should be informed about hygiene-based measures to reduce the risks, e.g. handwashing.

The UK National Screening Committee recommends against universal antenatal or newborn screening for CMV. Testing for CMV is usually offered only to women who develop symptoms of influenza, glandular fever or hepatitis (liver inflammation) during pregnancy, or for those whom a routine ultrasound scan detects fetal anomalies that suggests possible CMV infection.

The risk of harm to the fetus is greatest following primary CMV infection of the woman in early pregnancy, and appears to be very low following infection after 12 weeks of pregnancy. Babies with CMV infection at birth may have jaundice, a rash, enlarged liver or spleen, a small brain, or be small for their gestational age. Around 1 in 8 babies born with CMV infection will have clinically detectable signs at birth. The rest will not have any features detectable by clinical examination alone. Therefore, all infants with CMV infection at birth should be followed up at a minimum of up to 2 years of age or later, depending upon the disease status, to check hearing and brain development.

Following primary CMV infection in the first 12 weeks of pregnancy, if the woman starts taking the antiviral medicine valaciclovir (valacyclovir) it reduces the risk of the baby becoming infected.

Where CMV infection of the fetus in the womb has been confirmed (by amniocentesis, for example), regular ultrasound scans should be offered every 2–3 weeks until birth. Detailed assessment of the fetal brain is an essential part of these scans. Where maternal CMV infection occurs, but fetal infection is not confirmed, repeated ultrasound scans of the fetus should be offered every 2–3 weeks until birth.

In infected fetuses, as well as ultrasound scans, an MRI scan of the brain should be offered at 28–32 weeks of gestation (and sometimes repeated 3–4 weeks later) to assess for any signs of harm to the fetal brain.

All babies born to women with confirmed or suspected CMV infection should be tested for CMV with a urine or saliva sample within the first 21 days of life.

This is the second edition of this paper. It replaces the earlier edition published in November 2017 under the title *Congenital Cytomegalovirus Infection: Update on Treatment*.

In newborns with symptomatic CMV infection at birth, treatment with antiviral medicine (valganciclovir or ganciclovir) can reduce hearing loss in 5 out of 6 babies, and improve long-term brain development outcomes in some. There is no licensed vaccine for CMV.

1 | Introduction

Cytomegalovirus (CMV), a double-stranded DNA member of the human herpesvirus family, is the most common viral cause of congenital infection, affecting 0.48% of all live born infants in high-income countries and 1.42% in low- and middle-income countries.[1–4] 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 impairment.[5]

This Scientific Impact Paper summarises the issues around screening, diagnosis, prevention and treatment of CMV in pregnancy, utilising the best available evidence, and highlighting recent advances since the previous edition of this paper.

This guidance is for healthcare professionals who care for women, non-binary and trans people. Within this document we use the terms woman and women's health. However, it is important to acknowledge that it is not only women for whom it is necessary to access women's health and reproductive services in order to maintain their gynaecological health and reproductive wellbeing. Gynaecological and obstetric services and delivery of care must therefore be appropriate, inclusive and sensitive to the needs of those individuals whose gender identity does not align with the sex they were assigned at birth.

2 | Epidemiology

CMV infection may be acquired for the first time during pregnancy (primary infection), or women may experience non-primary infection, either by reactivation of prior CMV infection or by a new infection with a different strain of the virus. The most common source of infection to pregnant people is the saliva and urine of young children. Therefore, those who have regular contact with young children are at higher risk of acquiring CMV infection in pregnancy. The majority of women with primary CMV infection will remain asymptomatic.[6] However, a minority (about 10%) experience symptoms similar to those of infectious mononucleosis (glandular fever), including fever, joint aches, malaise, myalgia, cervical lymphadenopathy and, less commonly, hepatitis and pneumonia, but few suffer long-term sequelae.[7] Consistent with other herpesviruses, CMV can remain dormant lifelong at particular sites, primarily in the salivary glands, but can be reactivated at any time, including during pregnancy when shedding of the virus may be common (up to 43% in a meta-analysis).[8] Non-primary CMV infection is generally asymptomatic.

The clinical features of congenital CMV at birth include jaundice, petechial rash, blueberry muffin rash, hepatosplenomegaly, microcephaly and infants born small for gestational age. Around 13% of babies born with congenital CMV infection will have these clinically detectable signs at birth. The other 87% will not have any features detectable by clinical examination alone; therefore, many of these infants 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.[9, 10] Hearing and neurological sequalae are similar in infants following primary and non-primary maternal infection.[11]

Transmission of the virus to the fetus can occur antenatally by the transplacental route, during labour and birth through direct contact with cervicovaginal secretions or blood, or postnatally through breast milk.[12, 13] Transmission is more likely following maternal primary infection in pregnancy than non-primary infection.[14] If a woman has primary CMV in the first trimester, her chances of having a baby born with symptoms is 3.9–5.2%.[15] Following non-primary CMV infection in pregnancy, the risk of congenital infection is lower in the order of 1–2%; however, non-primary infections may account for up to half of symptomatic congenital CMV infections as reported by large registry-based cohorts.[2, 16]

Although CMV transmission from mother to infant is more likely in women with primary infection at the population level, especially in populations with high CMV seroprevalence, the majority (around half to two-thirds) of infants with congenital CMV infection are born to women with pre-existing CMV immunity, i.e. following non-primary infection.[17]

The risk of transmission of virus to the infant and therefore congenital CMV infection varies according to the gestation at which maternal primary infection occurs, as presented in Table 1. Several studies[18, 19] have reported that 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.[7, 20] A prospective study[21] followed 260 newborns for a median of 24 months and found that the proportion of early/late auditory/neurological sequelae was around 30% following maternal primary infection in the periconception period and first trimester, whereas there were no sequelae in fetuses born to women with second or third trimester primary infection. Other studies[19, 22] have reported similar findings. In a meta-analysis conducted by Chatzakis et al. comprising ten studies (up to 2942 fetuses),[23] similar trends of vertical transmission and severe fetal impairments after maternal primary CMV infection in different trimesters were observed (Table 1). However, whether there are other longer-term adverse sequelae resulting from congenital CMV infection in the second or third trimesters is not yet known. Fetuses with later trimester infection should still be monitored for growth restriction and infants should be followed-up for longer-term hearing and neurodevelopmental outcomes.

3 | Diagnosis of Congenital Cytomegalovirus

Serological testing for CMV should be offered to people who present with influenza-like symptoms, or symptoms of glandular

TABLE 1 | Risk of vertical transmission, congenital infection, or fetal defects in primary CMV infection (Adapted from *Chatzakis et al.*[23]

	Transmission rate	Fetal insult* if fetus is infected	Fetal insult if transmission is unknown	Symptomatic at birth if fetus infected	Symptomatic at birth if transmission unknown	SNHL or neurodevelopmental impairment if fetus is infected	SNHL or neurodevelopmental impairment if transmission is unknown
Periconception (between 1 week before and 5 weeks after the LMP)	21% (95% CI, 8.4–33.6)	28.8% (95% CI, 2.4–55.1)	6.0%	1.3% (95% CI, 0–4.5)	0.3%		
First trimester	36.8% (95% CI 31.9–41.6)	19.3% (95% CI 12.2–26.4)	7.1%	9.1% (95% CI 2.7–15.6)	3.3%	22.8% (95% CI 15.4–30.2)	8.4%
Second trimester	40.3% (95% CI 35.5–45.1)	0.9% (95% CI 0–2.4)	0.4%	0.3% (95% CI 0–1.1)	0.1%	0.1% (95% CI 0–0.8)	0%
Third trimester	66.2% (95% CI 58.2–74.1)	0.4% (95% CI 0–1.5)	0.3%	0.4% (95% CI 0–1.6)	0.3%	0% (95% CI 0–2.1)	0%

Abbreviations: LMP, last menstrual period; SNHL, sensorineural hearing loss.
*Fetal insult was defined as infants with symptoms at birth or terminations of pregnancy because of the presence of CMV-associated findings in the central nervous system (CNS) on ultrasonography or magnetic resonance imaging [MRI].

fever (with negative test results for Epstein–Barr virus [EBV]) or symptoms of hepatitis (A, B and C) during pregnancy. Also, for those whose routine ultrasound detects fetal anomalies suggestive of possible CMV infection, such as ventriculomegaly, microcephaly, calcifications, intraventricular synechiae, intracranial haemorrhage, periventricular cysts, cerebellar hypoplasia, cortical anomalies, echogenic bowel, fetal growth restriction/expected fetal weight less than third centile, pericardial effusion, ascites or fetal hydrops.[24]

For other viral infections, such as rubella (also known as German measles), 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 non-primary infection.
- There may be cross-reactivity with IgM because of another viral infection, e.g. EBV.
- IgM may be detected as a result of nonspecific polyclonal stimulation of the immune system.

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.[25] In general, a high avidity index (greater than 60%) is highly suggestive of past (more than 3 months) or non-primary infection, while a low avidity index (less than 30%) is highly suggestive of a recent primary infection (i.e. within the past 3 months).[26] If the avidity index is 30–60% (i.e. grey zone), maternal primary CMV infection cannot be excluded.[27]

The diagnosis of primary CMV infection in pregnancy can be made by one of the following findings:[28]

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 – indicating recent primary infection.

Maternal serology is still the mainstay for the diagnosis of primary maternal infection. Virological tests (polymerase chain reaction [PCR]) of maternal serum or urine correlate poorly with the timing of infection or neonatal outcomes so are less useful in the clinical setting.[6]

Diagnosis of non-primary CMV infection is not possible using serology. A rise in IgG levels does not confirm non-primary infection as this may be as a result of nonspecific polyclonal stimulation of the immune system. In practice, therefore, the only way of confirming non-primary CMV infection (whether reinfection or reactivation) is by invasive testing.

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 PCR,

generally real-time PCR. Detection of CMV DNA in the amniotic fluid/cord blood is diagnostic of fetal infection. Negative PCR does not completely rule out the possibility of congenital infection (the sensitivity is 85–95%) as late transplacental passage has been reported. However, neonates found to be infected at birth following a negative prenatal amniocentesis do not as a rule have sequelae, probably because they were infected after the first trimester.[29] 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 offered, therefore, after at least 17 weeks of gestation when fetal urination is established, and ideally after 20 weeks of gestation.[30, 31] Amniocentesis should also be delayed until 6-8 weeks from the timing of maternal infection in order to avoid a false negative result.[30]

It has been demonstrated that diagnosis of placental infection following maternal primary infection in early pregnancy is possible using PCR amplification of the CMV genome obtained via chorionic villus sampling (CVS).[32] This holds the promise that negative CMV-PCR in the trophoblast after 12 weeks could be used to exclude CMV-related embryopathy leading to sequelae. However, further long-term follow-up studies are required to confirm this hypothesis.

4 | Routine Antenatal Screening for CMV

Universal routine screening for CMV in pregnancy is not recommended as the disease itself, the available screening test and the available treatment do not fulfil the World Health Organization criteria for an effective screening programme.[33] Challenges to routine screening stem from the fact that a high level of symptomatic congenital CMV disease results from maternal non-primary infection, which is not amenable to serological diagnosis. Moreover, the available screening test cannot precisely identify timing of maternal infection, and cannot therefore reliably predict risk of fetal disease. Although there is robust evidence that valaciclovir may be an effective preventative therapy, the data remains limited. Therefore, routine prenatal screening is not yet recommended outside the research setting.[34–36] While serological screening for primary maternal CMV infection is reliable, it is not possible to diagnose non-primary infection using maternal serology. This means that a programme of routine screening would be of value in only around half of CMV cases, i.e. those with primary infection. However, as women who have primary infection in the first trimester represent those at greatest risk of congenital CMV and its sequelae (24-fold and 6-fold higher than in the general population, respectively), these individuals could potentially benefit greatly from such a screening programme.

The window from the detection of maternal CMV viraemia to positive serology (IgM then IgG) appears to be 1–2 weeks.[30] This means that by the time serology is positive, placental/fetal infection may have already occurred. Given that the primary aim of a screening programme is to try to prevent fetal infection, this presents a significant challenge, and it may be that any screening programme would require early and frequent maternal serological testing in the first trimester.

Nevertheless, there have been major advances in this area in more recent years, in particular: (1) the appreciation that significant neonatal sequelae occur only following first trimester infection,[23] so any screening could be focused on that period; and (2) valaciclovir treatment can significantly reduce the risk of congenital CMV and neurological sequelae,[37] bringing the prospect of a routine prenatal screening programme closer. However, the benefit and the cost-effectiveness of such a screening programme would be dependent upon the local epidemiology of CMV infection and would need to be assessed on a national basis.

Congenital CMV should be confirmed at birth (e.g. by urine or saliva swab CMV PCR testing 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.[38] There is evidence that treatment with valganciclovir or ganciclovir can reduce or prevent progression of SNHL in up to 84% of cases, and improve long-term neurodevelopmental outcomes in some infants.[39, 40] The diagnosis and management of congenital CMV in the neonate is beyond the scope of this paper and is outlined in other guidance.[41–43] Organisations such as CMV Action (cmvaction.org.uk) and Antenatal Results and Choices (www.arc-uk.org) are useful sources of emotional support and information for expectant parents.

5 | Prevention and Treatment

A proposal for management of CMV fetal infection is presented in Figure 1.[44]

5.1 | Primary Prevention of CMV Infection

There is no licensed vaccine for CMV. Two randomised controlled trials (RCTs) showed only modest (40–50%) efficacy in reducing the risk of CMV in young women.[45, 46] Candidate vaccines are progressing through clinical trials[47–49] and it is hoped that a vaccine for use in routine clinical practice may become available in the next decade.[50]

An alternative – and complementary – strategy to reduce the risk of CMV infection is behaviour modification in order to minimise direct contact with saliva and urine from other people, particularly from young children. Several studies have shown that hygiene-based measures have the potential to reduce the risk of CMV acquisition.[51] Hygiene-based measures can be summed up in three simple messages:

- Share with care (avoid sharing utensils, drinks or food that has already been tasted by someone else);
- Kiss with care (try to kiss young children on the forehead instead of directly on the lips);
- Wash with care (wash hands after contact with urine or saliva).

An RCT in the UK showed that a film-based antenatal intervention delivered in early pregnancy is acceptable and accessible to pregnant women and results in an increased knowledge about CMV, a change in attitudes towards personal

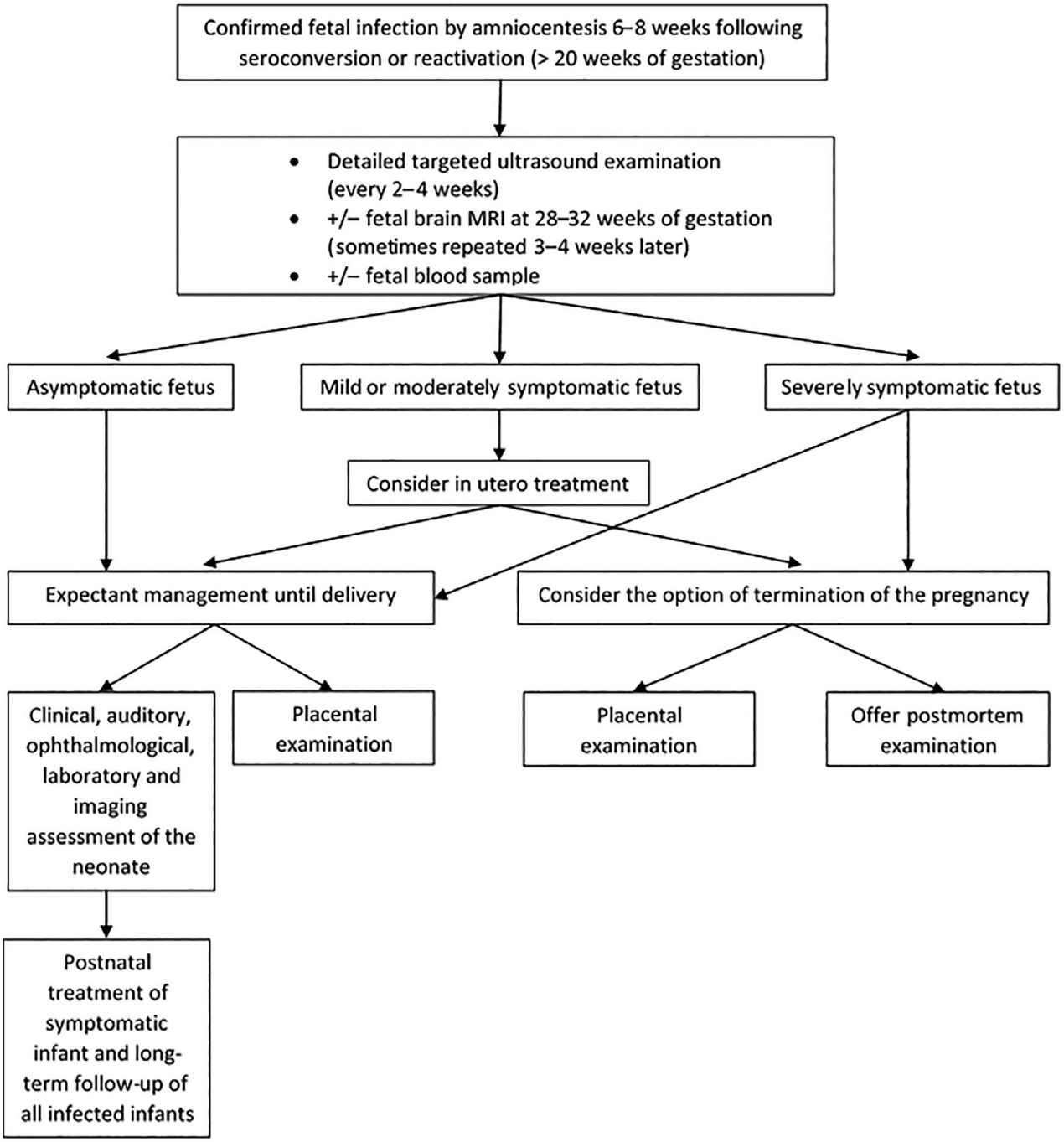

FIGURE 1 | Proposed management of congenital CMV infection (adapted from Benoist et al.[44])

susceptibility and severity, and adoption of risk-reducing behavioural change.[52] Several national and professional bodies recommend that all pregnant people should be offered information in the first trimester about congenital CMV and hygiene measures that could reduce the risk of acquiring CMV infection.[35, 53] However, in most countries, the first pregnancy visit and routine blood tests occur near the end of the first trimester, meaning that behavioural changes are unlikely to be able to reduce this risk. Therefore, efforts should be made to target women planning a pregnancy and at the time of self-referral for antenatal booking to reduce the risk of infection in the first trimester.

5.2 | Secondary prevention of CMV infection

5.2.1 | Antiviral drugs

In immunocompromised (non-pregnant) people, antiviral drugs licensed for use for CMV infection include ganciclovir, valganciclovir, cidofovir, foscarnet and valaciclovir. However, with the exception of valaciclovir, the teratogenic and toxic effects of these drugs preclude their use in pregnancy. Two studies have investigated the use of valaciclovir in pregnancies with CMV-infected symptomatic fetuses.[54, 55] Valaciclovir is a prodrug that is converted in vivo by esterases in the liver into the active drug

aciclovir. Valaciclovir is favoured because it has greater oral bioavailability than aciclovir (55% versus 10–20%).[56, 57] Aciclovir has an excellent safety profile in pregnancy.[58–60] However, both aciclovir and valaciclovir have limited antiviral activity against CMV.

5.2.2 | Valaciclovir for reducing the risk of transplacental transmission

A double-blind controlled trial[37] randomised 90 pregnant women with evidence of primary CMV infection during the periconceptional period and first trimester to valaciclovir 8g/day or placebo. Valaciclovir treatment was associated with a 71% reduction in the rate of fetal infection from 29.8% to 11.1% ($P=0.03$). Interestingly, treatment following primary maternal infection in the first trimester was associated with a reduction in fetal infection (48% versus 22%), but treatment of those infected in the periconceptional period was not (14% versus 8%), possibly because of greater interval between maternal infection and initiation of therapy. In an observational study that used propensity score matching and historical control group, the incidence of congenital CMV infection was 19% in those treated, compared with 44% those who were untreated.[61] Of note, there was no significant difference between the groups following periconceptional maternal primary CMV infection.[61] Moreover, another observational study reported 60% reduction in the risk of transplacental transmission following maternal primary CMV infection in the first trimester.[62] In another small study of 12 women, valaciclovir was discontinued in women who subsequently had a negative amniocentesis. However, new viraemia was noted in three of these women after discontinuation of valaciclovir and one of them gave birth to an infected newborn, highlighting the risk of transmission when valaciclovir is discontinued following a negative amniocentesis. Of note, no cases of symptomatic infection at birth were reported.[63] In an attempt to assess the cost-effectiveness of prenatal serological screening in the first trimester, combined with oral valaciclovir treatment, following maternal primary infection, it was demonstrated that 58–71% of severe cases of congenital CMV cases might have been prevented at a cost of 38 euros (approx. £32) per pregnancy.[64]

In summary, valaciclovir appears to be promising in prevention of fetal CMV infection, although more evidence from larger randomised series is needed. However, given that this drug is most effective in preventing transmission of CMV when started soon after maternal primary infection, universal first trimester maternal serological screening should be kept under review, as only with the implementation of national screening policies will the full potential of secondary prevention be realised.

5.2.3 | Hyperimmune globulin (HIG)

The other therapeutic agent that has been investigated is CMV hyperimmune globulin (HIG). Two RCTs published in 2014 and 2021 investigated the ability of HIG to prevent congenital CMV infection, and included 123 and 394 patients respectively. Both studies failed to demonstrate a reduced incidence of congenital CMV in women treated with HIG.[65, 66]

A study by Kagan et al.[67] in 2019 that used a higher dose of HIG (200 IU/kg compared with 100 IU/kg in other studies) given more frequently (every 2 weeks compared with every 4 weeks) reported a major reduction in fetal transmission compared with a historical untreated cohort (7.5% versus 35.2%, $P<0.0001$). This was not a randomised trial, and the difference may have been because of the higher dose/more frequent regimen, or because the HIG treatment was initiated soon after the presumed primary infection (10 days compared with 35 days for the Revello study,[65] for example). 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.[68–70]

Vlahava et al.[71] investigated the use of human CMV monoclonal antibodies (mAbs). They isolated mAbs from a seropositive donor and optimised them for antibody-dependent cellular cytotoxicity (ADCC), which can activate natural killer cells prior to the production of new virions. Cloned antibodies targeting a single antigen (UL141) were sufficient to mediate ADCC against CMV-infected cells, suggesting a potential future immunotherapeutic strategy against CMV (and other pathogens).

5.3 | Tertiary prevention of CMV infection

5.3.1 | Valaciclovir for treatment of congenital CMV infection

Jacquemard et al.[54] 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 with confirmed congenital CMV infection 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 (lower risk of CMV-related adverse 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, two had isolated unilateral SNHL and one had hearing loss, microcephaly and incontinentia pigmenti. By comparison with a historical control group, of 24 untreated symptomatic CMV-infected fetuses the outcome for 14 (58%) was termination of pregnancy, intrauterine fetal death or severe neonatal infection.[54] The remaining ten (42%) pregnancies resulted in healthy infants, compared with 71% in those who were treated and did not undergo termination.

Treatment with oral valaciclovir 8 g/day has been subsequently studied in a non-randomised phase II open label trial entitled 'In Utero Treatment of Cytomegalovirus Congenital Infection with Valacyclovir (CYMEVAL)'.[55] The median gestational age at the time of infection was 10 weeks and high dose valaciclovir was given for a median of 89 days to pregnant women carrying a moderately-affected fetus, presenting with non-severe ultrasound features (extracerebral ultrasound anomalies and/or mild ultrasound brain anomalies; see Table 2). Treatment with valaciclovir was associated with a significantly greater proportion of neonates born asymptomatic (82% with treatment versus 43% without treatment from a historical cohort). This study also provided reassuring safety and tolerance data for the use of valaciclovir in pregnancy. Nevertheless, these pregnant women would need to

TABLE 2 | Criteria to define a moderately-affected fetus, according to the inclusion criteria in the study by Leruez-Ville et al. (a multicenter, open-label, phase II study to assess the efficacy of valaciclovir for symptomatic CMV infected fetuses).[55]

At least one extracerebral anomaly 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 anomaly	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

Abbreviation: CMV, cytomegalovirus.
*The standard classification of ventriculomegaly is mild/moderate (< 15mm) and severe (≥ 15mm), and 'mild' and 'moderate' would both imply measurements of lateral ventricles < 15mm.

be monitored closely by a fetal medicine expert. Cases of acute renal failure have been reported in pregnancy within weeks of initiating oral valaciclovir therapy, but this resolved within a few days after stopping treatment.[61, 62] A small case series including nine singleton pregnancies and a dichorionic twin pregnancy reported the symptomatic infection rate at birth was 9% and the rate of late sequelae was 9% in those treated with oral valaciclovir.[63] It was demonstrated that this dose of valaciclovir reduced the risk of congenital CMV infection and neonatal sequelae, compared with rates reported in the literature for untreated women.

6 | 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 anomalies and laboratory parameters. There is now strong evidence that, in common with other viral infections in pregnancy, infection in the first trimester is associated with the greatest risk of more severe harm to the fetus/neonate.[19–23, 72] It appears that the main sonographic prognostic indicator is fetal cerebral anomalies.[73] Ultrasound features of congenital infection can appear as late as 12 weeks after maternal infection, so serial ultrasound for the remainder of pregnancy is warranted. Ultrasound and magnetic resonance imaging (MRI) should be considered as complementary imaging modalities for the investigation of the fetal brain;[74] 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. The combined predictive value of normal ultrasound and MRI evaluations after 30 weeks of gestation for an asymptomatic neonate, in fetuses known to be CMV-infected following amniocentesis, is at best 95%.[75] Following maternal primary infection in the first trimester, the combination of ultrasound and MRI at 25–28 weeks had negative predictive value (NPV) of 82% for symptomatic congenital CMV infection at birth.[76] The residual risk of SNHL with normal MRI and ultrasound scan was 17%.[76] In a multicentre study, the rate of structural anomalies detected exclusively by fetal MRI (but missed by ultrasound) was 10.5%.[77] Brain anomalies were detected exclusively at birth and not identified by ultrasound or MRI in 3.8% of fetuses with congenital CMV infection.[77]

Serial prenatal ultrasound plays a role in defining fetal prognosis; however, there is no evidence supporting the use of serial MRI. Serial MRI in fetuses with confirmed CMV infection may show mild changes, graded in one study as grade 1 (normal) or grade 2 (isolated frontal/parieto-occipital hyperintensity), which may not have clinical implications, but may cause unwarranted anxiety to parents.[78] Moreover, the evidence is not clear whether anomalies detected on MRI were truly not detectable on ultrasound scan (most of the studies that reported on additional findings on MRI did not repeat the ultrasound scan after the MRI to confirm that those anomalies were truly not detectable).

Prenatal fetal blood sampling has also been investigated for possible prognostic indicators, both virus-specific markers and non-specific 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 ($P = 0.02$).[79] Fabbri et al.[80] 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. Studies suggest that the platelet count in a fetal blood sample is an independent prognostic indicator of neonatal outcome, and that certain circumstances could justify the risk of fetal loss (in the order of 1–2%) associated with fetal blood sampling.[81] However, this view has proved controversial among clinicians, with some arguing that a 1–2% risk of fetal loss does not justify fetal blood sampling to obtain platelet count, which does not give sufficiently certain information upon which to base decisions.[82]

Prenatal diagnosis of CMV infection is challenging and options for prevention and treatment are limited. The severity of congenital CMV infection could be classified into asymptomatic, mild-to-moderately symptomatic and severely symptomatic (Figure 2).

In general, the options for management of confirmed fetal CMV infection are either conservative, in other words continuation of

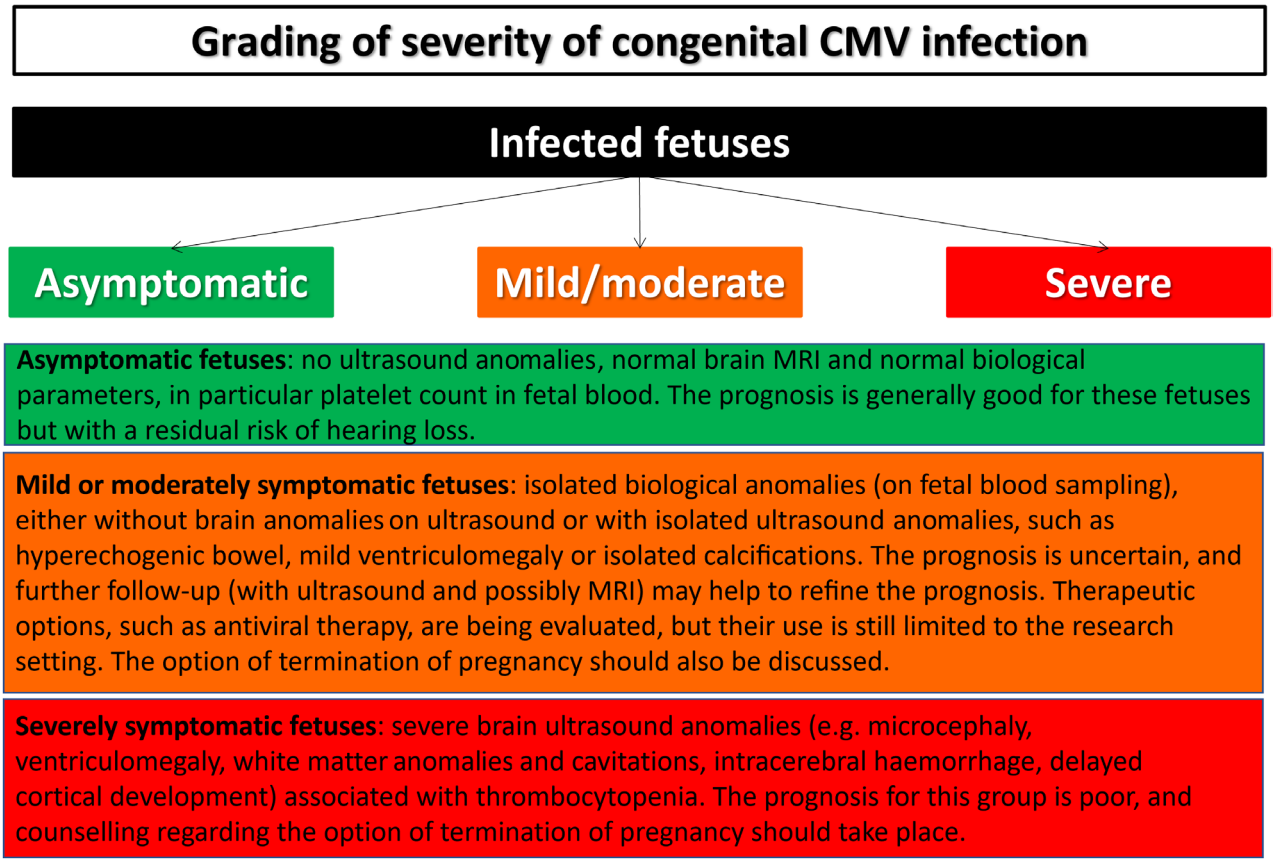

FIGURE 2 | Grading of severity of congenital CMV infection

Note: Fetal blood sampling for platelet count may not be available in all cases and centres.

* The standard classification of ventriculomegaly is mild/moderate (<15mm) and severe (≥15mm), and 'mild' and 'moderate' would both imply measurements of lateral ventricles <15mm.

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 HIG.[37, 54, 55, 65–67, 83]

7 | Opinion

- All pregnant women should be given information about infections such as CMV which can have an impact on the baby in pregnancy or during birth, and measures to mitigate these risks, e.g. by handwashing, in line with national guidance.[35] Efforts should be made to raise awareness among women who may be planning for a pregnancy and those self-referring to pre-conception services.
- The risk of significant neonatal/infant sequelae is greatest following primary maternal CMV infection early in pregnancy and seems to be negligible following maternal CMV infection later than the first trimester. However, longer term studies are needed in order to determine any potential sequalae occurring outside of infancy, therefore all infants with congenital CMV should continue to be followed-up for hearing and neurodevelopmental outcomes.[84]
- Following maternal primary CMV infection in the first trimester, oral valaciclovir treatment may be offered to reduce the risk of transplacental transmission when administered soon after infection.
- National screening recommendations need to be kept under review as new evidence emerges in order that the timely diagnosis, and therefore treatment, can be initiated.
- When fetal CMV infection has been confirmed by amniocentesis, serial ultrasound examination of the fetus should be offered every 2–3 weeks until birth. Detailed assessment of the fetal brain is an essential part of these examinations. When maternal CMV infection occurs, but fetal infection is not confirmed, serial ultrasound examination of the fetus should be performed every 2–3 weeks until birth.
- 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 anomalies, the role of fetal blood sampling to check platelet count should be considered.
- Infected fetuses may be classified into one of three prognostic categories:

    1. *Asymptomatic fetuses*: The prognosis is generally good for these fetuses but with a residual risk of hearing loss. Close monitoring is recommended for signs of progression.

2. *Mild or moderately symptomatic fetuses*: 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. Treatment with oral valaciclovir could be considered on an individual basis after detailed discussion with the parents. The option of termination of pregnancy should also be discussed.
3. *Severely symptomatic fetuses*: The prognosis is poor and counselling regarding the option of termination of pregnancy should take place.

- All infants born to women with confirmed or suspected CMV infection, should be tested for congenital CMV with a urine or saliva sample within the first 21 days of life.
- A birth plan should be documented in the maternal notes detailing the need for clinical examination and investigation.
- Concerted efforts should be made to support research related to maternal and congenital CMV and should be a priority to improve outcomes.

Conflicts of Interest

Full disclosure of interests are available on request.

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