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Recommendations and guidelines for perinatal practice

Guidelines on CMV congenital infection*

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Abstract

Congenital cytomegalovirus (CMV) infection occurs in 0.6–0.7% of all newborns and is the most prevalent infection-related cause of congenital neurological handicap. Vertical transmission occurs in around 30% of cases, but the fetus is not always affected. Symptomatic newborns at birth have a much higher risk of suffering severe neurological sequelae. Detection of specific IgG and IgM and IgG avidity seem to be the most reliable tests to identify a primary infection but interpretation in a clinical context may be difficult. If a seroconversion is documented or a fetal infection is suspected by ultrasound markers, an amniocentesis should be performed to confirm a vertical transmission. In the absence of a confirmed fetal infection with fetal structural anomalies, a pregnancy termination should be discouraged. Fetal prognosis is mainly correlated to the presence of brain damage. Despite promising results with the use of antiviral drugs and CMV hyperimmune globulin (HIG), results have to be interpreted with caution. Pregnant women should not be systematically tested for CMV during pregnancy. Managing CMV screening should be restricted to pregnancies where a primary infection is suspected or among women at high risk. The magnitude of congenital CMV disease and the value of interventions to prevent its transmission or to decrease the sequelae need to be established before implementing public health interventions. In this paper, aspects of CMV infection in the pregnant woman and her infant are reviewed.

Keywords: Amniotic fluid (AF); congenital cytomegalovirus (CMV); polymerase chain reaction (PCR).

Introduction

Human cytomegalovirus (CMV) is an opportunistic pathogen belonging to the herpesviridae family. Like other viruses in this family, it shares properties of latency and reactivation [18, 22, 78]. It is widely distributed and can spread through close interpersonal contact with infected body fluids, usually saliva, urine, blood or genital secretions. It is an endemic infection without seasonal variations.

In immunocompetent adults, primary infection is usually asymptomatic even during the acute stage. Fewer than 5% of pregnant women with primary infection are symptomatic, and an even smaller percentage suffers from a mononucleosis-like syndrome [77]. When symptoms are present, they are usually nonspecific and mild such as persistent low fever, muscle ache and lymph node enlargement. The clinical course of the infection does not seem to be affected by pregnancy. Laboratory tests may disclose atypical lymphocytosis with a slight rise in transaminase levels. Viral shedding occurs several months before the infection reaches the latent phase. Among children, viral shedding usually persists for years after a primary infection. Toddlers in day care constitute an important infectious source.

As occurs with other herpes viruses, CMV remains lifelong at specific sites and the viral replication cycle can

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be reactivated. Secondary infection can occur due to such reactivation or due to infection with a different strain (reinfection) [74, 66]. There is no licensed vaccine to prevent the CMV infection in seronegative individuals. The nature of primary maternal CMV infection makes prenatal counseling of women complicated.

Congenital infection

Congenital CMV infection is the most prevalent infection-related cause of congenital neurological handicap since rubella vaccination has become universal in developed countries [100]. CMV can cause a congenital infection during pregnancy through the placenta, during delivery through cervical secretions or blood and postnatally through breast milk [12]. CMV infection via breast milk in preterm infants is possible with different disease patterns.

The natural history of the disease is incompletely elucidated. CMV infection in pregnant women can be due to a primary infection or a secondary infection (reinfection or viral reactivation) [2].

Overall, congenital CMV seems to occur in one percent of all liveborn babies (excrete CMV in their urine), but many international studies have methodological limitations [1, 15, 35, 37, 48, 85, 90, 109]. The most reliable birth prevalence estimates come from universal screening of all births or a representative sample of births. A review by Kenneson in 2007 [23] found that the overall prevalence of congenital CMV infection in all liveborn infants in industrialized countries is likely to be 0.6–0.7%. These results are consistent with a recent meta-analysis with less restrictive inclusion criteria resulting in a wider dispersion of estimates, which reported an average birth prevalence of 0.65% [45]. This is more precise than the range of 0.2–2.5% often cited in the literature [45, 85, 110]. There is lack of epidemiological data on the magnitude of congenital CMV infection in various countries and worldwide geographic pattern of birth prevalence does not seem to follow a clear distribution (even within and between countries).

Adult seroprevalence in developed countries is around 50%, but in developing countries it may be as high as 90–100%. Three French studies have shown that 43.5–51.5% of pregnant women are seronegative and that 0.6–1.4% of the pregnant women acquire a CMV primary infection during pregnancy [1, 15, 23, 35–37, 45, 48, 85, 90, 109, 110]. These data are similar to those published in other developed countries [37]. The incidence of secondary maternal infections remains poorly documented [17, 71].

Vertical transmission occurs in around 30% [101] of infected mothers. Fetal infection does not equate to an affected fetus. Following fetal infection, the newborn can be symptomatic or not, and if so can develop neurological sequelae [2]. The prognosis of symptomatic infants is very poor, with the vast majority suffering from severe mental impairment and/or hearing loss.

A congenital CMV infection may cause permanent physical sequelae or impairments such as hearing loss, visual impairment, mental retardation or milder cognitive impairment and cerebral palsy (and also death). Damage in the fetal brain seems to be associated with an immune inflammatory response to CMV in the infected brain as well as that of a direct cytopathic effect of the virus on precursor cells of the neuroepithelium [13, 64].

Up to 90% of symptomatic infants will have neurological sequelae and the mortality rate can range from 2 to 30% [16, 75, 102]. Among the moderately symptomatic neonates, 65–75% will develop normally but 25–35% will have some degree of long-term handicap [86].

Among asymptomatic cases at birth, between 5 and 15% cases will also develop long-term developmental abnormalities, several months or years after birth [5, 28, 29], mainly sensorineuro-hearing loss which can be bilateral in up to 50% of cases [28, 80]. Long-term follow-up is essential as some of the major neurological deficits improve with time and other deficits like cognitive, learning disabilities, dyslexia, hyperactivity-inattention syndromes and behavioral difficulties become apparent as children grow older, at school age or later. The incidence and severity of the sequelae are poorly documented, particularly their long-term outcome. They are more serious when CMV infection is symptomatic in the neonate: 25.0% (95% CI: 3.2–65.1) to 43.7% (95% CI: 31.4–56.7) [3, 105] when compared with 8.6% (95% CI: 0–17.8) [3] in asymptomatic newborn infants. The characteristics of the long-term complications after vertical transmission following primary infection or secondary infection are not well known, particularly in the subgroup of asymptomatic infected newborns. Postnatal mortality due to CMV infection varies from 0 to 4.7% [70, 95].

Risks factors for congenital infection

Factors associated with a higher prevalence of CMV congenital infection have been identified but are neither very specific nor very predictive, such as young age and/or unmarried status at the time of the first pregnancy and low socio-economic status [36, 105]. Maternal seroprevalence for CMV increases with maternal age and parity [20]. Studies carried out in the United States have shown that employees in nurseries had a higher risk of seroconversion [69, 76]. The role of profession, however, as risk factor for congenital CMV infection has not been proven.

Primary infection or reinfection

The rate of transmission to infants born to mothers who had a primary infection or a recurrent infection (chronic infection, reactivation or reinfection with a new strain) during pregnancy was 32% and 1.4%, respectively [45].

The risk of severe consequences is much greater when the pregnant women experiences a primary infection [65, 78] and also when CMV infection is acquired in the first half of pregnancy [74]. Nevertheless, it is not universally accepted that *in utero* transmission rate is higher in late pregnancy. No data are available in immunocompromized patients, but the baseline risk of a fetal CMV infection may be higher.

Late congenital infections

It is difficult to study the effect of gestational age on the outcome of congenital CMV because it is often impossible to establish the time of maternal infection and no consistent policies of prenatal screening of CMV seroconversion exist. According to published data, almost all infants with symptomatic congenital infection were exposed in the first half of pregnancy [2, 21, 57, 100], but few cases of congenital disease have been reported following a third-trimester maternal infection, of which the majority had hearing loss [21, 57, 79]. In is unclear whether transmission rate is higher in late pregnancy [32] but it may be as high as 58–77% in late gestation [14, 21, 32, 88]. Revello and Gerna [91] reported transmission rates of 45.4% (49/108), 45.6% (21/46), and 78.6% (11/14) following primary infections in the first, second and third trimesters, respectively. In a recent study by Gindes et al. [32], 28 patients with late (>25 w) CMV infections were described. Vertical transmission was proved in 75% (21/28) of all cases when primary infection was acquired in the third trimester. None of the 20 live infected newborns had symptomatic congenital infection with an average of 33 months. In one case the patient elected to terminate the pregnancy based on CMV DNA detection in amniotic fluid (AF). Therefore, the severity of congenital disease is related inversely to gestational age and is much greater when infection occurs in the first trimester.

Secondary infection

Maternal preconceptional immunity against CMV infection gives relatively good protection to the fetus but the frequency and the severity of fetal infection following secondary maternal infection are poorly documented [111]. A recent study showed that young women who have naturally acquired preconceptional immunity to CMV are 69% less likely to give birth to an infant with congenital CMV infection than are those who are initially CMV seronegative (1% vs. 3%) [30]. Assuming that 70–80% of pregnant women are seropositive prior to conception, over 60% of the infants that were infected *in utero* are born to mothers with preconceptional immunity [74]. It is accepted that most infants of mothers with preconceptional immunity have less severe neonatal symptoms compared with those of mothers with primary infection [11, 30] as <10% will develop postnatal sequelae, mainly sensory neural hearing loss and chorioretinitis [50]. Severe congenital CMV disease and even intrauterine fetal death have been recently reported with secondary infection, however [17, 31, 42]. Secondary or recurrent maternal CMV infection may be an important cause of congenital CMV disease [4].

A study from Israel where usually CMV screening is performed during the first antenatal visit, reports six cases with a sonographically suspected fetal infection in mothers with a past exposure to CMV and no evidence of recent secondary CMV infection [111]. It would seem as maternal serology is not reliable to exclude conclusively congenital CMV infection when sonographic signs are evident.

Diagnosis

Maternal diagnosis

CMV infection occurs with a low rate of symptomatic cases and the symptoms are often non-specific, hence laboratory tests are needed. Diagnostic methods are non-invasive for the mother. ELISA tests are available for the detection of specific IgG and IgM. There is, however, a variability among their diagnostic accuracy (sensitivity, specificity) [87]. Different commercially available kits frequently yield discordant results, limiting their diagnostic value. Agreement between kits varies from 56% to 75% with a sensitivity of between 30% and 88% [51]. Table 1 summarizes the diagnostic tests for maternal CMV infection.

The presence of Anti-CMV IgM antibodies remains a good indicator of acute or recent infection. Nevertheless its presence can be correlated with other circumstances than primary infection: (1) pregnant women can produce IgM during reactivations or reinfections [52]; (2) anti-CMV IgM antibodies can be detected in some pregnant women 6–9 months after the end of the acute phase of primary infection [100]; (3) false positive results are common [51, 55] and may arise in patients with other viral infections (Parvovirus B19, Epstein Barr Virus, etc).

Table 1 Diagnosis of an acute maternal infection.

A) IgG seroconversion (2 consecutive maternal blood samples; the *de novo* appearance of virus-specific IgG in the serum of a pregnant woman who was previously seronegative)
B) Presence of Anti-CMV IgM and igG antibodies
1) IgM may be detected in other circumstances such as:
Reactivations or reinfections
Until more than one year after CMV primary infection
Interference due to rheumatoid factor of the IgM class or cellular antigen
False positive test if other viral infections (B19 Virus, Epstein Barr Virus, etc)
2) Anti-CMV IgG avidity test: if inconclusive results:
Low avidity → recent maternal infection
(threshold differs between virological methods)

The anti-CMV IgG avidity test seems to be the most reliable test to identify primary infection in pregnant women [26, 34, 52, 60]. Low avidity IgG indicates antibodies caused by acute or recent primary CMV infection, whereas high avidity indicates no current or recent primary infection [52]. Its measurement is recommended when IgM is present [7, 25, 34, 35, 53, 54]. Anti-CMV IgG avidity, performed before the 16th–18th week of pregnancy should identify all women who will have an infected fetus/newborn (sensitivity 100%) but after the 20th week, sensitivity seems to be reduced (62.5%) [53]. If a high avidity is found in the first 12–16 weeks of gestation, a recent infection can be ruled out.

When comparing different assays of IgG avidity, sensitivity and specificity for a recent primary CMV infection appeared to be very high [56]. Immunoblot is the gold standard test to confirm the presence of IgM antibodies in serum with a high sensitivity (100%) and specificity (100%) [56].

Nevertheless, no reference test is currently available. These tests are able to determine the serological status of the pregnant woman, and to support the diagnosis of maternal infection within the last three months with the presence of specific IgM, associated with the comparison of serological results in two consecutive maternal blood samples. The tests are technically easy to perform but the absence of standardization and the variability of their results according to the date of maternal infection makes the interpretation difficult especially by non-specialized laboratories. When an infection is suspected, samples should be tested in a reference laboratory for IgG avidity and to perform a specific PCR to reduce diagnostic errors.

Diagnosis of fetal infection

The goal is to diagnose congenital CMV infection and if so, to detect those fetuses which are associated with severe neurological handicap that might be eligible for an indication to terminate pregnancy (TOP) depending on the country's law. Table 2 summarizes the laboratory diagnosis of a fetal infection.

Amniocentesis A maternal CMV infection can be suspected in the three scenarios detailed in Table 2.

Apart of the diagnostic value of this procedure (detection of viral genome or isolation of the virus) the AF has been studied for prognostic evaluation. Indeed, CMV fetal viral load in AF or CMV strain polymorphism have been studied, but none of these two virological parameters seem to identify fetuses who will be symptomatic at birth. The results of the studies are contradictory [8, 33, 59, 81–83].

To diagnose fetal infection, an amniocentesis should then be performed to assess the presence of CMV in AF by PCR (polymerase chain reaction) (sensitivity and specificity, 90–98% and 92–98%, respectively) with respect to viral transmission from mother to fetus [27, 38, 58, 88, 94]. Viral isolation of the CMV virus from the AF is indicative of congenital infection too, but this procedure requires the long viral cultivation on fibroblasts and is less sensitive (70–80%).

Table 2 Laboratory diagnosis of a fetal infection.

Amniocentesis to assess the presence of CMV in the amniotic fluid by PCR
1) Indications:
Pregnant women with clinical signs compatible with a primary CMV infection
Presence of ultrasound abnormalities compatible with a fetal CMV infection
Serologic suspicion of a recent infection after a CMV screening (despite the absence of an indication)
2) When:
$\geq$21st week of pregnancy and $\geq$5–6 weeks after estimated onset of infection
3) Virological method:
PCR in the amniotic fluid (or viral isolation)
4) Result:
Viral DNA is detected: fetal infection is confirmed
No viral DNA detection: infection can be ruled out.
Viral load and strain polymorphism in amniotic fluid: not indicated.
Cordocentesis for fetal infection diagnosis: not indicated.

AF is the most appropriate material [24, 27, 38, 58, 88] and obviates the need for cordocentesis [108]. CMV could potentially be transmitted by antenatal diagnostic procedures by DNA in maternal blood but the risk seems to be small [56, 92]. AF should be sampled after the 21st week of gestation and at least 5–6 weeks after the estimated onset of infection, for several reasons: (1) the virus is only eliminated in fetal urine in sufficient amounts after 6–9 weeks of maternal infection [94], and (2) the risk of a severe fetal infection is higher if contracted early in pregnancy [79], (3) false negative results are common if the amniocentesis is performed earlier. The negative predictive value for fetal infection is almost 100%. A good performance of diagnostic and confirmatory tests as well as correct interpretation and communication of these results to pregnant women may significantly reduce the rate of unnecessary terminations of pregnancy [39].

Fetal blood Fetal blood sampling (FBS) by cordocentesis involves a risk of miscarriage of 0.5–1% and does not give any additional diagnostic value and carries a high risk of fetal demise and therefore, should not be performed. A recent report by Benoist et al. [10] suggests that despite the high procedure related loss rate, FBS should be performed for fetal platelet count determination in fetuses with known CMV infection because of its own independent prognostic value for a bad outcome (including disseminated infection when termination of pregnancy (TOP) have been performed or symptomatic disease in newborns). This should, therefore, be

considered as part of the prognostic evaluation but not for diagnostic purposes.

Ultrasound The goal of prenatal assessment of CMV congenital infection is to identify fetuses that will be symptomatic at birth and will have an abnormal psychomotor development. The most powerful tools to predict an adverse outcome are ultrasound or MRI assessments of fetal anatomy. Ultrasound is a non-invasive technique that discloses structural and/or growth abnormalities caused by CMV infection. Nevertheless, it only identifies around 25% of infected babies [107]. Recently, Guerra et al. [40] have shown that the positive predictive value of ultrasound for symptomatic CMV infection was low (35.29%) for all fetuses exposed *in utero* (maternal infection), and increased (78.26%) for congenitally infected fetuses (proved by the positive AF).

Fetal ultrasound features related to CMV infection are numerous and non-specific. Among these, an abnormal feature in the fetal brain on ultrasound is likely to be predictive of neurologically symptomatic neonates [10, 62, 103].

If a congenital infection is diagnosed, all patients should be screened for brain anomalies such as ventriculomegaly, criteria for visceral disease such as fetal growth restriction, hepato-splenomegaly [97, 98], hyperechogenic bowel, liver calcifications, and ascites. Unfortunately, lesions (especially cerebral) may evolve during pregnancy and may be seen when TOP is no longer possible in certain countries. Cortical developmental disorders will not be seen before 26 weeks, therefore, examinations performed later in gestation might be more diagnostic. Recently, La Torre et al. [49] compared the placental thickness (measured between 16 and 36 weeks of gestation) of 92 women with primary CMV infection during pregnancy and 73 CMV-seropositive pregnant women without primary CMV infection. They reported that primary maternal CMV infection and fetal or neonatal disease are associated with sonographically thickened placentas. More studies are required to confirm this finding.

Magnetic resonance imaging Some studies have shown that MRI may provide additional information in the infected fetus, especially to assess the fetal brain of those with a normal ultrasound, and especially when ultrafast sequences can be performed. Picone et al. [84] reported 46% of brain abnormal findings in 13 infants with a normal ultrasound assessment and in all 14 cases with abnormal brain by ultrasound. Nevertheless, MRI might be misleading before 26 weeks. The number of cases in this study was too small and all cases were evaluated between 24 and 37 weeks' gestation. Despite promising results, no final conclusions can be drawn regarding the use of MRI in CMV-infected fetuses (Table 3). In the high-risk group of proven infected fetuses, MRI could provide a theoretically better assessment of the development of the white matter and the cerebral cortex than does ultrasound because of the poor performance of ultrasound alone [40, 41]. The optimal gestational age to perform MRI is probably around 32–34 weeks.

Neonatal diagnosis and follow-up

A congenitally acquired CMV infection should always be confirmed at birth.

Clinical diagnosis Table 4 describes the outcome of neonates and infants who congenitally acquire CMV infection *in utero*. Around 10% of infected newborns will be symptomatic at birth [28] and the risk of severe sequelae is greater among this group of infants.

Ninety percent of congenitally infected newborns are asymptomatic. About 15% of these infants have progressive hearing loss that is usually unilateral. In addition, some have suggested cognitive sequelae in these children [18].

Infants who are symptomatic (10%) are usually small for gestational age and have hepatomegaly, splenomegaly, thrombocytopenia (petechiae, purpura), jaundice, microcephaly, seizures, abnormal neurologic examination, and feeding problems [55]. Their incidence will vary depending on the time of examination. Brain abnormalities found on CT scan include periventricular cysts and calcifications, ventriculomegaly, vasculitis, hydranencephaly, and neuronal migration abnormalities [34]. Ocular abnormalities include chorioretinitis, retinal scars, optic atrophy, and central vision loss [26]. Sensorineural hearing loss occurs in almost 70% of congenitally infected infants and this condition is almost always progressive. Less commonly, endocrinopathies such as diabetes mellitus or Graves disease have been observed. The presence of microcephaly, intracranial calcifications, or

Table 3 Imaging and CMV congenital infection.

A) Screening of fetal infection = diagnostic value
Ultrasound features related to CMV infection are numerous and non-specific
If structural and/or growth abnormalities are observed, CMV infection can be suspected: maternal serologies should be obtained (if IgG negative, CMV infection can be ruled out) (if igG is positive, amniocentesis for CMV genome detectioncan be proposed)
B) Prediction of an adverse outcome among infected fetuses = prognostic value
Infected fetus with ultrasound abnormalities is at risk to be symptomatic at birth
Fetal brain abnormalities are associated with a high risk for the newborn to be symptomatic
Ultrasound or MRI are the most powerful tools to predict an adverse outcome
Unfortunately, brain examinations are more efficient when performed later in gestation (especially MRI).

Table 4 Newborns with a prenatal CMV infection.

A) Residual prenatal infection
Microcefalia, periventricular calcifications
Poor prognosis, cerebral palsy (90%), cognitive impairment, visual impairment
Perinatal mortality 2–30%
B) Active infection
Sepsis like, thrombocytopenia
Sensorial hearing loss, cognitive impairment, visual impairment (25–35%)
C) Asymptomatic
Sensorial hearing loss 5–15%

other CT abnormalities with chorioretinitis predicts poor neurodevelopmental outcome [18].

Perinatal infection is usually asympmtomatic and usually occurs from three weeks to six months of age but may cause a septic syndrome (hepatomegaly, splenomegaly, lymphocytopenia, neutropenia, thrombocytopenia, elevated liver aminotransferases, and pneumonia). These symptoms appear to be transient and have no effect on neonatal outcome (growth, necrotizing enterocolitis, bronchopulmonary dysplasia) [60].

Laboratory findings Laboratory findings include elevated aminotransferases, direct and indirect serum bilirubin, thrombocytopenia, and hemolytic anemia [55]. Detection of CMV IgG in the neonate is not very helpful in making a diagnosis of congenital infection due to passive transfer of antibody across the placenta. CMV IgM detection in the newborn suggests congenital infection, but usually needs to be confirmed with viral culture [18] or viral PCR in urine. The presence of specific IgM in neonatal serum also confirms a congenital infection, but is only present in 70% of infected babies [89].

The reference method for diagnosing congenital CMV infection involves isolating the virus in cell culture from urine collected within three weeks of birth (urine culture or CMV-DNA testing by PCR) (Table 5). After three weeks, a positive CMV result in urine might well be the consequence of exposure to infected vaginal secretions at delivery, or through breast feeding, or untested transfusions [22]. If virus is isolated from the urine, the infected babies should be monitored. If viral isolation is negative, the baby is considered uninfected and no further tests are required. Infected neonates should be evaluated at 1, 3, 6 and 12 months of age and thereafter annually until school age. Monitoring includes physical, neurological and anthropometric evaluation; neurodevelopmental evaluation; auditory brainstem responses; *ophthalmologic examination*; blood sampling for laboratory tests (complete blood count, platelet count, transaminase level, direct and indirect bilirubin levels); and urine sampling for virus isolation. CMV-infected offspring should undergo an extended follow-up to identify sequelae with delayed onset.

Table 5 Postnatal diagnosis and follow-up.

Congenitally infection should be confirmed at birth within three weeks
Test: Urine culture or CMV-DNA testing by PCR If infection is confirmed: classify according to the presence or absence of clinical and laboratory abnormalities as symptomatic or asymptomatic Follow-up: 1, 3, 6 and 12 months of life and annually until school age to (detection of sequela with delayed onset).
Monitoring: Physical, neurological and anthropometric evaluation: Neurodevelopmental evaluation, auditory brainstem responses; *fundus oculi*; Laboratory tests: Complete blood count, platelet count, transaminase level, bilirubin levels (direct and indirect) Urine sampling for virus isolation.
If a symptomatic infection diagnosed later in the neonatal period: CMV-PCR can be performed on blood adsorbed on Guthrie cards, collected at birth can be used to reassess fetal status at birth.

CMV genome detection using PCR on blood adsorbed on Guthrie cards (dried blood spot), collected at birth for neonatal screening for metabolic and hereditary diseases seems to be a sensitive and specific test for late diagnosis of congenital CMV infection [99]. Vauloup-Fellous et al. [106] reported high sensitivities and specificities of real-time PCR on dried blood spots; respectively, 94.7–100% and 97.3–94.7% in relation with the virological method used. Nevertheless, the authors observed a lesser detection threshold for real time PCR in blood spots than in urine samples. It can be of great value when there is a strong clinical suspicion of congenital CMV infection [9]. Tests for viral DNA using neonatal blood dried on paper could be used to better understand and monitor the true burden of congenital CMV but also to identify delayed onset sequelae such as sensorineural deafness, abnormalities of cortical development, neonatal cholestasis [9].

Management options

Currently, no therapeutic options are available except for clinical trials. Several promising options have been described.

Hyperimmune globulin

In the pregnant woman with primary CMV infection, the use of CMV-specific immune globulin, though still investigational, is gathering attention and may prove to be a valuable therapy [96]. To date, preliminary results on treatment of CMV congenital infection during pregnancy are available from two studies. Nigro et al. [72] published the retrospective results of a non-randomized clinical trial

using intravenous CMV hyperimmune globulin (HIG) for CMV maternal primary infection. In a first group of 45 infected women with a CMV positive amniocentesis (treatment group), 31 were given 1–3 infusions of 200 UI of HIG while 14 elected not to have the treatment. In the 31 treated women, only one delivered an infant with CMV disease whereas 7 of 14 non-treated women delivered severely symptomatic infants with neurological involvement. In a second group ("preventive group"), 37 women with primary infection received 100 U of HIG monthly until delivery and 65 did not. The main outcome criterion in this second group was the proportion of infected newborns. Sixteen percent of the treated women compared to 40% of untreated women delivered an infected baby ($P = 0.02$). Considering this protocol and results, several remarks can be made. In the first part of the study, the rate of severe infection with neurological involvement in the infants of the 14 non-treated women (50%) was surprisingly high compared to the 10% of severe infection usually reported in the literature. Even more surprising, 14 infected fetuses with ultrasound abnormalities including ventriculomegaly, ascites, hepatosplenomegaly, intrauterine growth retardation, liver and bowel hyperechogenicity and periventricular echodensities, seemed to have completely recovered following HIG administration. In the second part of the study, vertical transmission was 16% and 40% with and without treatment, respectively.

A more recent publication by the same group reported the regression of fetal cerebral abnormalities by primary CMV infection following hyperimmunoglobulin therapy in three patients. Their sensorial, mental and motor development at follow-up was normal at 4, 4.7, and 7 years of age. In contrast, the two infants born of untreated mothers had signs and symptoms of severe CMV cerebropathy [73].

Moxley et al. [67] also reported a case of fetal hydrops that resolved after maternal and fetal intravenous administration of CMV HIG. These results have to be interpreted with caution and highlight the necessity of evaluating further this therapeutic option. Although antiviral drugs are commonly used for prophylaxis of CMV disease in recipients of solid organ transplants, currently there are no indications for IgG as prophylaxis for CMV disease in recipients of solid organ transplants [43].

Antiviral treatments

Treatment options for fetal CMV are limited. A number of antiviral drugs are active against CMV. Three of them (ganciclovir, cidofovir and foscarnet) are licensed to treat immunocompromised patients. Nevertheless, all these drugs have common limitations that are clinically relevant such as toxicities, drug-drug interactions, poor bioavailability and the development of drug resistance. Currently, potential teratogenic effects and well known toxicity of available drugs do not support their use in pregnancy. The development of new anti-CMV compounds to treat the infected immunocompromised patient are currently at different stages of trial, several of these compounds are very promising in term of efficacy and toxicity. It will be long before they can be tested for treatment of congenital CMV infection.

Aciclovir (ACV) and its pro-drug Valaciclovir (VACV) are active against CMV. Even if its use in pregnant women is not licensed, ACV was given for more than 20 years to pregnant women for herpes simplex infection without any significant reported side effects. Jacquemard et al. [44], recently reported the results of a prospective pilot trial of oral VACV in fetuses infected by CMV. Twenty pregnancies including 21 fetuses were treated at 28 weeks (median, range: 22–34) for 7 weeks (median, range: 1–12). Pregnancies with confirmed fetal CMV infection (positive PCR in AF) were treated with oral VACV (8 g/day). Data were compared with an untreated group of 24 infected fetuses. In both groups, the outcome was recorded. To establish the pharmacokinetic features of the drug, fetal viral load and drug concentrations were monitored in AF and in fetal blood (FB) as well as therapeutic concentrations in maternal and FB. AF and FB sampling were performed at 26 weeks (SD ± 3 weeks) and controlled at 32 weeks (SD ± 3 weeks). The viral load in FB decreased significantly after 1–12 weeks of treatment ($P = 0.02$). Among the 21 fetuses in the treated group, 10 are developing normally at between one and five years of age. Two infants (both 2 years) had severe isolated unilateral deafness. One neonate presented with microcephaly and severe deafness but was also diagnosed with *incontinentia pigmenti*. Six out of seven cases that eventually requested TOP had evidence of *in utero* progression of the disease with worsening cerebral lesions. One fetus died *in utero*. Overall, the outcome was unfavorable in 11/21 (52.4%) treated fetuses vs. 14/24 (58.3%) in untreated fetuses, who had either TOP, intrauterine fetal demise (IUFD) or severe congenital infection; the remaining 10 infants remained healthy at follow-up. These preliminary results suggest that VACV could be considered in cases where TOP is declined, and perhaps indicated for infected fetuses without abnormalities at cerebral imaging. A randomized controlled trial to study this treatment option has recently been accepted by the French public health authorities and is being conducted.

Table 6 summarizes *in utero* treatment options for infected fetuses. Globally, several potential interventions have been proposed for congenital CMV, such as hygiene education to prevent primary infection among pregnant women [19], prenatal maternal screening to identify candidates for HIG [72] or antiviral therapies [61], and newborn screening for early diagnosis of delayed hearing loss [29] or treatment with antiviral therapy [46]. These public health interventions, however, are seldom implemented due to concerns about safety, effectiveness, or cost-effectiveness, and due to lack of awareness

Table 6 *In utero* treatment options for infected fetuses.

If a fetal infection is confirmed: careful risk assessment of the risk of long of permanent sequela and different options should be discussed
Abnormalities on ultrasound or MRI No present → low risk of sequela. TOP not indicated Present → TOP should be offered if in accordance with local laws
If TOP can only be performed until the 22–24 week: inform patient on the risk of long-term sequela despite the absence of abnormal imaging
Antivirals and intravenous CMV hyperimmune globulin: very promising but results have to be interpreted with caution. Currently their use not is not recommended outside randomized controlled trials.

about the magnitude of the burden of congenital CMV disease.

Termination of pregnancy

When a fetal symptomatic infection is diagnosed and confirmed, the patient should be carefully assessed for the risk of long permanent sequela and different management options should be discussed. If local laws permit, TOP might be offered. When local laws only authorize TOP up to the 22–24 weeks, the patient should be informed on the risk of long-term sequelae despite the absence of abnormal imaging.

Neonatal treatment

The newborn infant can be treated when prenatal CMV infection is recognized. Newborn infant, preterm or term, can be treated when there is an active clinical infection (sepsis like) and, especially, persistent thrombocytopenia. Treatment of acquired asymptomatic congenital or perinatal acquired CMV infection in the newborn is not currently recommended. Treatment of those with symptomatic infection remains controversial, but may be of benefit in the short-term (viral sepsis-like syndrome caused by CMV, pneumonia, severe refractory thrombocytopenia) [25], and long-term (sensorial hearing loss, microcephaly) [7, 54]. The most effective option for the treatment of life- or sight-threatening CMV disease at any age is the nucleoside-analog ganciclovir. For the newborn with congenital CMV infection, the value of ganciclovir appears to preserve hearing; other improvements in overall neurodevelopmental status are inferred but remain to be proven [98]. Although doses of ganciclovir have ranged from 6 to 12 mg/kg/dose, 6 mg/kg per dose every 12 h intravenously for six weeks appears to be effective [53]. Intravenous ganciclovir administered for six weeks improves hearing outcomes in infants with symptomatic congenital cytomegalovirus (CMV) disease involving the central nervous system. The median dose of oral valganciclovir is 16 mg/kg. Neutropenia developed in 38% of subjects. Valganciclovir oral solution provides plasma concentrations of ganciclovir comparable to those achieved with administration of intravenous ganciclovir [47, 68].

Prevention

Prevention is difficult because the virus is ubiquitous and infection is common. Development of a CMV vaccine is one of the highest health priorities, but availability of a licensed vaccine to prevent CMV infection in seronegative individuals is not imminent [6].

Primary infection

The nature of primary maternal CMV infection complicates prenatal counseling. Pregnant women at risk of acquiring CMV may be counseled on how CMV may be transmitted and on hygienic measures that could be implemented. Although very controversial, there are some practices that might minimize the risk for congenital infection. Seronegative women of childbearing age should be aware of prevention measures including [4, 53, 56]: 1) good hand washing with soap and water after contact with diapers or oral secretions, 2) evaluate women for CMV who develop a mononucleosis-like illness during pregnancy, 3) female are taking cares who of infants or children should be educated concerning CMV, 4) susceptible non-pregnant women working with infants or children should not routinely be transferred to other work situations, 5) pregnant women working with infants and children should be informed of the risk of acquiring CMV, 6) routine laboratory testing for CMV antibody in female workers is not recommended but can be performed to determine immune status.

The prevention behaviors (i.e., hand washing, not sharing drinking glasses or eating utensils with young children, and not kissing young children on the mouth) appear to be generally acceptable. These are prevention behaviors that have the potential to substantially reduce CMV-related permanent disability in children. However, results suggest that few women are aware of CMV or of these prevention behaviors [93].

CMV can also be transmitted by sexual intercourse but the role of seropositive or seroconverting partners has also to be elucidated [63].

Should pregnant women be screened for CMV?

Before implementing a screening program for CMV during pregnancy, its feasibility, acceptability by the target population and benefit-risk should be assessed. The aim of antenatal screening would be to decrease the incidence of the serious complications caused by congenital CMV infection in infected infants. Systematic screening

of the pregnant women could lead to: (I) anxiety, (II) an increased number of amniocentesis and therefore of miscarriages, (III) an unjustified number of termination of pregnancies (TOP) that would be performed even in the absence of a bad prognosis such as ultrasound markers. TOP may be restricted in some countries after certain weeks of pregnancy and such policy may be difficult to undertake.

Updated estimates of the impact of congenital CMV are needed for increased awareness of the true burden of congenital CMV infection and disease, allocation of public health resources, and determination of the cost-effectiveness or cost-benefit of potential interventions [45]. No evaluation of the cost of a systematic CMV screening policy is available. The absence of a consensual algorithm in the management of these cases makes any estimate even more difficult.

Currently, no country performs systematic screening for CMV infection among pregnant women as universal screening for CMV primary infection is not recommended. Nevertheless in certain areas, largely uncontrolled serologic screening is increasingly performed with the objective of prenatal diagnosis. However, the appropriateness of screening for CMV infection in pregnant women is controversial. Most primary infections are asymptomatic (up to 90%), it is difficult to establish fetal/neonatal prognosis and there are no well established preventive measures as well as curative treatment of fetal infection.

Things to avoid include: 1) recovery of CMV from the cervix or urine of women at or before delivery does not require a cesarean section, 2) the benefits of breastfeeding far outweigh the minimal risk of acquiring CMV from breastfeeding mother, and 3) although preliminary data suggest the potential benefit of IVIG to prevent congenital CMV infection, the study was not randomized or controlled and did not evaluate the financial, logistic, and clinical (false positive) problems associated with screening of a large obstetrical population.

Perinatal infection

Preterm infants below 1000 g and 30 weeks may be at high risk of acquiring a symptomatic CMV infection. There are some practices that may minimize this risk for perinatal infection. Most nurseries provide CMV seronegative or leukocyte reduced blood products to newborns. No evidence has yet been found in preterm neonates for sequelae related to CMV infection acquired via breast milk. The administration of fresh breast milk to very premature neonates who constitute a population at risk is controversial [104]. Pasteurization and freezing breast milk at -20° may reduce or eliminate the viral load and the transmission of CMV in human milk, although it may also reduce some of its benefits [104].

Conclusions and perspectives

Congenital CMV infection is the most prevalent infection-related cause of congenital neurological handicap. Overall, prevalence of congenital CMV infection in all liveborn infants in industrialized countries is likely to be 0.6–0.7%. Vertical transmission occurs in around 30% but the fetus is not always affected. If the newborn is symptomatic at birth, prognosis is poorer and a high risk of severe neurological sequelae exists. The majority of severe cases develop after a maternal primary infection during the first half of pregnancy. Nevertheless, late congenital infections and even secondary infections may cause permanent sequelae but are much less severe. A maternal infection is confirmed if an IgG seroconversion is documented in two consecutive blood samples. Anti-CMV IgG avidity test may add some benefit if results are inconclusive.

If a seroconversion is documented or a fetal infection is suspected by ultrasound markers, women should undergo an amniocentesis to evaluate if a congenital infection has occurred. The test should be performed at least after 21–22 weeks of pregnancy and a positive test is associated with a likely primary infection that occurred at least six weeks earlier. A congenitally acquired CMV infection should be confirmed at birth (presence of CMV in urine).

Diagnosis and management of fetal infection is complex and should be performed by a multidisciplinary team or in a specialized Unit of Fetal Medicine. Currently, this diagnosis involves primarily the assessment of fetal prognosis and the question of termination of an infected/affected fetus. In the absence of a confirmed fetal infection, a pregnancy termination should then be discouraged.

If a congenital infection is confirmed, fetal prognosis is difficult to establish. Serial ultrasound examinations should be performed to assess mainly the presence of brain damage.

Current treatment options for fetal CMV are very limited. Despite promising results with antiviral drugs and CMV HIG, they have to be interpreted with caution. The potential teratogenic effect and toxicity of the current available drugs do not support their use in pregnancy.

Pregnant women should not be systematically tested for CMV during pregnancy. Managing CMV screening should be restricted to pregnancies where a primary infection is suspected (maternal clinical signs or fetal ultrasound markers) or among women at high risk (day care centers, immunocompromised patients: HIV, solid organ transplant, etc.),

The real magnitude of the burden of congenital CMV disease and the value of interventions to prevent congenitally acquired CMV or to decrease the sequelae should be established before implementing public health interventions.

References

[1] Ahlfors K, Ivarsson SA, Johnsson T, Svanberg L. Primary and secondary maternal cytomegalovirus infections and their relation to congenital infection. Analysis of maternal sera. Acta Paediatr Scand. 1982;71:109–13.

[2] Ahlfors K, Forsgren M, Ivarsson SA, Harris S, Svanberg L. Congenital cytomegalovirus infection: on the relation between type and time of maternal infection and infant's symptoms. Scand J Infect Dis. 1983;15:129–38.

[3] Ahlfors K, Ivarsson SA, Harris S, Svanberg L, Holmqvist R, Lernmark B, et al. Congenital cytomegalovirus infection and disease in Sweden and the relative importance of primary and secondary maternal infections. Preliminary findings from a prospective study. Scand J Infect Dis. 1984;16:129–37.

[4] Ahlfors K, Ivarsson SA, Harris S. Secondary maternal cytomegalovirus infection – A significant cause of congenital disease. Pediatrics. 2001;107:1227–8.

[5] Anderson KS, Amos CS, Boppana S, Pass R. Ocular abnormalities in congenital cytomegalovirus infection. J Am Optom Assoc. 1996;67:273–8.

[6] Arvin AM, Fast P, Myers M, Plotkin S, Rabinovich R. Vaccine development to prevent cytomegalovirus disease: report from the National Vaccine Advisory Committee. Clin Infect Dis. 2004;39:233–9.

[7] Baccard-Longere M, Freymuth F, Cointe D, Seigneurin JM, Grangeot-Keros L. Multicenter evaluation of a rapid and convenient method for determination of cytomegalovirus immunoglobulin G avidity. Clin Diagn Lab Immunol. 2001;8:429–31.

[8] Barbi M, Binda S, Caroppo S, Primache V, Dido P, Guidotti P, et al. CMV gB genotypes and outcome of vertical transmission: study on dried blood spots of congenitally infected babies. J Clin Virol. 2001;21:75–9.

[9] Barbi M, Binda S, Primache V, Caroppo S, Didò P, Guidotti P, et al. Cytomegalovirus DNA detection in Guthrie cards: a powerful tool for diagnosing congenital infection. J Clin Virol. 2000;17:159–65.

[10] Benoist G, Salomon LJ, Jacquemard F, Daffos F, Ville Y. The prognostic value of ultrasound abnormalities and biological parameters in blood of fetuses infected with cytomegalovirus. Br J Obstet Gynaecol. 2008;115:823–29.

[11] Benshushan A, Brezenzinki A, Ben-David A, Nadjari M. Early recurrent CMV infection with severe outcome to the fetus. Acta Obstet Gynecol Scand. 1998;7:694–5.

[12] Bhide A, Papageorghiou AT. Managing primary CMV infection in pregnancy. Br J Obstet Gynaecol. 2008;115: 805–7.

[13] Bissinger AL, Sinzger C, Kaiserling E, Jahn G. Human cytomegalovirus as a direct pathogen: correlation of multiorgan involvement and cell distribution with clinical and pathological findings in a case of congenital inclusion disease. J Med Virol. 2002;67:200–6.

[14] Bodeus M, Hubinnont C, Goubau P. Increased risk of cytomegalovirus transmission in-utero during late gestation. Obstet Gynecol. 1999;93:658–60.

[15] Bodeus M, Hubinont C, Goubau P. Increased risk of cytomegalovirus transmission in utero during late gestation. Obstet Gynecol. 1999;93:658–60.

[16] Boppana SB, Pass RF, Britt WJ, Stagno S, Alford CA. Symptomatic congenital cytomegalovirus infection: neonatal morbidity and mortality. Pediatr Infect Dis J. 1992; 11:93–9.

[17] Boppana SB, Fowler KB, Britt WJ, Stagno S, Pass RF. Symptomatic congenital cytomegalovirus infection in infants born to mothers with preexisting immunity to cytomegalovirus. Pediatrics. 1999;104:55–60.

[18] Burny W, Liesnard C, Donner C, Marchant A. Epidemiology, pathogenesis and prevention of congenital cytomegalovirus infection. Expert Rev Anti Infect Ther. 2004; 2:881–94.

[19] Cannon MJ, Davis KF. Washing our hands of the congenital cytomegalovirus disease epidemic. BMC Public Health. 2005;5:70.

[20] Chandler SH, Alexander ER, Holmes KK. Epidemiology of cytomegaloviral infection in a heterogeneous population of pregnant women. J Infect Dis. 1985;152:249–56.

[21] Daiminger A, Bäder U, Enders G. Pre- and periconceptional primary cytomegalovirus infection: risk of vertical transmission and congenital disease. Br J Obstet Gynaecol. 2005;112:166–72.

[22] Demmler GJ. Congenital cytomegalovirus infection. Semin Pediatr Neurol. 1994;1:36–42.

[23] Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. Rev Med Virol. 2007;17:355–63.

[24] Donner C, Liesnard C, Brancart F, Rodesch F. Accuracy of amniotic fluid testing before 21 weeks' gestation in prenatal diagnosis of congenital cytomegalovirus infection. Prenat Diagn. 2004;14:1055–9.

[25] Eggers M, Metzger C, Enders G. Differentiation between acute primary and recurrent human cytomegalovirus infection in pregnancy, using a microneutralization assay. J Med Virol. 1998;56:351–8.

[26] Eggers M, Bader U, Enders G. Combination of microneutralization and avidity assays: improved diagnosis of recent primary human cytomegalovirus infection in single serum sample of second trimester pregnancy. J Med Virol. 2000;60:324–30.

[27] Enders G, Bäder U, Lindemann L, Schalasta G, Daiminger A. Prenatal diagnosis of congenital cytomegalovirus infection in 189 pregnancies with known outcome. Prenat Diagn. 2001;21:362–77.

[28] Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. N Engl J Med. 1992;326:663–7.

[29] Fowler KB, Dahle AJ, Boppana SB, Pass RF. Newborn hearing screening: will children with hearing loss caused by congenital cytomegalovirus infection be missed? J Pediatr. 1999;135:60–4.

[30] Fowler KB, Stangno S, Pass RF. Maternal immunity and prevention of congenital cytomegalovirus infection. J Am Med Assoc. 2003;289:1008–11.

[31] Gaytant MA, Rours JR, Steengers AP, Galama J, Semmekrot BA. Congenital cytomegalovirus infection after recurrent infection: case reports and review of the literature. Eur J Pediatr. 2003;162:248–53.

[32] Gindes L, Teperberg-Oikawa M, Sherman D, Pardo J, Rahav G. Congenital cytomegalovirus infection following primary maternal infection in the third trimester. Br J Obstet Gynaecol. 2008;115:830–5.

[33] Gouarin S, Gault E, Vabret A, Cointe D, Rozenberg F, Grangeot-Keros L, et al. PCR quantification of human cytomegalovirus DNA in amniotic fluid samples from

mothers with primary infection. J Clin Microbiol. 2002; 1767–72.
[34] Grangeot-Keros L, Mayaux MJ, Lebon P, Freymuth F, Eugene G, Stricker R, et al. Value of cytomegalovirus (CMV) IgG avidity index for the diagnosis of primary CMV infection in pregnant women. J Infect Dis. 1997;175:944–6.
[35] Grangeot-Keros L, Simon B, Audibert F, Vial M. Should we routinely screen for cytomegalovirus antibody during pregnancy? Intervirology. 1998;41:158–62.
[36] Gratacap-Cavallier B, Morand P, Dutertre N, Bosson JL, Baccard-Longère M, Jouk PS, et al. Cytomegalovirus infection in pregnant women. Seroepidemiological prospective study in 1,018 women in Isere. J Gynecol Obstet Biol Reprod (Paris). 1998;27:161–6.
[37] Griffiths PD, Campbell-Benzie A, Heath RB. A prospective study of primary cytomegalovirus infection in pregnant women. Br J Obstet Gynaecol. 1980;87:308–14.
[38] Guerra B, Lazzarotto T, Quarta S, Lanari M, Bovicelli L, Nicolosi A, et al. Prenatal diagnosis of symptomatic congenital cytomegalovirus infection. Am J Obstet Gynecol. 2000;183:476–82.
[39] Guerra B, Simonazzi G, Banfi A, Lazzarotto T, Farina A, Lanari M, et al. Impact of diagnostic and confirmatory tests and prenatal counseling on the rate of pregnancy termination among women with positive cytomegalovirus immunoglobulin M antibody titers. Am J Obstet Gynecol. 2007;196:221e1–6.
[40] Guerra B, Simonazzi G, Puccetti C, Lanari M, Farina A, Lazzarotto T, et al. Ultrasound prediction of symptomatic congenital cytomegalovirus infection. Am J Obstet Gynecol. 2008;198:380.e1–7.
[41] Guerra B, Simonazzi G, Puccetti C, Lanari M, Farina A, Lazzarotto T, et al. Ultrasound prediction of symptomatic congenital cytomegalovirus infection. Am J Obstet Gynecol. 2008;198:380.e1–7.
[42] Henrich W, Meckies J, Dudenhausen JW, Vogel M, Enders G. Recurrent cytomegalovirus infection during pregnancy: ultrasonographic diagnosis and fetal outcome. Ultrasound Obstet Gynecol. 2002;19:608–11.
[43] Hodson EM, Jones CA, Strippoli GF, Webster AC, Craig JC. Immunoglobulins, vaccines or interferon for preventing cytomegalovirus disease in solid organ transplant recipients. Cochrane Database Syst Rev. 2007;2.
[44] Jacquemard FYM, Picone O, Costa JM, Romand S, Jacz-Aigrain E, Daffos F, et al. Cytomegalovirus intrauterine infection: pharmacokinetics of valacyclovir administration to the mother and changes in DNA viral load in amniotic fluid and fetal blood. Br J Obstet Gynaecol. 2007;114:1113–21.
[45] Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol. 2007;17:253–76.
[46] Kimberlin DW, Lin CY, Sánchez PJ, Demmler G, Dankner W, Shelton M, et al. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: a randomized, controlled trial. J Pediatr. 2003;143:16–25.
[47] Kimberlin DW, Acosta EP, Sánchez PJ, Sood S, Agrawal V, Homans J, et al. Pharmacokinetic and pharmacodynamic assessment of oral valganciclovir in the treatment of symptomatic congenital cytomegalovirus disease. J Infect Dis. 2008;197:836–45.
[48] Kumar ML, Nankervis GA, Jacobs IB, Ernhart CB, Glasson CE, McMillan PM, et al. Congenital and postnatally acquired cytomegalovirus infections: long-term follow-up. J Pediatr. 1984;104:674–9.
[49] La Torre R, Nigro G, Mazzocco M, Best AM, Adler SP. Placental enlargement in women with primary maternal cytomegalovirus infection is associated with fetal and neonatal disease. Clin Infect Dis. 2006;43:994–1000.
[50] Lagasse N, Dhooge I, Govaert P. Congenital CMV – infection and hearing loss. Acta Otorhinolaryngol Belg. 2000;54:431–6.
[51] Lazzarotto T, Brojanac S, Maine GT, Landini MP. Search for cytomegalovirus-specific immunoglobulin M: comparison between a new western blot, conventional western blot, and nine commercially available assays. Clin Diagn Lab Immunol. 1997;4:483–6.
[52] Lazzarotto T, Spezzacatena P, Pradelli P, Abate DA, Varani S, Landini MP. Avidity of immunoglobulin G directed against human cytomegalovirus during primary and secondary infections in immunocompetent and immunocompromised subjects. Clin Diagn Lab Immunol. 1997;4: 469–73.
[53] Lazzarotto T, Varani S, Spezzacatena P, Gabrielli L, Pradelli P, Guerra B, et al. Maternal IgG avidity and IgM detected by blot as diagnostic tools to identify pregnant women at risk of transmitting cytomegalovirus. Viral Immunol. 2000;13:137–41.
[54] Lazzarotto T, Galli C, Pulvirenti R, Rescaldani R, Vezzo R, La Gioia A, et al. Evaluation of the Abbott AxSYM cytomegalovirus (CMV) immunoglobulin M (IgM) assay in conjunction with other CMV IgM tests and a CMV IgG avidity assay. Clin Diagn Lab Immunol. 2001;8:196–8.
[55] Lazzarotto T, Gabrielli L, Lanari M, Guerra B, Bellucci T, Sassi M, et al. Congenital cytomegalovirus infection: recent advances in the diagnosis of maternal infection. Hum Immunol. 2004;65:410–5.
[56] Lazzarotto T, Guerra B, Lanari M, Gabrielli L, Landini MP. New advances in the diagnosis of congenital cytomegalovirus infection. J Clin Virol. 2008;41:192–7.
[57] Liesnard C, Donner C, Brancart F, Gosselin F, Delforge ML, Rodesch F. Prenatal diagnosis of congenital cytomegalovirus infection: prospective study of 237 pregnancies at risk. Obstet Gynecol. 2000;95:881–8.
[58] Lipitz S, Yagel S, Shalev E, Achiron R, Mashiach S, Schiff E. Prenatal diagnosis of fetal primary cytomegalovirus infection. Obstet Gynecol. 1997;89:763–7.
[59] Lukacsi A, Tarodi B, Endreffy E, Babinszki A, Pal A, Pusztai R. Human cytomegalovirus gB genotype 1 is dominant in congenital infections in South Hungary. J Med Virol. 2001;65:537–42.
[60] Macé M, Sissoeff L, Rudent A, Grangeot-Keros L. A serological testing algorithm for the diagnosis of primary CMV infection in pregnant women. Prenat Diagn. 2004;24: 861–3.
[61] Maine GT, Lazzarotto T, Landini MP. New developments in the diagnosis of maternal and congenital CMV infection. Expert Rev Mol Diagn. 2001;1:19–29.
[62] Malinger G, Lev D, Zahalka N, Ben Aroia Z, Watemberg N, Kidron D, et al. Fetal cytomegalovirus infection of the brain: the spectrum of sonographic findings. AJNR Am J Neuroradiol. 2003;24:28–32.
[63] Malm G, Engman ML. Congenital cytomegalovirus infections. Semin Fetal Neonatal Med. 2007;12:154–9.
[64] McCarthy M, Auger D, Whittemore SR. Human cytomegalovirus causes productive infection and neuronal injury in differentiating fetal human central nervous system neuroepithelial precursor cells. J Hum Virol. 2000;3:215–28.

[65] Mocarski ES, Courcelle CT. Cytomegaloviruses and their replication. Fields Virology, 4th edition. Boston: Lippincott Williams & Wilkins. 2001;2629–73.
[66] Mosca F, Pugni L. Cytomegalovirus infection: the state of the art. J Chemother. 2007;19 (Suppl 2):46–8.
[67] Moxley K, Knudtson EJ. Resolution of hydrops secondary to cytomegalovirus after maternal and fetal treatment with human cytomegalovirus hyperimmune globulin. Obstet Gynecol. 2008;111:524–6.
[68] Müller A, Eis-Hübinger AM, Brandhorst G, Heep A, Bartmann P, Franz AR. Oral valganciclovir for symptomatic congenital cytomegalovirus infection in an extremely low birth weight infant. J Perinatol. 2008;28:74–6.
[69] Murph JR, Souza IE, Dawson JD, Benson P, Petheram SJ, Pfab D, et al. Epidemiology of congenital cytomegalovirus infection: maternal risk factors and molecular analysis of cytomegalovirus strains. Am J Epidemiol. 1998;147:940–7.
[70] Nankervis GA, Kumar ML, Cox FE, Gold E. A prospective study of maternal cytomegalovirus infection and its effect on the fetus. Am J Obstet Gynecol. 1984;149:435–40.
[71] Natali A, Valcavi P, Medici MC, Dieci E, Montali S, Chezzi C. Cytomegalovirus infection in an Italian population: antibody prevalence, virus excretion and maternal transmission. New Microbiol. 1997;20:123–33.
[72] Nigro G, Adler SP, La Torre R, Best AM. Passive immunization during pregnancy for congenital cytomegalovirus infection. N Engl J Med. 2005;353:1350–62.
[73] Nigro G, Torre RL, Pentimalli H, Taverna P, Lituania M, de Tejada BM, et al. Regression of fetal cerebral abnormalities by primary cytomegalovirus infection following hyperimmunoglobulin therapy. Prenat Diagn. 2008;28: 512–7.
[74] Ornoy A, Diav-Citrin O. Fetal effect of primary and secondary cytomegalovirus infection in pregnancy. Repro Toxic. 2006;21:399–409.
[75] Pass RF, Stagno S, Myers GJ, Alford CA. Outcome of symptomatic congenital cytomegalovirus infection: results of long-term longitudinal follow-up. Pediatrics 1980;66:758–62.
[76] Pass RF, Hutto C, Lyon MD, Cloud G. Increased rate of cytomegalovirus infection among day care center workers. Pediatr Infect Dis J. 1990;9:465–70.
[77] Pass RF, Boppana S. Cytomegalovirus In: Jeffries DJ, Hudson CN (Eds.). Viral infection in obstetrics and gynaecology. New York: Arnold, 1999;35–6.
[78] Pass RF. Cytomegalovirus infection. In: Knipe DM, Howley PM, Griffin DE, Lamb RA, Martin MA, Roizman B, et al. (Eds). Field's virology, 4th edition. Philadelphia: Lippincott-Williams & Wilkins, 2001;2675–705.
[79] Pass RF, Fowler KB, Boppana SB, Britt WJ, Stagno S. Congenital cytomegalovirus infection following first trimester maternal infection: symptoms at birth and outcome. J Clin Virol. 2006;35:216–20.
[80] Peckham CS, Stark O, Dudgeon JA, Martin JA, Hawkins G. Congenital cytomegalovirus infection: a cause of sensorineural hearing loss. Arch Dis Child. 1987;62:1233–7.
[81] Picone O, Costa JM, Leruez-Ville M, Ernault P, Olivi M, Ville Y. Cytomegalovirus (CMV) glycoprotein B genotype and CMV DNA load in the amniotic fluid of infected fetuses. Prenat Diagn. 2004;24:1001–6.
[82] Picone O, Costa JM, Leruez-Ville M, Ernault P, Olivi M, Ville Y. Cytomegalovirus (CMV) glycoprotein B genotype and CMV DNA load in the amniotic fluid of infected fetuses. Prenat Diagn. 2004;24:1001–6.
[83] Picone O, Costa JM, Chaix ML, Ville Y, Rouzioux C, Leruez-Ville M. Human cytomegalovirus UL144 gene polymorphisms in congenital infections. J Clin Microbiol. 2005;43:25–9.
[84] Picone O, Simon I, Benachi A, Brunelle F, Sonigo P. Comparison between ultrasound and magnetic resonance imaging in assessment of fetal cytomegalovirus infection. Prenat Diagn. 2008;28:753–8.
[85] Preece PM, Blount JM, Glover J, Fletcher GM, Peckham CS, Griffiths PD. The consequences of primary cytomegalovirus infection in pregnancy. Arch Dis Child. 1983;58: 970–5.
[86] Ramsay ME, Miller E, Peckham CS. Outcome of confirmed symptomatic congenital cytomegalovirus infection. Arch Dis Child. 1991;66:1068–9.
[87] Revello MG, Percivalle E, Gerna G. Immunoglobulin M to the membrane of uninfected fibroblasts in primary human cytomegalovirus infections. Microbiologica. 1986;9:127–38.
[88] Revello MG, Sarasini A, Zavattoni M, Baldanti F, Gerna G. Improved prenatal diagnosis of congenital human cytomegalovirus infection by a modified nested polymerase chain reaction. J Med Virol. 1998;56:99–103.
[89] Revello MG, Zavattoni M, Baldanti F, Sarasini A, Paolucci S, Gerna G. Diagnostic and prognostic value of human cytomegalovirus load and IgM antibody in blood of congenitally infected newborns. J Clin Virol. 1999;14:57–66.
[90] Revello MG, Zavattoni M, Furione M, Lilleri D, Gorini G, Gerna G. Diagnosis and outcome of preconceptional and periconceptional primary human cytomegalovirus infections. J Infect Dis. 2002;186:553–7.
[91] Revello MG, Gerna G. Pathogenesis and prenatal diagnosis of human cytomegalovirus infection. J Clin Virol. 2004;29:71–83.
[92] Revello MG, Furione M, Zavattoni M, Tassis B, Nicolini U, Fabbri E, et al. Human cytomegaloviris (HCMV) DNAemia in the mother at amniocentesis as a risk factor for iatrogenic HCMV infection of the fetus. J Infect Dis. 2008;197:593–6.
[93] Ross DS, Victor M, Sumartojo E, Cannon MJ. Women's knowledge of congenital cytomegalovirus: results from the 2005 HealthStyles survey. J Womens Health (Larchmt). 2008;17:849–58.
[94] Ruellan-Eugene G, Barjot P, Campet M, Vabret A, Herlicoviez M, Muller G, et al. Evaluation of virological procedures to detect fetal human cytomegalovirus infection: avidity of IgG antibodies, virus detection in amniotic fluid and maternal serum. J Med Virol. 1996;50:9–15.
[95] Saigal S, Lunyk O, Larke RP, Chernesky MA. The outcome in children with congenital cytomegalovirus infection. A longitudinal follow-up study. Am J Dis Child. 1982;136:896–901.
[96] Schleiss MR, Mark R, Schleiss MD. Congenital Cytomegalovirus Infection: Update on management strategies. Curr Treat Options Neurol. 2008;10:186–92.
[97] Schmidt W, Yarkoni S, Jeanty P, Grannum P, Hobbins JC. Sonographic measurements of the fetal spleen: clinical implications. J Ultrasound Med. 1985;4:667–72.
[98] Senoh D, Hata T, Kitao M. Fetal liver length measurement does not provide a superior means for prediction of a small for gestational age fetus. Am J Perinatol. 1994;11: 344–7.
[99] Shibata M, Takano H, Hironaka T, Hirai K. Detection of human cytomegalovirus DNA in dried newborn blood filter paper. J Virol Methods. 1994;46:279–85.

[100] Stagno S, Pass RF, Cloud G, Britt WJ, Henderson RE, Walton PD, et al. Primary cytomegalovirus infection in pregnancy: incidence, transmission to fetus, and clinical outcome. J Am Med Assoc. 1986;256:1904–8.
[101] Stagno S, Pass RF, Cloud G, Britt WJ, Henderson RE, Walton PD, et al. Primary cytomegalovirus infection in pregnancy: incidence, transmission to fetus, and clinical outcome. J Am Med Assoc. 1986;256:1904–8.
[102] Stagno S. Cytomegalovirus. In: Remington JS, Klein JO (Eds.) Infectious diseases of the fetus and newborn infant, 5th edition. Philadelphia: Saunders, 2001;389–424.
[103] Steinlin MI, Nadal D, Eich GF, Martin E, Boltshauser EJ. Late intrauterine cytomegalovirus infection: clinical and neuroimaging findings. Pediatr Neurol. 1996;15:249–53.
[104] Stronati M, Lombardi G, Di Comite A, Fanos V. Breast-feeding and cytomegalovirus infections. J Chemother. 2007;19 (Suppl 2):49–51.
[105] Tookey PA, Ades AE, Peckham CS. Cytomegalovirus prevalence in pregnant women: the influence of parity. Arch Dis Child. 1992;67:779–83.
[106] Vauloup-Fellous C, Ducroux A, Couloigner V, Marlin S, Picone O, Galimand J, et al. Evaluation of cytomegalovirus (CMV) DNA quantification in dried blood spots: retrospective study of CMV congenital infection. J Clin Microbiol. 2007;45:3804–6.
[107] Ville Y. The megalovirus. Ultrasound Obstet Gynecol. 1998;12:151–3.
[108] Weiner CP. The role of cordocentesis in fetal diagnosis. Clin Obstet Gynecol. 1988;31:285–92.
[109] Yow MD, Lakeman AD, Stagno S, Reynolds RB, Plavidal FJ. Use of restriction enzymes to investigate the source of a primary cytomegalovirus infection in a pediatric nurse. Pediatrics. 1982;70:713–6.
[110] Yow MD, Williamson DW, Leeds LJ, Thompson P, Woodward RM, Walmus BF, et al. Epidemiologic characteristics of cytomegalovirus infection in mothers and their infants. Am J Obstet Gynecol. 1988;158:1189–95.
[111] Zalel Y, Gilboa Y, Berkenshtat M, Yoeli R, Auslander R, Achiron R, et al. Secondary cytomegalovirus infection can cause severe fetal sequelae despite maternal preconceptional immunity. Ultrasound Obstet Gynecol. 2008;31:417–20.

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