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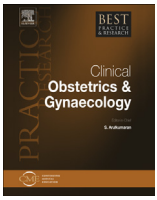

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Fetal cytomegalovirus infection

Marianne Leruez-Ville, M.D., PhD. [a, b],
Yves Ville, M.D., FRCOG [a, c, *]

[a] EA 73-28, Université Paris Descartes, Sorbonne Paris Cité, Paris, 75005, France
[b] AP-HP, Hôpital Necker-E.M., Laboratoire de Microbiologie Clinique. Centre national de Référence Cytomegalovirus- Laboratoire associé, Paris, 75015, France
[c] AP-HP, Hôpital Necker-E.M., Maternité, Unité de Médecine Fœtale, Paris, 75015, France

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Cytomegalovirus (CMV) congenital infection affects 0.7% of live births worldwide and is the leading cause of congenital neurological handicap of infectious origin. However, systematic screening for this infection has not been implemented in pregnancy or at birth in any country. This apparent paradox had been justified by persisting gaps in the knowledge of this congenital infection: uncertain epidemiological data, difficulty in the diagnosis of maternal infection, absence of validated prenatal prognostic markers, unavailability of an efficient vaccine and scarcity of data available on the treatment. However, in the last decade, new data have emerged towards better management of this congenital infection, including solid epidemiological data, good evidence for the accuracy of diagnosis of maternal CMV infection and good evidence for the feasibility of predicting the outcome of fetal infection by a combination of fetal imaging and fetal laboratory parameters. There is also some evidence that valaciclovir treatment of mothers carrying an infected fetus is feasible, safe and might be effective. This review provides an update on the evidence for diagnosis, prognosis and treatment of congenital infection in the antenatal period. These suggest a benefit to a proactive approach for prenatal congenital infections.

* Corresponding author. Hôpital Necker-E.M., Unité de Médecine Fœtale, 149 rue de Sèvres, 75015 Paris, France. Tel.: +33 1 44 49 49 62; Fax: +33 1 44 49 49 60.
E-mail address: ville.yves@gmail.com (Y. Ville).

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Epidemiology of CMV fetal infection

The epidemiology of congenital cytomegalovirus infection has been described by numerous concordant studies published over the last thirty years and is now well established (level III).

Congenital CMV (cCMV) infection has a birth prevalence of 0.7% worldwide [1]. However, birth prevalence varies according to the level of CMV immunity in pregnant women. The birth prevalence is the highest (>1%) in countries where maternal seroprevalence is high (>95%) such as most African and Asian countries. In countries with low maternal seroprevalence (around 50%) such as most European countries, the birth prevalence is the lowest around 0.4%. This reflects the burden of cCMV following maternal secondary infection. Indeed, fetal infection may follow maternal primary infection during pregnancy but also maternal secondary infection which happens in women already immune for CMV before pregnancy. The ratio between fetal infections related to maternal primary infections and those related to maternal secondary infections depends on the seroprevalence rate in pregnant women. In highly seroimmune populations, almost all fetal infections are related to secondary maternal infections [2]. In countries with intermediate CMV seroprevalence ($\approx$70%) such as the US, 25% of congenital infections are expected to be related to primary maternal infections and the other 75% to maternal secondary infections [3]. In countries with low maternal seroprevalence such as most European countries ($\approx$50%) an equal ratio between fetal infections related to primary infection and those related to maternal secondary infection is expected [4,5].

In a meta-analysis based on 15 studies with a total of 117,986 infants screened, the percentage of infected children with CMV-specific symptoms at birth was 12.7%, the percentage of symptomatic children with permanent sequelae was 40-58% and the percentage of children without symptoms at birth who developed permanent sequelae was estimated to be 13.5% [1]. In most studies the definition of a symptomatic neonate is a neonate with clinical and/or laboratory abnormalities (petechia, microcephaly, hepatosplenomegaly, fetal growth restriction (FGR), chorioretinitis, thrombocytopenia, hepatitis and hearing loss). In older studies, hearing loss was not tested at birth and this criterion was not included in the definition of a symptomatic neonate. A first study reported that severe symptoms at birth and long-term sequelae were seen much more frequently among neonates infected after a maternal primary infection than in those infected after a secondary infection [6]. However, the results of early first report have been challenged by more recent data from longitudinal studies published by the same group and by others, indicating that the fetal morbidity related to maternal secondary infection is in fact as high as that related to maternal primary infection. In a series of 300 neonates (176 infected after maternal primary infection and 124 after maternal secondary infection), the proportion of symptomatic neonates was 11% in both groups and the proportion of hearing loss was also 10% in both groups [7]. In another long-term follow-up study, non-primary infections contributed substantially to the burden of childhood congenital CMV disease: half of the children presenting with moderate to severe outcomes were born from mothers with non-primary infections [8].

The epidemiology and pathophysiology of maternal secondary infections are not well understood.(level I) They could be related to either a reactivation of the endogen CMV strain or to a reinfection with a new CMV strain and the relative contribution of both mechanisms to the burden of secondary infection is unknown. The high genetic variability of the CMV genome with 4.7% variability between strains at nucleotide level could explain the possibility of re-infection [9]. The likelihood of reinfection in pregnant women was suggested by the evidence of the acquisition of new CMV antibody specificities between serum samples collected before and after pregnancy in seropositive women who delivered an infected neonate [10]. (level II).

Diagnosis of maternal infection

The diagnosis of primary CMV infection in pregnancy is ascertained when seroconversion is documented with the presence of CMV specific IgG in the serum of a pregnant women who was previously tested IgG negative in a serum, sample collected earlier in pregnancy. (level III) However, the opportunity to diagnose seroconversion is rarely feasible in the absence of screening and prospective monitoring.

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