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Congenital Cytomegalovirus Infection: Management Update

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Congenital cytomegalovirus infection: management update

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STRUCTURED ABSTRACT

Purpose of review: Until recently, management options in congenital cytomegalovirus infection (cCMV) have been either conservative or termination of pregnancy. However, medical therapies aimed at reducing the risk of infection and/or its severity have recently been investigated.

Recent findings: In a phase 2 open label, non-randomised trial, valaciclovir was given to women carrying a CMV-infected fetus. Valaciclovir was associated with a greater proportion of asymptomatic neonates when compared with a historical cohort (82% vs 43%). However, the study design and the small number of treated women limit its applicability. Even though initial observational data suggested that hyperimmune globulin (HIG) therapy in pregnancy was associated with a significantly lower risk of cCMV, its efficacy has not been borne out in a subsequent phase 2 randomised, placebo controlled, double blind study (cCMV 30% in the HIG group, 44% in the placebo group (p=0.13)). Furthermore, 11% of fetuses in the HIG group had transient or permanent abnormalities, compared with 16% in the placebo group.

Summary: Valaciclovir might have a promising role in the antenatal treatment of cCMV infection, but definitive recommendations require further research. The use of HIG should currently be limited to the research setting.

Key words: Congenital Cytomegalovirus Infection, antenatal treatment, antiviral drug, valaciclovir, human immunoglobulin

INTRODUCTION

Cytomegalovirus (CMV) is the commonest cause of congenital infection, the leading non-genetic cause of sensorineural hearing loss (SNHL), the major infectious cause of infant malformation in developed countries and a major cause of neuro-disability [1,2]. It is estimated to account for up to 10% of cases of cerebral palsy [3]. The incidence of congenital CMV is estimated at 0.64%, while the incidence of symptomatic infection at birth is 0.07% [4-7]. Congenital CMV infection affects 40,000 infants in the United States annually [8]. In the UK, 1-2 in every 200 neonates will be born with congenital CMV. Of these, around 13% will be symptomatic at birth, with a similar proportion developing problems later in childhood [9]. Moderate or severe outcomes were reported in 11% of children with congenital CMV identified through population screening [9].

ANTENATAL SCREENING

Because routine CMV screening does not meet several of the criteria for an effective screening test, not least the fact that there is no effective preventative treatment, in most countries it is not recommended outside of the research setting [10,11]. Currently, therefore, serological testing for CMV is offered only to women with influenza-like symptoms during pregnancy or in whom ultrasound detects fetal abnormalities suggestive of possible CMV infection. It is important to acknowledge a number of arguments that support routine screening during pregnancy: firstly, congenital CMV infection is more common than Down's syndrome, which also has no treatment; secondly, if prevention is to be given an opportunity to be effective then screening is necessary; thirdly, the symptoms and ultrasound features lack specificity; fourthly, severe cases are more likely to be diagnosed, giving women the

option of possible termination if infection is identified and investigated. Focusing on a different setting, a UK cost analysis of targeted screening using salivary swabs integrated within the newborn hearing screening programme, with subsequent treatment for congenital CMV-related SNHL in otherwise asymptomatic infants, resulted in an estimated cost per case that compares favourably with other screening programmes [12]. Despite some compelling reasons for antenatal screening, congenital CMV does not adequately fulfill the criteria for the implementation of a screening programme.

Pre-natal diagnosis of CMV infection is challenging and options for prevention and treatment are limited. The current approach to the antenatal management of congenital CMV is illustrated in Figure 1.

PREVENTION

There is no licensed vaccine for CMV nor is one likely for some time. An alternative strategy to reduce the risk of infection is behaviour modification in order to minimise contact with CMV. The primary source of CMV in pregnancy is the saliva and urine of infected young children, in whom viral shedding can persist for several years. Simple hygiene-based measures such as handwashing after contact with urine or saliva, and avoiding sharing utensils, drinks or food with young children can reduce the risk of CMV acquisition.

Several studies have investigated such measures in pregnancy [13-16]; however, most have been underpowered or non-randomised. In a cluster randomised trial,

seronegative women with children under the age of three years were randomised to a day care centre that included information on hand hygiene and glove use or to one that did not. There was no difference in the seroconversion rates between the intervention and control groups. However, in the subgroup of women who had a child shedding CMV, those pregnant before enrolment had a significantly lower seroconversion rate than women attempting pregnancy (5.9% versus 41.7%; p=0.008) [14]. This suggests that such educational interventions to reduce CMV acquisition in pregnancy are more likely to be effective during pregnancy than before, probably because pregnant women are more motivated to adhere to these recommendations. In the most recent published study, seronegative women with a child less than 36 months received preventative information from a midwife or obstetrician in oral and written forms. The seroconversion rate in these women was 1.2% compared to 7.6% in a group of pregnant women who did not receive such advice in pregnancy ($p<0.001$) providing further evidence that risk reduction is possible [16]. A study assessing the feasibility of an educational intervention to reduce the risk of congenital CMV in the UK (Reducing Acquisition of CMV through antenatal Education; RACE-FIT) has started in 2017 (http://cmvaction.org.uk/news/new-uk-research-project-will-educate-pregnant-women-about-cmv).

PRENATAL DIAGNOSIS AND PROGNOSIS

Diagnosis of CMV infection in pregnancy is based on measurement of CMV-specific IgG and IgM immunoglobulins in the maternal blood. The presence of IgM is not diagnostic of recent primary CMV infection as IgM may persist for many months after the primary infection. IgM may also be detected during a secondary infection, and

there may be cross-reactivity with IgM due to another viral infection, e.g. Epstein Barr virus. Finally, IgM may be detected as a result of non-specific polyclonal stimulation of the immune system. IgG *avidity* testing is therefore often used in order to better define the timing of the infection (i.e. before or during pregnancy). Avidity levels are quantified by the avidity index which describes the proportion of IgG bound to the antigen following treatment with denaturing agents [17]. In general, a high avidity index (greater than 60%) is highly suggestive of past (greater than three months earlier) or secondary infection, while a low avidity index (less than 30%) is highly suggestive of recent primary infection (i.e. within the past three months) [18]. Maternal viraemia is a useful adjunct when suspecting seroconversion at 12 weeks [19]. Diagnosis of secondary CMV infection can be difficult. A rise in IgG levels does not confirm secondary infection as this rise may be due to non-specific polyclonal stimulation of the immune system. In practice, therefore, the only way of confirming secondary CMV infection is by invasive testing.

Diagnosis of fetal infection is made by identification of the viral genome (DNA) by polymerase chain reaction (PCR), generally real time PCR, in the amniotic fluid following amniocentesis. Virus isolation has a higher specificity but lower sensitivity than PCR and is now rarely used. Depending on the virological method used, sensitivity ranges between 75% and 100%, with specificity between 67% and 100% [17,20-23]. Amniocentesis should not be performed before 20 weeks' gestation when fetal urination is well established. Furthermore, following primary maternal infection, the infective process will not lead to CMV excretion in the fetal urine until an average of 6-8 weeks later [24]; for this reason amniocentesis should be delayed until this point. In fact, most false negative amniocentesis results are likely to be attributed to the amniotic fluid being sampled too early in pregnancy or too early after the primary infection, and some studies suggest that when sampling conditions are ideal, the

sensitivity of prenatal diagnosis by PCR is close to 100% [24]. Occasionally false negatives may be explained by late transmission of the virus. One study found that 8% of neonates with negative amniocentesis showed viral excretion at birth [25]; however, on follow-up none developed any sequelae. Because of the small risk of false positive and false negative PCR amniocentesis results, neonatal testing to confirm the diagnosis is essential [26,27].

Following prenatal diagnosis of fetal CMV infection, the main aim is to predict the risk of symptomatic neonatal infection, which is associated with poor outcome. Accurate prenatal prediction of poor prognosis for affected infants has proved challenging; estimates are based largely on three factors: 1. Timing of the infection; 2. Presence and type of fetal abnormalities; 3. Laboratory parameters. It appears that, in common with other viral infections, the risk of vertical transmission increases with gestation. However, the association between the timing of infection and *severity* of fetal/neonatal outcome is less well defined. As the diagnosis of congenital CMV infection is often incidental, severe ultrasound abnormalities are described more often than subtle findings. Ultrasound findings can be categorised as fetal cranial, fetal extracranial, and placenta/amniotic fluid abnormalities. It appears that the main sonographic prognostic indicator is fetal cerebral abnormalities [28]. Farkas et al reported that if the antenatal ultrasound examination of the fetal brain was normal, then normal early neuropsychological outcome was likely [28]. When both ultrasound and MRI of the fetal brain are normal prenatally, the neonatal outcome is generally good [29]. The combined predictive value of a normal ultrasound and MRI evaluation to predict an asymptomatic neonate, in fetuses with a positive amniocentesis and when imaging was performed up to the third trimester, after 30 weeks, is at best 95% [30]. Fetal laboratory findings, including viral load, thrombocytopenia (platelet count <

100,000/mm^3) and raised alanine aminotransferase (>80 IU/ml) in the fetal blood may bridge this 5% gap.

In a recent study the risk assessment of infected fetuses for being symptomatic at birth has been shown to be possible as early as the time of diagnosis; ultrasound abnormalities and either amniotic fluid viral load or fetal blood profile (viral load and platelet count) were independent prognostic factors of symptomatic congenital CMV at birth [31]. Both fetal platelet count and blood viral load were better predictors than amniotic fluid viral load. The combined negative predictive values of ultrasound and viral load in amniotic fluid and that of ultrasound and fetal blood parameters were 95% and 100%, respectively [31]. Interestingly, when investigating the non-severe ultrasound features, the positive predictive values of ultrasound alone and in combination with amniotic fluid viral load or with fetal blood parameters were 60%, 78%, and 79%, respectively [31].

PRENATAL THERAPY

The aim of prenatal therapy is either to prevent mother-to-child transmission of CMV or to treat the CMV-infected fetus during pregnancy with the aim of reducing the risk of, and/or severity of, symptomatic infection in the infant.

CMV hyperimmune globulin treatment to prevent antenatal mother-to-child transmission

CMV human immunoglobulin (HIG) is a pooled, high-titre preparation derived from donors with high antibody titres. The rationale for its use is based on the observation

that primary maternal CMV infection carries a higher mother-to-child transmission risk (approximately 30%) compared to the risk in reactivation or reinfection (1.4%) [32]. Its role was investigated in two clinical trials [33,34] and two observational studies [35,36]. Nigro et al [33] conducted a non-randomised clinical trial using CMV HIG in women with a recent primary CMV infection and unknown fetal status before 21 weeks' gestation who declined amniocentesis; these women were offered monthly HIG 100 u/kg. Six of the 37 (16%) women who received HIG had neonates with congenital CMV infection compared to 19/47 (40%) women who did not receive HIG. Unfortunately, the efficacy of CMV HIG has not been borne out in a phase 2 randomised placebo controlled double blind study [34]. This study included a total of 124 women with primary CMV infection at 5 to 26 weeks' gestation [34]. These women were randomly assigned within 6 weeks after the presumed primary infection to receive either HIG or placebo every 4 weeks until 36 weeks of gestation or until the detection of CMV in the amniotic fluid. The primary end-point was congenital infection diagnosed at birth or amniocentesis positive for CMV. The rate of congenital infection was 30% in the HIG group compared to 44% in the placebo group (a non-significant difference; p=0.13) [34]. This study found no significant difference between the two groups in the risk of transmission, the levels of virus specific antibodies, T cell mediated immune response or viral DNA in the blood. The clinical outcome of congenital infection at birth was similar in the two groups. However, the number of adverse obstetric events, including preterm birth, pre-eclampsia and intrauterine fetal growth restriction, was higher in the HIG group compared to the placebo group (13% versus 2%) [34].

Given these conflicting findings, HIG is not routinely recommended and should currently be reserved for use in a research setting only. Another large phase III

randomized placebo-controlled double-blinded trial assessing HIG in pregnancy is currently underway (clinicaltrials.gov: NCT01376778).

CMV hyperimmune globulin treatment to treat the CMV-infected fetus prenatally

Four prospective and two retrospective studies treating small numbers of pregnant women diagnosed with congenital CMV infection have demonstrated a trend to efficacy using CMV HIG [33,35,37-40]. Nigro et al [33] conducted a non-randomised clinical trial in women with primary CMV whose amniotic fluid was positive for CMV; they were offered CMV HIG at a dose of 200 u/kg. Only 1/31 (3%) of neonates had symptomatic CMV disease compared with 7/14 (50%) of women not treated. The authors concluded that HIG therapy was associated with a significantly lower risk of congenital CMV infection, especially symptomatic infection. In the recent randomized, placebo-controlled double-blind trial by Revello et al [34], 7/61 (11%) fetuses of women treated with 100 IU/kg CMV HIG every 4 weeks had transient or permanent abnormalities, compared with 10/62 (16%) fetuses in the placebo group (a non-significant trend). Based on these conflicting findings, HIG should not be recommended as antenatal treatment, and should currently be reserved for use in a research setting only.

Antiviral treatment to prevent antenatal mother-to-child transmission

A randomized, phase II double-blinded clinical trial is planned to evaluate the efficacy of valaciclovir (ValACV) to prevent mother-to-child transmission following primary maternal infection (clinicaltrials.gov identifier NCT02351102). The current use of

antiviral treatment to prevent mother-to-child transmission outside of the research setting is not recommended.

Antiviral treatment to treat the CMV-infected fetus prenatally

In immunocompromised (non-pregnant) patients, three anti-CMV drugs are licensed for use, namely ganciclovir, cidofovir and foscarnet, but their teratogenic and toxic effects preclude their use in pregnancy. Aciclovir (ACV) and its oral prodrug ValACV have been shown to have some effect against CMV in immunocompromised patients [41-43]. In a pilot observational study, Jacquemard et al treated pregnant women with primary CMV with oral ValACV 8g/day [44]. Twenty pregnancies with 21 fetuses were treated at 28 weeks' gestation (range 22-34 weeks) for 7 weeks (range 1-12 weeks). Therapeutic concentrations of the drug were achieved in both maternal and fetal blood, and the viral load in fetal blood decreased significantly after 1 to 12 weeks of treatment. In terms of outcome, seven cases had termination of pregnancy and had evidence of *in utero* progression of the disease with worsening cerebral lesions, or died in utero. A further two infants had severe isolated unilateral deafness. One child had microcephaly with severe deafness but was also diagnosed with incontinentia pigmenti. The remaining 10 infants were developing normally at follow-up, at one to five years of age. By comparison, the outcomes of 24 untreated symptomatic CMV-infected fetuses were as follows: 14 (58%) had termination of pregnancy, intrauterine fetal death or severe neonatal infection. The remaining 10 infants were healthy at follow-up.

Oral ValACV was investigated in a recent open-label, single-group assignment phase II clinical trial entitled 'in utero treatment of cytomegalovirus congenital infection with

valacyclovir (CYMEVAL) [45]. Oral ValACV 8g per day was given for a median of 89 days to pregnant women carrying a moderately infected fetus (Table 1) [45]. When compared with a historical cohort obtained by a meta-analysis of the literature, ValACV significantly increased the proportion of asymptomatic neonates from 43% without treatment to 82% with treatment. This study also provided safety data for the use of valacyclovir in pregnancy [45]. However, the study design and the small number of ValACV-treated women are limitations, and therefore further studies are currently being planned (none listed in clinicaltrials.gov yet).

A proposal for management of cytomegalovirus fetal infection is illustrated in Figure 2. In neonates with symptomatic congenital CMV infection, there is a role for postnatal val/ganciclovir treatment, which should be commenced within the first four weeks of life. There is evidence that treatment can reduce or prevent progression of SNHL in some infants [46].

CONCLUSION

Antenatal oral ValACV might have a promising role in the antenatal treatment of congenital cytomegalovirus. The published findings on the role of HIG are conflicting, and therefore HIG is not recommended, and should currently be reserved for use in the research setting only.

KEY POINTS

- Routine screening for congenital cytomegalovirus infection is not recommended outside the research setting.

- There is currently no licensed vaccine against cytomegalovirus.

- An alternative strategy for prevention of congenital cytomegalovirus infection is to reduce the risk of acquisition of CMV infection through modification of behavior, education of the pregnant women and the healthcare professionals.

- When fetal cytomegalovirus infection has been confirmed by amniocentesis, an important role of prenatal management is to identify the fetuses at risk of symptomatic neonatal disease.

- Antenatal oral valacyclovir appears promising in reducing the risk of symptomatic cytomegalovirus disease at birth in mild or moderately symptomatic fetuses. Due to the limitations of the quality of the evidence, more studies are needed.

- HIG is not routinely recommended in view of the recent evidence of lack of effectiveness and potential harm, and should currently be reserved for use in the research setting only.

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Conflicts of interest: None

Table 1. Criteria to define moderately infected fetus, as defined by the inclusion criteria in the study by Leruez-Ville et al [45].

At least 1 extracerebral abnormality compatible with fetal CMV infection	
	Fetal growth restriction
	Abnormal amniotic fluid volume
	Ascites and/or pleural effusion
	Skin oedema
	Hydrops
	Placentomegaly >40mm
	Hyperechogenic bowel
	Hepatomegaly >40mm
	Splenomegaly >30mm
	Liver calcifications
And/or 1 isolated cerebral abnormality	
	Moderate isolated ventriculomegaly (<15mm)
	Isolated cerebral calcification
	Isolated intraventricular adhesion
	Vasculopathy of lenticulostriate vessels
And/or laboratory findings of generalised CMV infection in fetal blood	
	Fetal viraemia >3000 copies/mL
	Fetal platelet count <100,000/mm^3

Figure Legends

Figure 1. Proposed approach to the antenatal management of Congenital CMV infection

Figure 2. Proposed management of congenital cytomegalovirus infection

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of fetal cytomegalovirus infection with a sample of amniotic fluid positive for viral DNA and/or fetal blood from 2008 through 2013. Using a combination of targeted ultrasound examination along with viral load in amniotic fluid and in fetal blood together with platelet count would enable risk assessment of infected fetuses for being symptomatic at birth as early as the time of initial diagnosis. The results should be validated in prospective studies.

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Figure

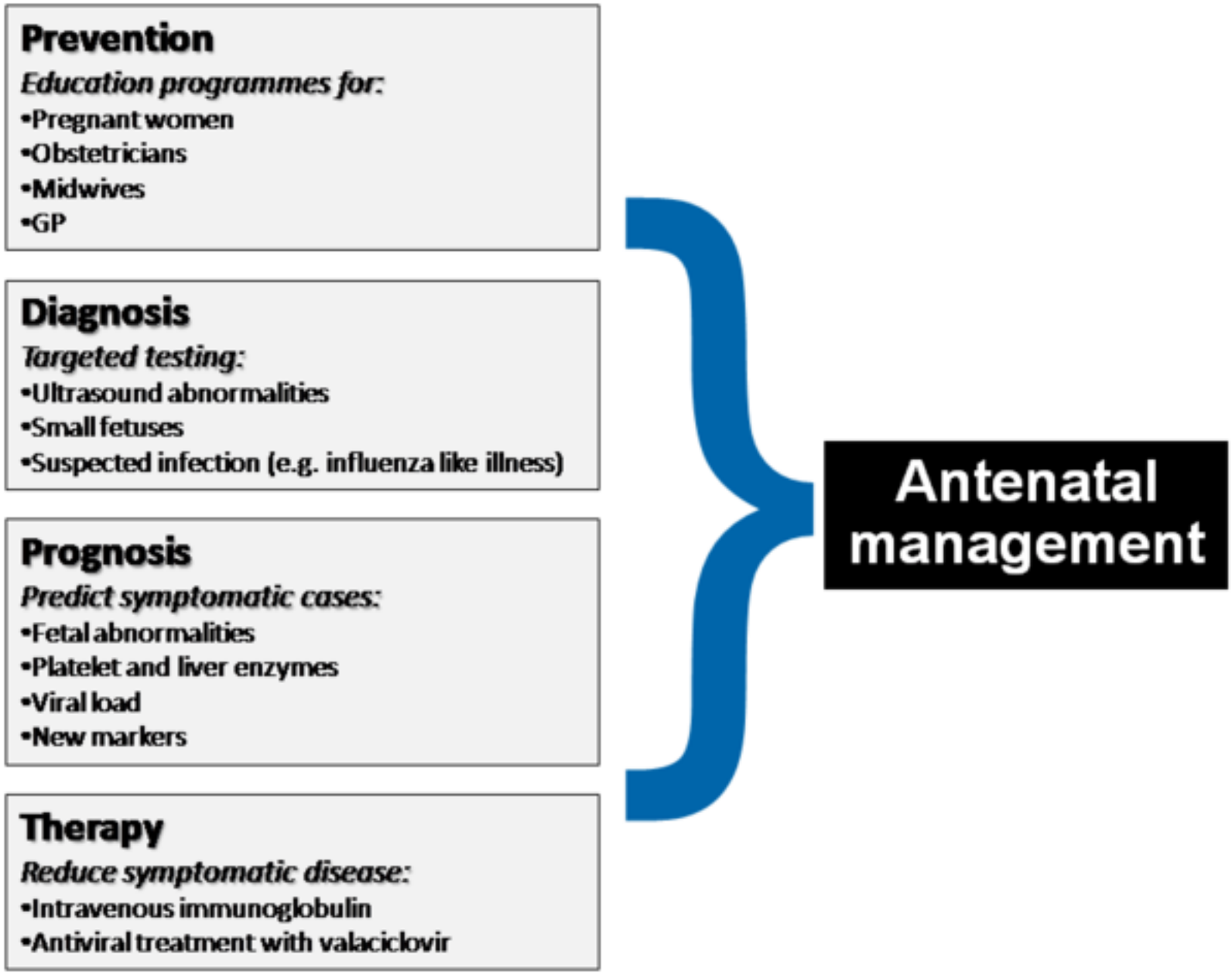

Figure 1. Proposed approach to the antenatal management of Congenital CMV infection

Figure

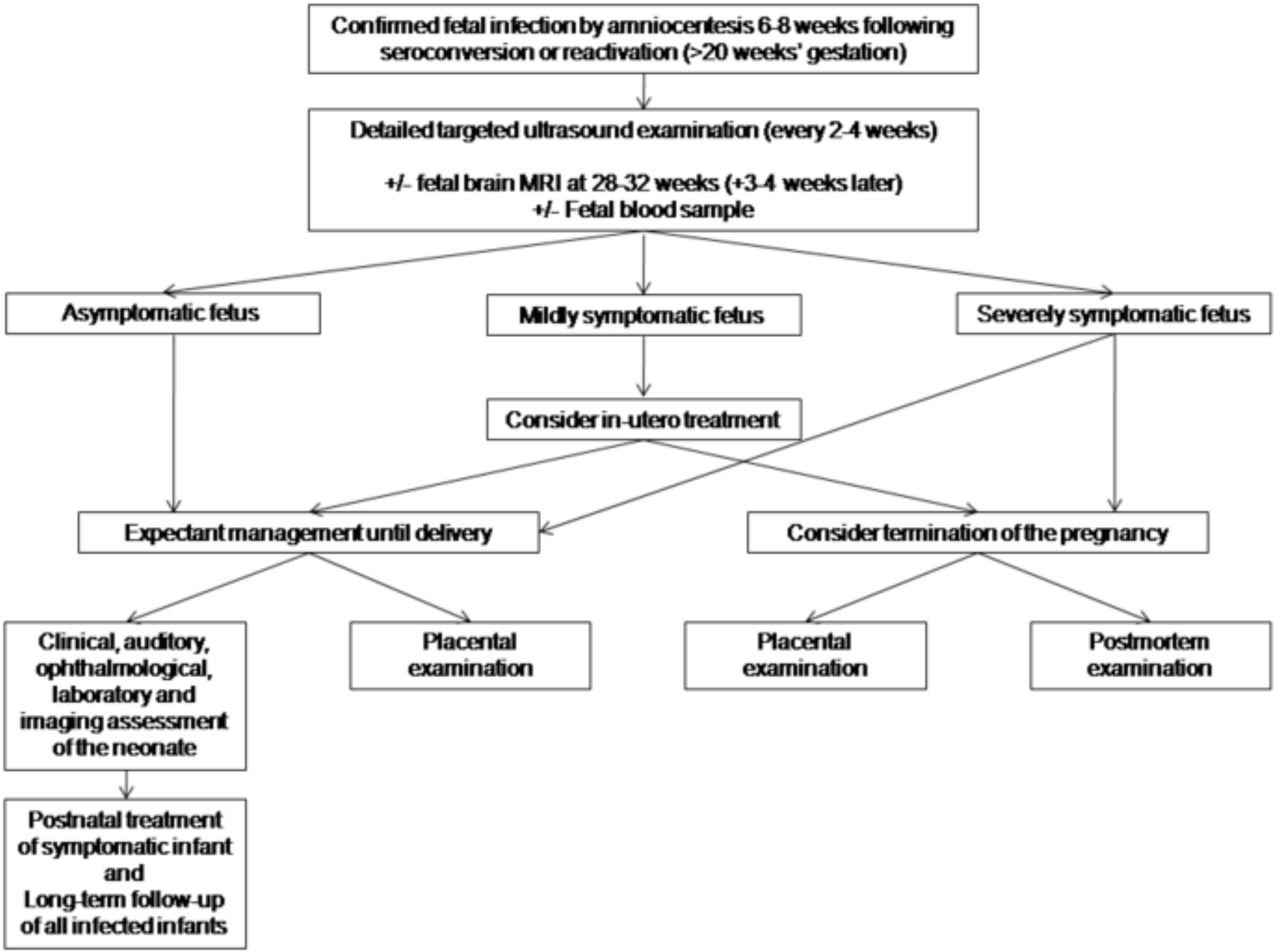

Figure 2. Proposed management of congenital CMV infection (adopted from Benoist et al 2013)

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