Management of Pregnancies with Confirmed Cytomegalovirus Fetal Infection

Guillaume Benoist^{a, b} Marianne Leruez-Ville^c Jean François Magny^d
François Jacquemard^e Laurent J. Salomon^a Yves Ville^a

^aDepartment of Obstetrics and Maternal-Fetal Medicine, GHU Necker-Enfants Malades, AP-HP, Université Paris Descartes, Paris, ^bDepartment of Obstetrics and Maternal-Fetal Medicine, CHU Caen, Caen, and ^cDepartment of Virology, GHU Necker-Enfants Malades, AP-HP, Université Paris Descartes, ^dDepartment of Neonatology, Institut de Puériculture, and ^eDepartment of Obstetrics and Maternal-Fetal Medicine, CH Poissy, Université Paris Ouest, Paris, France

Key Words

Cytomegalovirus • Prenatal diagnosis • Magnetic resonance imaging • Ultrasound • Prognosis

Abstract

Systematic screening for cytomegalovirus (CMV) maternal infection is not recommended in most countries. Nevertheless, primary CMV infection will occur in around 1% of women. The vertical transmission rate is estimated to be around 30–50%. Newborns with congenital CMV infection remain asymptomatic in the majority of cases and around 10% will present with a wide range of abnormalities. Fetal infection can be diagnosed by amniocentesis with amplification of the viral genome in the amniotic fluid by polymerase chain reaction. This prenatal diagnosis is mainly performed when ultrasound abnormalities are observed. The purpose of this mini-review is to describe the management options when a fetus is known to be infected.

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Background Objectives

Cytomegalovirus (CMV) is the most frequent cause of congenital viral infection. The prevalence of CMV infection is around 0.5–1% of all live births, and it is the leading infectious cause of sensorineural hearing loss (SNHL) and mental retardation [1]. As other *Herpesviridae*, fetal CMV infection can develop following both primary and secondary maternal infection (reinfections and recurrences). Vertical transmission occurs in around 30–40% following primary infection and 2–3% following secondary infection [2]. The effects on unborn and newborn babies are widely variable. It is estimated that only 5–10% of infected newborns will have symptoms at birth, whereas around 90% of congenitally infected infants are asymptomatic, although 5–15% of them will develop SNHL (related to imaging of the central nervous system (CNS)) [3].

Prenatal diagnosis of CMV congenital infection has developed more rapidly than prognostic and therapeutic possibilities, and this review summarizes the current management options during fetal life.

Data Sources

The MEDLINE database (<http://www.ncbi.nlm.nih.gov/pubmed/>) and the Cochrane Library (<http://www.cochrane.org/>) were used to conduct a literature search to locate relevant articles up until January 2012. The search was restricted to articles published in English and French. Priority was given to articles reporting results of original research, although review articles and commentaries were also consulted. Guidelines published by organizations or institutions such as the Royal College of Obstetrics and Gynaecology (RCOG) (<http://www.rcog.org.uk/>), the American College of Obstetricians and Gynecologists (ACOG) (<http://www.acog.org/>) and the Canadian Society of Gynaecology and Obstetrics (SOGC) (http://sogc.org/index_f.asp) and the World Association of Perinatal Medicine (WAPM Perinatal Infections Working Group) (<http://www.wapm.info/>) [4] were reviewed, and additional studies were located by reviewing references cited in identified articles.

Results and Discussion

Conditions for the Diagnosis of Fetal Infection

CMV fetal infections are mainly diagnosed when ultrasound (US) abnormalities are observed or when maternal seroconversion is diagnosed during pregnancy following indicated or nonindicated testing. This 'wild' screening could be observed in up to 20–40% of all pregnancies in the greater Paris area (France) in 2002 as in other metropolises [5].

The diagnosis of primary CMV infection in pregnant women is based on serological tests with detection of specific type G (IgG) and type M (IgM) immunoglobulins. Seroconversion confirms primary infection but is usually difficult to identify in the absence of any available preconceptional serum specimen. Detection of specific IgM does not always indicate a recent primary infection because they may (1) persist for months after primary infection, (2) be detected during secondary infection, (3) be the consequence of cross-reactivity with IgM elicited by a primary infection with another virus (e.g. Epstein-Barr), and (4) be observed through polyclonal stimulation of the immune system. Therefore, it is imperative that each case of positive IgM result in pregnancy should be interpreted with caution. IgG avidity testing is widely used to identify the timing of primary infection (before or after pregnancy) in cases with positive IgM [6]. Detection of a low avidity index indicates an acute primary

infection within the 3 previous months, while a high avidity index excludes a primary infection within the 3 previous months. Therefore, the avidity results should be interpreted accordingly with gestational age. Moreover, one should be aware that the avidity index depends upon the technique used because the CMV IgG kits available are not standardized [7].

It is currently impossible, without recurring to invasive tests, to establish the diagnosis of secondary CMV infection (reinfection or reactivation). An increase in IgG does not ascertain secondary infection as it may be due to nonspecific polyclonal stimulation of the immune system.

Methods for the Diagnosis of Fetal Infection

Isolation of the virus or the viral genome (DNA) in the amniotic fluid (AF) is the method of choice for the diagnosis of fetal infection. CMV can be detected in the AF by conventional viral isolation, rapid culture or molecular assays. Virus isolation has a higher specificity but has a lower sensitivity than polymerase chain reaction (PCR). In recent years, PCR has become a reliable technique in reference laboratories, generally the most recent real-time PCR. The efficacy of these methods has been evaluated in several studies and is dependent upon the virological method used (nested, one-round or real-time PCR): sensitivity and specificity range between 75 and 100% and between 67.3 and 100%, respectively [8–12]. The false-negative results reported were explained in most cases by inappropriate timing of amniocentesis. Following seroconversion or reactivation, the process leading to CMV excretion in the fetal urine will take an average of 6–8 weeks and this interval should be respected in order to avoid false-negative prenatal diagnosis [12]. Amniocentesis should be performed once fetal urination is well established and therefore not before 20 weeks. When the conditions of sampling are ideal [13], the sensitivity of prenatal diagnosis by PCR has been reported to be close to 100%. Rare cases of false-positive results have also been reported when the neonate was not infected. These false-positive diagnoses may be explained by contamination of the AF with maternal blood during amniocentesis if the mother had a positive CMV DNAemia at the time of sampling. Indeed, Revello et al. [14] showed that CMV DNA may be recovered in the blood of nearly 50% of immunocompetent patients up to 3 months after primary CMV infection. However, a more likely explanation for these false-positive results is a laboratory contamination occurring during PCR testing. Generalization of semiautomated real-time PCR should

help to overcome the risk of contamination and to achieve quasi-absolute specificity for prenatal diagnosis of CMV infection [15]. Even when timing of prenatal diagnosis is optimal (after 20 weeks and 6–8 weeks after maternal seroconversion), false-negative results may occur (i.e. a negative CMV detection in the AF and positive at birth). These cases are likely to be due to a late transmission of the virus. Altogether, around 8% of neonates born following a negative prenatal diagnosis will show viral excretion at birth. However, to date, none of these infants showed any symptoms as reported in the literature [16]. Therefore, in all cases, the prenatal diagnosis has to be confirmed by virus or viral genome retrieval in the urine of the newborn. Saliva has recently been proven to be a reliable method for the detection of CMV congenital infection in the newborn [17, 18]. Real-time PCR in dried blood spots has also been evaluated for CMV screening at birth and has a lower sensitivity when compared with saliva rapid culture, limiting its value as a screening test as well as a diagnostic tool [19]. Nevertheless, Leruez-Ville and colleagues [20, 21] have reported that this virological method can be useful to identify congenital CMV in a population of neonates with a high risk of sequelae as well as for retrospective diagnosis of CMV congenital infection.

Aims of the Management when the Fetus Is Infected

When a fetus is infected, the main objective is to predict the prognosis at birth. Clinical presentation of neonatal CMV infection varies widely between asymptomatic and severely symptomatic newborns with intermediate forms. Clinical, imaging and biological signs in the infected neonates are the main prognostic endpoints.

Approximately 10% of the infants born with congenital CMV infection have signs and symptoms at birth. Only half of these symptomatic infants have disseminated multiorgan involvement named cytomegalic inclusion disease (CID). Other infants have mild or subclinical manifestations of the disease. In the typical form of CID, many organs are involved, mainly the reticuloendothelial system, and the CNS. The main clinical abnormalities observed in the newborns with CID are: hepatomegaly, splenomegaly, microcephaly, jaundice, petechiae, hypotonia/lethargy or seizures [22, 23]. Elevated alanine aminotransferase, conjugated hyperbilirubinemia and thrombocytopenia are the main laboratory abnormalities [22, 23]. Other manifestations occasionally present in symptomatic newborns include: pneumonitis [24], dental defects [25], ocular defects (chorioretinitis, strabismus and optic atrophy, cataracts,

microphthalmos, necrosis, calcifications, blindness, anterior chamber and optic disk malformations and papillary membrane vestiges) [22, 26], and hearing loss, intrauterine growth retardation (IUGR) and prematurity [22]. Overall, in this symptomatic subgroup of congenitally infected infants, the mortality rate is around 15–30%. Death is often due to multiorgan involvement with severe hepatic dysfunction, bleeding, disseminated intravascular coagulation and secondary bacterial infection. In this condition, death mainly occurs in the first weeks of life. Around 90% of the symptomatic infected newborns who survive will develop some degree of disability including psychomotor retardation usually associated with microcephaly and other neurological impairments, SNHL, visual impairment and expressive language delays.

At the other extreme of the spectrum of CMV congenital infection are the asymptomatic forms of the disease. Without any systematic screening policy at birth, these infected newborns are most frequently left undiagnosed. Nevertheless, it has been reported that approximately 15% of asymptomatic children will develop some degree of hearing loss following congenital CMV infection [27]. Globally, CMV causes around 10% of congenital SNHL [28, 29]. This deficit may be present at birth or develop later in childhood usually during the first year of life, with a great variability in the severity ranging from unilateral high-frequency losses to profound bilateral losses [27, 30]. Development of new diagnostic tools such as dried blood spots (DNA detection in Guthrie cards) helps to retrospectively attribute SNHL to congenital CMV infection [20, 31, 32].

Thus, the main aim during prenatal management is to predict the risk of symptomatic neonatal infection. During fetal life, a 'poor outcome' is usually defined by the merging cases where the pregnancy is terminated with the presence of the significant signs of CMV infection at postmortem examination together with infants born with typical CID. However, we could hypothesize that dissociated features such as the presence of cytomegalic inclusions in the kidneys associated with isolated periventricular calcifications do probably not reflect a high risk of symptomatic infection should the pregnancy be carried on to term. There is therefore a bias in the literature regarding correlations of postmortem results following prenatal diagnosis with an overestimation of the likely severity of the disease. There is a need for a more objective evaluation of these cases.

Prenatal Criteria for the Prediction of the Severity of the CMV Fetal Infection?

Awareness on CMV infection started as a neonatal issue. The increasing ability of US investigation to identify abnormalities, as well as the development of molecular biological tools (such as PCR), has made it a prenatal issue.

Primary or Secondary Infection

Overall, the vertical transmission rate was found to be 20–40% in pregnant women with primary infection and 0.2–2.2% in previously known seropositive women undergoing recurrent infection during pregnancy [33–36]. Nevertheless, irrespective of the type of infection, severe congenital infections have been reported and it seems that protection provided by a previous CMV infection is only partial [37–39]. Secondary infections comprise both recurrences occurring after a previous primary infection, and so with the same viral strain, and reinfections that are due to another viral strain [33, 37, 40, 41]. Nevertheless, the differentiation between these two types of infections is very difficult based on laboratory tests and complicated by the lack of information related to the serologic status of the pregnant woman at the beginning of pregnancy without any systematic screening.

Gestational Age at Maternal Infection

Gestational age at maternal infection can modify the consequences of the CMV infection on the conceptus, firstly because the risk of vertical transmission is variable at the three trimesters, and secondly because of the various outcomes related to the timing of fetal infection.

Daiminger et al. [42] tried to estimate the risk of congenital CMV infection and disease following primary maternal infection around the time of conception compared with the risk during later stages of pregnancy. They reported preconceptional (between 8 and 2 weeks before onset of the last menstrual period) in 3 women and this did not lead to congenital infection. Periconceptional infection (between 1 week before and 5 weeks after last menstrual period) occurred in 20 women and congenital infection occurred in 9 cases (45%). Timing was less precise (between 8 weeks before and 5 weeks after last menstrual period) in an additional 10 women, and in 3 cases a congenital infection was diagnosed. In this study, primary infections occurring between 6 and 20 weeks' gestation and between 20 and 38 weeks resulted in transmission rates of 30% (27/89) and 58% (18/31), respectively.

Revello et al. [43] also studied primary CMV infections occurring in pregnant women within 3 months before (preconceptional) or within 4 weeks after (pericon-

ceptional) the last menstrual period. One (9.1%) of 11 newborns born to 12 women with preconceptional infection was subclinically infected. In the periconceptional group, intrauterine transmission occurred in 4 (30.8%) of 13 pregnancies for which the virological outcome was known. The risk of vertical CMV transmission was further investigated by the same authors in 14 women who had primary CMV infection 2–18 weeks before their last menstrual period [44]. One (8.3%) of the 12 newborns examined at birth was found to be subclinically infected. Recently, Hadar et al. [45] studied 59 patients with primary periconceptional CMV infection (within 4 weeks prior to the last reported menstrual period and up to 3 weeks following the expected date of the missed menstrual period) and observed a 25.5% rate of vertical transmission. Thus, preconceptional primary CMV infection has a transmission rate that is significantly higher than that observed in an unselected neonatal population but significantly lower than that associated with maternal infection during pregnancy.

When maternal infection is diagnosed later during the pregnancy, the transmission rate might be higher. In 1986, Stagno et al. [34] reported the association between gestational age and the risk of vertical transmission. In this study the authors did not find any difference in the transmission rate when they compared pregnancies where maternal CMV infection occurred between weeks 4 and 22, 16 and 27, and 23 and 40. Nevertheless, more recent studies reported a higher rate of vertical transmission with advanced gestational age. Gindes et al. [46] studied 28 women with primary CMV infection acquired after 25 weeks' gestation and observed a vertical transmission rate of 75%. Nevertheless, none of the 20 live infected newborns had symptomatic congenital infection. One pregnancy was terminated at 34 weeks following evidence of prenatal infection. Bodeus et al. [47] studied 123 pregnant women who developed a primary CMV infection. In this study, the mean rate of intrauterine transmission was 57.5%, but the authors found a statistically significant difference between early seroconversion (during the first trimester) and late seroconversion (during the third trimester) (36.0 vs. 77.6%; $p < 0.001$) and the risk of transmission calculated for seroconversion during the second trimester was intermediate (44.9%).

More important than this point, an association was also noted between the gestational age at maternal infection and the outcome of the fetus, but the strong relationship between gestational age at the time of maternal CMV infection and outcome of fetal infection is not well defined. It has been shown that almost all infants with

Table 1. Fetal US abnormalities related to CMV congenital infection

Non-CNS abnormalities	CNS abnormalities
Intrauterine growth retardation	Microcephaly
Hydrops	Hydrocephaly
Ascites	Ventriculomegaly
Pericardial effusion	Increased periventricular echogenicity
Pleural effusion	Calcifications
Skin edema	Periventricular pseudocysts
Hyperechogenic bowel	Intraventricular synechiae
Hepatomegaly-splenomegaly	Malformations of cortical development: lissencephaly-pachygyria, oligo-/pachygyria, polymicrogyria, schizencephaly
Liver calcifications	Cerebellar abnormalities: vermian hypoplasia, cerebellar hemorrhage, calcifications, cysts
Placentomegaly	
Oligohydramnios/anhydramnios	
Polyhydramnios	

symptomatic congenital infection were exposed in the first half of pregnancy [8, 34, 42, 48]. However, Steinlin et al. [49] reported 7 children who presented with a clinical complex of signs (microcephaly, sensorineural hearing impairment, behavior problems, ataxia, hypotonia and developmental problems) and imaging abnormalities (calcifications or dysmyelination) after CMV infection thought to have occurred in the third trimester of the pregnancy. However, the method used for dating maternal infection in this study was imprecise.

One of the main reasons for the imprecision about the role played by the timing of maternal infection is the lack of evidence of seroconversion without any systematic serologic screening program and the clinical features of the maternal infection (asymptomatic in around 90% of cases).

To determine whether congenital CMV infection following primary maternal infection during the first trimester of pregnancy is more likely to lead to CNS lesions than that occurring later in pregnancy, Pass et al. [50] used serum collected during pregnancy from mothers of newborns with congenital CMV infection and categorized the maternal infection as first trimester (<13 weeks) or later based on dates and results of IgG and IgM assays for CMV antibodies. They studied the outcome of infected newborns based on this categorization. They observed that SNHL was found in 8/34 (24%) of children in the first-trimester group, compared with 1/40 (2.5%) in the later infection group ($p = 0.01$, relative risk 9.6). Considering any CNS disability (hearing loss, mental retardation, cerebral palsy, seizures, chorioretinitis), the authors observed that 11/34 (32%) first-trimester cases were affected compared with 6/40 (15%) in the later infection group ($p = 0.07$, relative risk 2.2). None of the latter group had

more than one disability, compared with 4 (12%) of the first-trimester group ($p = 0.04$). An association between outcome and gestational age at the time of maternal infection was suggested in reports in the 1980s by Ahlfors et al. [48] and Stagno et al. [34], but these included very few cases of congenital infection that could be categorized as first trimesters. More recently, Liesnard et al. [8] reached similar conclusions based on a date of fetal infection established by testing of AF and/or fetal blood. They studied 55 cases of congenital CMV infection from 237 pregnancies undergoing prenatal evaluation and found that 10/38 (26%) cases infected before 20 weeks of gestation had severe disease compared with only 1/16 (6.2%) infected after 20 weeks.

Fetal Morphological Abnormalities

Without established screening programs in pregnancy, the most frequent circumstances for prenatal diagnosis of CMV infection is the fortuitous discovery of an abnormal or unusual US finding possibly related to CMV congenital infection. Nevertheless, sensitivity of US determination of fetal infection is poor (around 15%) [51]. This may explain that severe abnormalities are described more often than subtle findings. Nevertheless, in this study, the authors observed that, when the result of the CMV PCR in the AF is known, the ability of US examination to depict even subtle abnormalities is increased [51].

We can divide the US findings in three categories: fetal cerebral or extracerebral abnormalities and placental AF abnormalities. The main US findings are reported in table 1.

Cerebral US features of fetal CMV infection have been recently reviewed by Malinger et al. [52]. Briefly the most

frequent abnormalities observed are: ventriculomegaly [53], increased periventricular echogenicity or halo [54, 55], microcephaly [56, 57], calcifications [58, 59], periventricular pseudocysts, intraventricular synechiae, abnormalities of the cortical development [60–62] and of the cerebellum and the posterior cisterna fossa [63] or cerebral hemorrhage [64, 65].

Extracerebral fetal abnormalities are nonspecific but can also suggest fetal infection. The wide spectrum of extracerebral US findings illustrates the affinity of CMV for endothelial cells, which explains the large number of organs possibly involved. The main extracerebral US features of fetal CMV infection are: IUGR [66], splenomegaly [67], hepatomegaly, hyperechogenic bowel [68–71], isolated pleural or pericardial effusion and ascites or hydrops [72–74], and cardiomegaly [75].

Fetal infection begins after a long latency period of the virus inside the maternal monocytes, leading after several weeks to placental infection. Placenta also plays a particular role, both of reservoir and barrier. Thus, CMV is reaching the fetal compartment in only one third of the cases. The role of the placenta can be illustrated by studies about CMV infections in twins showing possible discrepancies between the two fetuses (infected-noninfected and symptomatic-asymptomatic) [76, 77]. A thickened placenta with a heterogeneous appearance associated with the presence of calcifications suggests placentitis as a first step into fetal infection. The virus is then released from the placenta and reaches the fetal circulation where it disseminates into fetal organs. La Torre et al. [78] evaluated the diagnostic value of placental thickening in women with primary infection during pregnancy. They observed significantly thicker placentas when fetuses or newborns were infected by CMV compared with those of control mothers.

The time interval between maternal infection and fetal US abnormalities is poorly described in the literature, and can vary considerably between fetuses. Nigro et al. [65] described a case of maternal CMV infection at 6 weeks' gestation, in which the US signs of fetal CMV infection (intraventricular hemorrhage) appeared at 20 weeks' gestation. The time interval between maternal infection and US findings was 14 weeks. Enders et al. [11] in a series of 189 congenital infections with known outcomes reported a 12-week interval between infection and the appearance of US abnormalities (maternal seroconversion at 14 weeks' gestation). Picone et al. [79] recently reported a case of periconceptional infection in a HIV-positive pregnant women (<6 weeks' gestation) and appearance of US abnormalities at 36 weeks. These observa-

tions probably justify a prolonged US follow-up (until delivery) even if fetal infection is diagnosed early during the pregnancy [80].

The presence of US abnormalities (mainly cerebral abnormalities) is the main prognostic factor [81]. Farkas et al. [82] evaluated the neurodevelopmental outcome of CMV-infected fetuses with normal serial neurosonographic examinations and observed that the normality of this follow-up predicted a normal early neuropsychological outcome. These conclusions led to evaluate the place for fetal cerebral magnetic resonance imaging (MRI) examination.

The development of fetal MRI has become an asset in the assessment of infected fetuses [83–85]. MRI using both T₁ and T₂ sequences could help define the onset of fetal infection. Sulcation has been precisely described by MRI [86]. Lissencephaly may reflect injury before 16 or 18 weeks, whereas polymicrogyria is likely to follow injury of the brain at 18–24 weeks, and finally cases with normal gyral patterns would have probably been injured during the third trimester showing diffuse heterogeneity in the white matter [83].

The normality of these two investigation methods increases reassurance regarding the absence of fetal brain abnormalities [82, 87, 88]. Similarly, the combination of targeted US examination and MRI in the third trimester in known infected fetuses provides with a 95% sensitivity on the identification of CNS lesions related to CMV infection. Lipitz et al. [89] have also shown that the outcome of congenital primary CMV infection with normal prenatal US and MRI examinations is favorable. On the contrary, Manara et al. [90] have shown that, among 14 symptomatic CMV-infected children, white matter involvement was very variable and unrelated to the clinical course, while cortical development and ventriculomegaly were associated to a poor outcome except SNHL.

Overall, we can consider that US and MRI are complementary for the study of the fetal brain as has been shown by de Vries et al. [53] in a pediatric cohort. Nevertheless, the prognostic value of several MRI signs such as white matter signal abnormalities remain to be evaluated. Furthermore, false-positive MRI observations have been reported [88].

Virological Parameters

Rivera et al. [91] reported that in children with symptomatic CMV congenital infection, IUGR, petechiae, hepatomegaly-splenomegaly, hepatitis, thrombocytopenia and intracerebral calcifications were associated with the development of SNHL in univariate analysis, whereas no CNS abnormalities were predictive of hearing loss.

Furthermore, the infants who develop hearing loss have a higher urine CMV titers than those with normal hearing. This predictive value of the urine CMV titer can be extrapolated during fetal life, as AF is representative of the fetal urine.

At least four studies [13, 92–94] have compared viral load levels in AF between groups of symptomatic and asymptomatic fetuses. The median viral loads in these studies were higher in the AF of symptomatic fetuses than in the AF of asymptomatic fetuses; however, this difference reached statistical significance in only one study [92]. Moreover, high viral loads ($\geq 10^6$ copies/ml) were reported in the AF of fetuses that were born with asymptomatic infection and low viral loads ($\leq 10^3$) were associated with the presence of severe US abnormalities in some fetuses [93]. These differences may be explained by the methodology used. Indeed, real-time PCR amplified the viral genome, which probably reflects the combination of the accumulation of the virus inside the AF since the CMV is excreted in urine by the fetus and the clearance of the AF itself. A correlation between AF viral load and time elapsed since seroconversion has been observed [92].

CMV genotypes have also been studied as prognostic factors. Nevertheless, studies about glycoprotein B or UL144 gene sequences did not show strong correlations with the fetal outcome [93, 95, 96].

Lanari et al. [97] have observed that the mean viral load in neonatal blood (determined by quantitative PCR) was significantly higher in symptomatic infected newborns ($p = 0.20$). This difference was more marked when only infants with clinical abnormalities consistent with CID were considered. The mean viral load determined by quantitative PCR in neonatal blood was also significantly higher in newborns that developed sequelae after a follow-up period of at least 12 months ($p = 0.01$). The sensitivity, specificity, positive and negative predictive values of a DNA load $\geq 10^3/10^5$ polymorphonuclear leukocytes for the presence of disability at 12 months of life was 90, 70.4, 53 and 95%, respectively [97].

Available data on the prognostic value of fetal blood parameters are scarce and only a few studies have been published so far [81, 91, 98, 99]. In Revello et al. [98], antigenemia, viremia and DNA load were found to be higher in fetuses with abnormalities than in asymptomatic fetuses, but the difference was significant only for antigenemia. However, a very high viral load in fetal blood was only discovered in symptomatic fetuses.

Nonspecific fetal blood parameters have also been studied. Rivera et al. [91] have reported that thrombocytopenia (platelet count $< 100,000/\text{mm}^3$), alanine amino-

transferases ($> 80 \text{ IU/ml}$), and direct bilirubin ($> 4 \text{ mg/dl}$) were associated with symptoms at birth with odds ratios of 2.4, 7.1, and 2.8, respectively. Nevertheless, it seems that the only interesting parameter would be thrombocytopenia. Indeed, Boppana et al. [100] reported that among symptomatic CMV-infected newborns with normal cerebral scan (CT), 56% had thrombocytopenia, and among fetuses with abnormal CT, 86% had thrombocytopenia ($p = 0.015$). Recently, Kang et al. [101] also reported that close follow-up of neurodevelopmental sequelae is required among clinically asymptomatic infants with isolated thrombocytopenia.

Benoist et al. [81] retrospectively analyzed data collected prospectively in 73 fetuses infected by CMV diagnosed by positive CMV PCR in AF. Fetal blood sampling was performed for evaluation of platelet count, plasma levels of aminotransferases and γ -glutamyl transpeptidases, presence of viremia, and specific fetal IgM. In univariate analysis, only thrombocytopenia and the presence of any US abnormality were associated with a poor outcome ($p < 10^{-4}$ for both abnormalities). In the multivariate analysis, both thrombocytopenia and the presence of US abnormalities remained significant independent predictors of a poor outcome. Based on univariate logistic regression, odds ratios for a poor outcome were 1.24, 7.2, 22.5 and 25.5 for each $10,000\text{-mm}^3$ decrease in platelet count $< 100,000/\text{dl}$, the presence of noncerebral US, any US and cerebral US abnormalities, respectively.

Dreux et al. [102] reported the results of a retrospective assay of β_2 -microglobulin in the fetal serum of 15 infected CMV fetuses and proposed to use it as a marker of fetal infection (CMV and toxoplasmosis). Recently, Fabbri et al. [99] evaluated the usefulness of fetal blood sampling for the prediction of outcome in 94 blood samples from fetuses with CMV fetal infection following maternal primary infection. Blood sample markers were retrospectively compared in symptomatic and asymptomatic fetuses with congenital infection. Univariate analysis showed that most nonviral and viral markers were significantly different in symptomatic ($n = 16$) compared with asymptomatic ($n = 31$) fetuses. Receiver operating characteristics analysis indicated that, with reference to an established cut-off for each marker, the best nonviral factors for differentiation of symptomatic from asymptomatic congenital infection were β_2 -microglobulin and platelet count, and the best virological markers were fetal IgM and DNAemia. β_2 -Microglobulin alone or combination of these four markers reached the optimal diagnostic efficacy (sensitivity 85.7%, specificity 100%, positive predictive value 100%, negative predictive value 93.8%).

Fig. 1. Proposed management for CMV fetal infection.

These studies have therefore shown that platelet count in fetal blood is an independent prognostic factor and could justify the risk of fetal loss associated with fetal blood sampling [103]. Fetal blood testing is justified when fetal infection is established and mainly in the ‘intermediate’ prognostic group, therefore when the fetus shows noncerebral US findings or when the pregnant woman requires as much information on the prognosis as possible.

Therapeutic Options

Three licensed anti-CMV drugs (ganciclovir, cidofovir and foscarnet) are being used successfully in immu-

nocompromised patients. However, their potential teratogenic effects and their well-known toxicity (mainly hematological and renal adverse effects) do not support their use in pregnancy. To date, preliminary results on treatment of fetal CMV infection during pregnancy are available from two studies with promising results.

Jacquemard et al. [104] have shown the pharmacological efficacy of oral valacyclovir (8 g/day) (VACV) in a pilot study of 21 cases of CMV congenital infections with US abnormalities. They reported that therapeutic concentrations were achieved in maternal and fetal blood, and that the viral load in fetal blood decreased significantly after 1–12 weeks of treatment. Twenty pregnancies including 21 fetuses were treated at 28 weeks (median, range 22–34) for 7 weeks (median, range 1–12) and 10 infants were developing normally at between 1 and 5 years of age. Two infants (both aged 2 years) had severe isolated unilateral deafness. One neonate presented with microcephaly and severe deafness but was also diagnosed with incontinentia pigmenti. The 7 remaining cases that eventually required termination of pregnancy had evidence of in utero progression of the disease with worsening cerebral lesions or died in utero. By comparison, the outcome of 14/24 (58.3%) untreated symptomatic infected fetuses was poor with either termination of pregnancy, intrauterine fetal demise or severe congenital infection disease of the neonate; the remaining 10 infants were healthy at follow-up. Thus, maternal oral administration of VACV leads to therapeutic concentrations in the maternal and fetal compartments, with a decrease in fetal blood viral load. This therapeutic approach is currently being studied using a phase 2 trial entitled ‘In Utero Treatment of Cytomegalovirus Congenital Infection with Valacyclovir (CYMEVAL)’ which is currently recruiting participants (<http://clinicaltrials.gov/>).

The second therapeutic strategy is based on immunoglobulin therapy. Several cases of treatments with this therapeutic option have been reported [105, 106]. Nigro et al. [107] have published the retrospective results of a nonrandomized clinical trial using intravenous CMV hyperimmune globulin (HIG) for maternal primary CMV infection. They used HIG in two groups. One group comprised women whose AF contained CMV and who were offered intravenous CMV HIG at a dose of 200 U/kg of maternal weight and one group consisting of women with a recent primary infection and unknown fetal status before 21 weeks’ gestation who declined amniocentesis and were offered monthly HIG (100 U/kg i.v.). In the therapy group, only 1/31 women (3%) who were treated gave birth to an infant with CMV disease (symp-

tomatic at birth and handicapped at 2 or more years of age), as compared with 7 of 14 (50%) women who did not receive the treatment. In the prevention group, 37 women received HOG, and 6/37 (16%) of them had infants with congenital CMV infection, as compared with 19/47 women (40%) who did not receive HIG. These authors concluded that HIG therapy was associated with a significantly lower risk of congenital CMV infection, especially symptomatic infection, after maternal primary infection. This hypothesis has been evaluated in a randomized study entitled 'Efficacy Study of Human Cytomegalovirus (HCMV) Hyperimmune Globulin to Prevent Congenital HCMV Infection (CHIP)' with inclusions completed but still unpublished results (<http://clinicaltrials.gov/>). Nigro et al. [108] have also shown that HIG can induce a regression of fetal cerebral abnormalities in a small series of fetal infections consecutive to maternal primary infections.

The same study group reported the results of a case-control study of the outcome in 32 congenitally infected and symptomatic children and concluded that HIG were efficient for decreasing the severity of disabilities caused by CMV infection after a primary maternal infection during pregnancy [109].

Conclusion: Proposed Management for CMV Fetal Infection (fig. 1)

When a fetus is CMV infected, serial targeted US examination has to be performed every 3–4 weeks. This follow-up should be continued up until delivery.

Transabdominal as well as transvaginal US examination should ensure thorough examination of the fetal

brain as appropriate [110–113]. In our practice, fetal blood sampling is systematically discussed for platelet count but probably takes its better place when noncerebral US abnormalities are observed.

Fetal cerebral MRI is performed at 28–32 weeks and sometimes 3–4 weeks later, using T₁, T₂ and diffusion sequences considering its value for reassurance of parents as well as its ability to study the posterior fossa and the cortical development [114].

Infected fetuses are then classified into three categories: (1) Asymptomatic fetuses defined as fetuses with normal biological parameters in fetal blood, no US abnormalities and normal cerebral MRI. The prognosis is considered to be good with a residual risk of hearing loss [82]. (2) Severely symptomatic fetuses with severe US abnormalities (hydrops, microcephaly, ventriculomegaly measuring >15 mm, white matter abnormalities and parenchymatous cavitations, intracerebral hemorrhages, delayed cortical development, etc.) associated with thrombocytopenia. In this context, termination of pregnancy is found to be acceptable at maternal request. (3) Mild or moderately symptomatic fetuses defined as fetuses with isolated biological abnormalities without brain abnormalities on US or with isolated US abnormalities such as hyperechogenic bowel, mild ventriculomegaly or isolated calcifications. The prognosis is uncertain and follow-up will refine the prognosis. Therapeutic options including VACV are discussed in these cases.

This management is probably facilitated by legal systems that allow termination of pregnancy to be performed irrespective of gestational age when the prognosis is considered to be poor. Preterm delivery is not indicated in fetal CMV infection.

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