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Neonatal and short-term outcome after late vertical transmission in congenital CMV-infected fetuses following primary first-trimester maternal seroconversion

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ABSTRACT

Objective To document the course of neonatal and short-term outcomes in pregnancies after first trimester CMV (cytomegalovirus) seroconversion and negative amniotic fluid (AF) CMV PCR.

Methods We included 375 patients with a first-trimester CMV seroconversion and amniocentesis at ≥21 weeks. Termination of pregnancy (TOP) was offered in case antenatally severe CMV-related fetopathy was documented either by ultrasound or by MRI. AF CMV PCR-negative fetuses underwent a PCR CMV on neonatal urine (NU). Perinatal and short-term infant outcomes were investigated by a questionnaire, sent to parents.

Results AF CMV PCR was positive in 118/375 cases (31.4%). TOP was performed in 46/118 (38.9%) and fetal demise occurred twice. Questionnaires were sent to 327 patients with an overall response rate of 77%. Three groups were considered: Group 1: the early infected group (AF CMV PCR positive; N=62), group 2: the late infected group (AF CMV PCR negative, NU CMV PCR positive; N=7) and group 3: the control group (AF+NU CMV PCR negative; N=160). Compared with group 3, group 1 was more frequently symptomatic at birth (6.2% vs 19.4%; p=0.006). In short-term follow-up, hearing impairment (23.5%; p<0.001), mild motor deficit - defined as abnormal early motor development or the need for physiotherapy in later life (21.6%; p=0.005) - and subnormal vision (15.7%; p=0.02) were significantly more frequent. Compared with group 3, group 2 showed more often jaundice (57.1%; p=0.04) and petechiae (28.6%; p=0.04) at birth, but other short-term symptoms were lacking.

Conclusion Although neonates may screen positive on urine for CMV after an AF CMV negative PCR, they show rarely and only mild sequelae in early life.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Primary maternal cytomegalovirus (CMV) infection in the first trimester carries a risk of 30% of vertical transmission to the fetus and about 10–15% of the CMV-infected fetuses will present mild-to-severe symptoms at birth or in later life.

WHAT THIS STUDY ADDS

⇒ CMV primary seroconversion in the first trimester of pregnancy does not result in severe neonatal sequelae if a negative amniotic fluid CMV PCR is encountered.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Patients can be reassured about the neurodevelopmental outcome after a primary CMV infection in the first trimester in the absence of amniotic fluid CMV DNA.

INTRODUCTION

Cytomegalovirus (CMV) infection complicates up to 2.5% of all pregnancies.[1] Primary maternal CMV infection in the first trimester carries a risk of 30–40% of vertical transmission to the fetus. [2] Only 10–15% of the CMV-infected fetuses will present mild-to-severe symptoms at birth or in later life such as sensorineural hearing loss, visual impairment, psychomotor impairment and mental retardation. Despite the potentially severe consequences, universal screening in pregnancy is not recommended to date.[3]

On CMV seroconversion during pregnancy, women should be informed about the frequency and severity of the sequelae such as audiological, visual and neurodevelopmental deficits. Amniotic fluid CMV PCR (AF PCR) analysis 6–8 weeks at the earliest after seroconversion enables diagnosis of fetal infection. In case of a positive AF PCR, fetal transabdominal and transvaginal neurosonography as well as fetal MRI addresses the impact on the fetal brain. On the diagnosis of congenital CMV infection, parents are confronted with an emotionally stressful follow-up. In cases of severe late fetal sequelae termination of pregnancy (TOP) can be justified according

to legal legislation. Hearing loss or visual impairment, however, remains undetected prenatally. However, after a negative AF PCR at midgestation following a first-trimester primary maternal seroconversion, fetuses may become symptomatic at birth or in later life.

We studied the outcome of infants after a maternal primary CMV infection before 14 weeks of gestation and who subsequently underwent an amniocentesis at midgestation. The outcomes of children with vertical transmission were compared with those of non-infected children.[4]

MATERIAL AND METHODS

Study population

This retrospective study includes pregnancies complicated by a primary CMV seroconversion before 14 weeks of gestation and subsequent amniocentesis around 21 weeks of gestation in the period between November 2006 and March 2019 in the University Hospitals of Leuven, Belgium. Patients were excluded if: (1) screening for CMV infection on neonatal urine (NU), saliva or cord blood had not been performed, (2) if pregnant women with CMV seroconversion were treated with intravenous immune globulins (3) and if data collection was incomplete.

All pregnancies with a positive AF CMV PCR (group 1) were closely monitored with ultrasound 2 weekly and with an additional MRI around 30 weeks. TOP was offered in cases with severe fetal central nervous system (CNS) ultrasound and MRI findings. The remaining live born children underwent a standardised CMV-follow-up postnatally: examination by paediatrician, cranial ultrasound, eye fundus and ear examination (standard and brain-evoked responsive audiometry in case of reduced hearing).

AF CMV PCR-negative fetuses underwent a PCR CMV on NU. When NU returned positive (group 2), these neonates were investigated similarly as group 1. In group 3, AF and NU negative PCR for CMV, no additional investigation was performed.

Data collection

For postnatal data collection, a purpose-made questionnaire was distributed to patients after obtaining informed consent.[4–16] This questionnaire gathered parent-reported information on neonatal health, neurological outcomes, hearing outcomes, ophthalmic outcomes and educational progress.

Data on the presence of hepatosplenomegaly and chorioretinitis at birth in CMV-infected children were requested from the paediatricians who examined the neonate. The questionnaire was sent in 2016 including the cases from November 2006 to December 2015. The same questionnaire was addressed end of 2019 to the cases included from January 2016 to March 2019. In case of a positive abnormal result reported on the questionnaire, parents could prove this by documents provided by a healthcare worker. Regarding negative answers on the questionnaire, we argue that parents consider their child 'normal'.

Study design

Primary maternal CMV infection in the first trimester was defined as a change from IgG-negative to IgG-positive serology for CMV up to 14 weeks of gestation. Amniocenteses were performed starting from the 21st week of gestation. All AF CMV PCR analysis was performed in the same laboratory. After birth, vertical transmission was detected by PCR on NU within 72 hours after delivery. This allowed for defining three groups: (group 1) the early infected fetuses with a positive AF PCR, (group 2) the late infected fetuses with negative AF PCR but with a positive NU PCR for CMV and (group 3) the fetuses with no CMV infection (control group). Characteristics of the study population at birth are shown in figure 1. Gestational age and biometry at birth (weight and head circumference), measured in absolute terms and percentiles, are compared between the control group and both the early and the late infected group. Preterm birth was defined as a delivery before <37 weeks of gestation, a small for gestational age as a birth weight below the 10th percentile for gestational age. Microcephaly was diagnosed if the head circumference measured less than the mean by more than 3 SD. Symptomatic CMV disease was considered at the occurrence of at least one of the following: petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction, microcephaly or chorioretinitis. Overall motor deficit (abnormal early motor development) was defined as a need for physiotherapy in later life. Evaluation of early psychomotor development referred to global and fine motor abilities (eg, the ability to walk before the age of 18 months), language skills (uttering the first words before the age of 2 years) and social skills.[11] Hearing loss was investigated by an ENT specialist and classified into mild (loss of 24–40 dB), moderate (loss of 41–60 dB), severe (loss of 61–80 dB) and profound (loss of over 81 dB). Visual impairment, investigated by ophthalmologists, was classified into normal (vision of 20/40 or better), subnormal (vision less than 20/40, better than 20/200 or poor fixation) and severe impairment (less than 20/200 or no fixation). Learning disability at school age was defined as the repeating of a class or the need for adjusted education. Behaviour problems were analysed and defined by child psychiatrists using the Behaviour Problems Inventory (BPI-01). The median age of follow-up was 4 years (range 1–8).

Statistical analysis

Serological and clinical data were collected in a customised database using FileMaker Pro V.17 (Claris, Cupertino, California, USA). For analysis data were anonymised. Statistical analysis included Student's t-test to compare the means and frequencies were compared using Fisher's exact test.

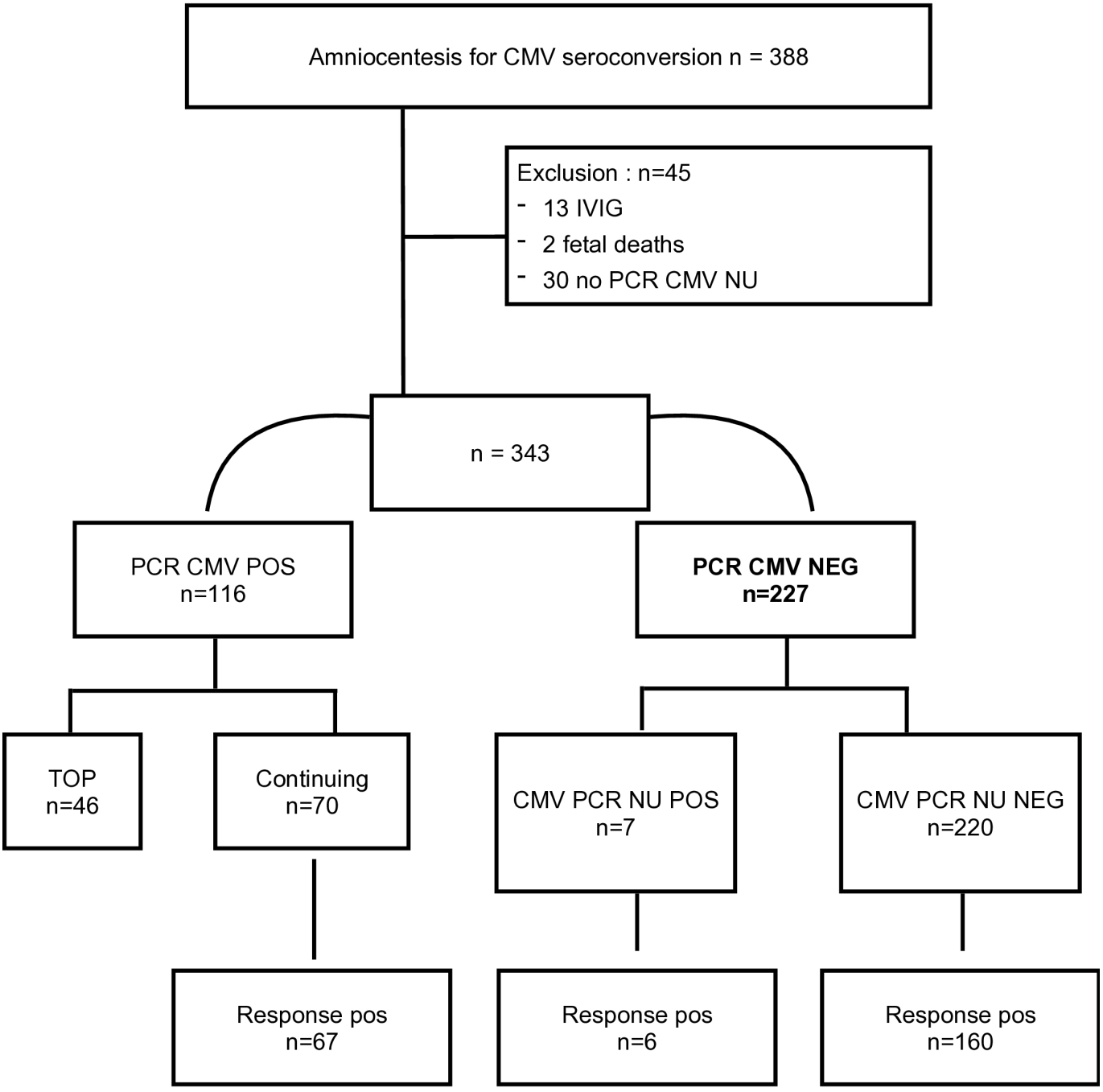

Figure 1 Flowchart summarising inclusions and exclusion criteria. In the study period, 388 patients underwent amniocentesis for CMV seroconversion. 375 patients with first-trimester CMV seroconversion and amniocentesis at ≥21 weeks were included. Termination of pregnancy was offered in case antenatally severe CMV-related fetopathy was documented either by ultrasound or by MRI. Amniotic fluid CMV PCR-negative fetuses underwent a PCR CMV on neonatal urine (NU). Perinatal and short-term infant outcomes were investigated by a questionnaire, sent to parents. CMV, cytomegalovirus; IVG, intravenous immune globulins; NEG, negative; POS, positive.

RESULTS

A total of 388 amniocenteses for CMV PCR were performed during the study period. Of these, 45 patients were excluded from analyses either because of prenatal administration of immune globulins (n=13), fetal demise (n=2) or absence of CMV PCR NU (n=30). amniotic fluid (AF) CMV PCR was positive in 116/343 (33.8%) cases leading to a TOP in 46 pregnancies with severe CMV fetopathy (46/116=39.6%). Of the remaining 70 ongoing pregnancies, 62 patients (88%) responded to the questionnaire (=group 1). AF PCR revealed no CMV DNA in 227 cases (227/343: 66.2%). In 220/227 pregnancies CMV PCR test on NU was negative (96.9%) (=group 3). The response rate to the questionnaire in this group was 160/220 (72.7%). In 7/227 (3.1%) pregnancies CMV PCR test on NU appeared positive (=group 2), indicating

Table 1 Characteristics at birth

	Control (n)	Early infected (n)	Late infected (n)	P value early/control	P value late/control	P value early/late
N	160	62	7			
M:F	76:84	35:27	4:3			
Gestational age: median + (range) (weeks)	39 (32–42)	39 (36–41)	38 (38–40)			
Preterm birth	5 (3.1%)	2 (3.2%)	0 (0%)	1.00	1.00	1.00
Mean birth weight (g) + (SD)	3447 (491)	3378 (525)	3492 (424)	0.35	0.79	0.52
Mean birth weight percentile + (SD)	56 (26)	52 (29)	72 (24)	0.27	0.11	0.06
Small for gestational age	4 (2.5%)	6 (9.7%)	0 (0.0%)	**0.03**	1.00	1.00
Mean head circumference at birth (cm) + (SD)	34.7 (1.4)	34.3 (1.4)	34.5 (0.9)	0.06	0.43	0.65
Mean head circumference percentile at birth + (SD)	56 (26)	48 (30)	63 (18)	**0.04**	0.66	0.08

Characteristics of the three different groups at birth.
Group 1: the early infected fetuses with a positive AF PCR.
Group 2: the late infected fetuses with negative AF PCR but with a positive NU PCR for CMV.
Group 3: the fetuses with no CMV infection (control group).
Bold values signifies p< 0.05.
AF, amniotic fluid; CMV, cytomegalovirus; NU, neonatal urine.

late vertical transmission. Six parents responded to the questionnaire (85.7%) (figure 1).

Mean gestational age at delivery, preterm birth rates and mean birth weights are comparable between the three groups. The prevalence of small for gestational age infants, compared with group 3 is significantly higher in group 1 (9.7% vs 2.5%; p=0.03). Mean head circumferences are comparable in the three groups, although when expressed in percentiles, a significant difference is noted between group 1 and group 3 (48th vs 56th percentile; p=0.04). Microcephaly occurred in only two cases; however, there was no significant difference in frequency in the three groups (table 1).

The frequencies of various clinical findings at birth are shown in table 2. Overall, compared with group 3, group 1 but not group 2 presented significantly more

Table 2 Symptoms at birth

	Control	Early infected	Late infected	P value early/control	P value late/control	P value early/late
N	160	62	7			
HC<3 SD	1 (0.6%)	1 (1.6%)	0 (0.0%)	0.48	1.00	1.00
Abnormal neurological examination	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.00	1.00	1.00
Jaundice	31 (19.3%)	11 (17.7%)	4 (57.1%)	0.85	**0.04**	**0.04**
Mild	16 (10.0%)	6 (9.7%)	3 (42.9%)	1.00	**0.03**	**0.04**
Moderate	11 (6.9%)	5 (8.1%)	0 (0.0%)	0.78	1.00	1.00
Severe	3 (1.9%)	0 (0.0%)	1 (14.3%)	0.56	0.16	0.10
Petechiae	6 (3.8%)	8 (12.9%)	2 (28.6%)	**0.03**	**0.04**	0.27
Mild	6 (3.8%)	6 (9.7%)	2 (28.6%)	0.10	**0.04**	0.18
Moderate	0 (0.0%)	2 (3.2%)	0 (0.0%)	0.08	1.00	1.00
Severe	0 (0.0%)	0 (0.0%)	0 (0.0%)	1.00	1.00	1.00
Hepatosplenomegaly	0 (0.0%)	1 (1.6%)	0 (0.0%)	1.00	1.00	1.00
Chorioretinitis	0 (0.0%)	1 (1.6%)	0 (0.0%)	1.00	1.00	1.00
Symptomatic at birth*	10 (6.2%)	12 (19.4%)	2 (28.6%)	**0.006**	0.08	0.62

Bold values signifies p< 0.05.
*Symptomatic at birth: petechiae, hepatomegaly, splenomegaly, intrauterine growth restriction, microcephaly and chorioretinitis.
HC, head circumference.

Table 3 Symptoms in short-term follow-up

	Control N (%)	Early infected N (%)	Late infected	P value early/ control	P value late/ control	P value early/late
N	122	51	6*			
Median age (years) (range)	3.4 (1–8)	4.0 (1–8)	4.4 (1–8)			
Abnormal early psychomotor development	2 (1.6)	2 (3.9)	0 (0.0%)	0.58	1.00	1.00
Logopedics	3 (2.5)	9 (17.6)	0 (0.0%)	**<0.001**	1.00	0.58
Physiotherapy	3 (2.5)	5 (9.8)	0 (0.0%)	0.05	1.00	1.00
Overall motor deficit†	7 (5.7)	11 (21.6)	0 (0.0%)	**0.005**	1.00	0.58
Hearing impairment	1 (0.8)	12 (23.5)	0 (0.0%)	**<0.001**	1.00	0.33
Unilateral mild–severe	1 (0.8)	2 (3.9)	0 (0.0%)	0.21	1.00	1,00
Unilateral profound	0 (0.0)	8 (15.7)	0 (0.0%)	**<0.001**	1.00	0.58
Bilateral	0 (0.0)	2 (3.9)	0 (0.0%)	0.09	1.00	1.00
Subnormal vision	5 (4.1)	8 (15.7)	0 (0.0%)	**0.02**	1.00	0.58
Severe impaired vision	0 (0.0)	0 (0.0)	0 (0.0%)	1.00	1.00	1.00
Scholastic backwardness	3 (2.6)	1 (2.0)	0 (0.0%)	1.00	1.00	1.00
Behavioural problems	4 (3.3)	5 (9.8)	0 (0.0%)	0.13	1.00	1.00

Bold values signifies p< 0.05.
*Excluded: children younger than 1 year; children on which insufficient data about short-term follow-up was obtained.
†Overall motor deficit: number of children who had an abnormal early psychomotor development and needed logopedics and physiotherapy in later life.

often symptoms at birth (p=0.006 and p=0.62, respectively); at birth petechiae are significantly more frequent in both group 1 (12.9%; p=0.03) and group 2 (28.6%; p=0.04), compared with group 3 (3.8%); jaundice was observed significantly more frequent in group 2 (57.7%), compared with both group 3 (19.3%; p=0.04) and group 1 (17.7%; p=0.04). Both hepatosplenomegaly and chorioretinitis are present in only one newborn in group 1 (not significant (NS)).

Table 3 shows an overview of symptoms in short-term follow-up (median 4 years range 1–8). Overall reduced motor development was observed more frequently in group 1 compared with group 3 (21.6% vs 5.7%; p=0.005). In group 2, no symptoms in the short-term follow-up were noted.

Based on the questionnaire deviant psychomotor development showed in eight children over time in group 3: delayed or mildly disturbed language/speech development (n=5), reduced fine motor skills (n=2) and need for psychomotor education (n=1).

Varying degrees of hearing impairment were diagnosed in 12 children (23.5%) in group 1 compared with group 3 (p<0.001), in which one child had unilateral mild-to-severe hearing loss (0.8%). In group 2, no hearing loss was reported. Severe impaired vision was not reported in any group. However, subnormal vision was significantly more frequent in group 1 (n=8; 15.7%) compared with group 3 (n=5; 4.1%) (p=0,02). In group 2, no subnormal vision was reported.

Learning disability at school age was similarly low in the three groups: one child (2.0%) in group 1, no children in group 2 and three children (2.6%) in group 3. Abnormal behaviour affected five children (9.8%) in group 1, none in group 2 and four children (3.3%) in group 3 (NS)

DISCUSSION

This retrospective study aimed to investigate symptoms at birth and in later life related to a maternal primary CMV infection before 14 weeks of gestation with confirmation of fetal infection either by amniocentesis around 21 weeks, and a neonatal urinary CMV PCR. We conclude that there is no severe neonatal impairment after a mean follow-up of 4 years (range 1–8 years). Therefore we can reassure parents with a primary CMV seroconversion before 14 weeks of gestation after a negative AF PCR.

All pregnancies were closely monitored with serial ultrasound scans including transabdominal and transvaginal fetal neurosonography and fetal MRI. Severe CMV-related CNS findings allowed the possibility of TOP even late in gestation after approval by a multidisciplinary team. As such, this policy reduces significantly serious congenital CMV (cCMV)-related CNS sequelae in our population. Microcephaly did not occur in our neonatal population whereas it has been reported in up to 36–53% of symptomatic children at birth.[11 15 17 18] However, the mean head circumference percentile at birth appeared significantly smaller in the early infected group (p=0.04). The frequency of demise among symptomatic infants is commonly reported to be 10–30%.[19] In our study, no postnatal deaths were reported. This is mainly related to the TOP policy in case of severe late findings. In our early CMV-infected group (group 1), the sequelae at birth and short-term

follow-up are comparable with the literature. Hearing deficiency, which is the most common symptom cannot adequately be predicted prenatally. Neonates in the late CMV-infected group did not show symptoms at the short-term follow-up, therefore it is possible to reassure the parents of having a negative AF PCR result. Nevertheless, mild audiological, visual and neurodevelopmental sequelae are described in the literature.[4 20] A recent systematic review and meta-analysis on CMV infection during pregnancy and negative amniocentesis report no severe neonatal symptoms.[21] Their pooled data report on women infected in the periconceptional period and in the first, second and third trimesters. Because cCMV is predominantly an embryopathy, we decided to only include first-trimester CMV seroconversion patients. With a higher number of included patients and a mean follow-up of 4 years (range 1–8 years), the outcome of our study is in line with the meta-analysis.

Overall about 10–15% of children with cCMV infection show clinical symptoms at birth such as petechiae, hepatosplenomegaly, intrauterine growth restriction, microcephaly and chorioretinitis. [22] In our study, 20.3% of all (19.4% in early infected (group 1) and 28.6% in late infected group (group 2)) infected children were symptomatic at birth. This difference in prevalence can be explained by over-reporting the presence of symptoms by parents in our study, while in other studies these symptoms were observed by clinicians only. The prevalence of hepatosplenomegaly (8.3%) and chorioretinitis (8.3%) in children symptomatic at birth is low compared with the literature (39–60% and 11–14%, respectively). Hearing loss is present in 23.5% of the children of early CMV-infected pregnancies, and increases to 38.4% in the neonatal symptomatic subgroup; in the asymptomatic subgroup, it was still 18.4%. Our results are in line with the literature showing that 22–65% of children with symptomatic infection have sensorineural hearing loss compared with only 6–23% of the children with asymptomatic infection. Of all CMV-infected children 10–15% suffer from hearing loss.[23 24] Rivera *et al* reported petechiae and intrauterine growth restriction as the only independently predictive markers of hearing loss. [25] Miller *et al* reported a slight risk (7%) of developing sequelae, mostly partial unilateral hearing loss, after second-trimester infection.[26] None of the late infected fetuses (group 2) in our study presented with hearing loss. Also, Pass *et al* noted sensorineural hearing deficits in a small number (2.5%) of late-infected fetuses.[27]

Compared with the control group (group 3), subnormal vision was significantly more frequent in early CMV-infected fetuses (group 1). No subnormal vision was noted in the late-infected group (group 2). None of the children were visually severely impaired. Coats *et al* observed subnormal vision in 5% and severely impaired vision in 17% of CMV-infected children symptomatic at birth, caused either by cortical, optic nerve and/or retinal abnormalities.[28] The difference in our results is hard to explain. The obtained ophthalmological reports were always very concise, which may have influenced the categorisation of the visual impairment.

Noyola *et al* described major motor dysfunction in 36.5% of symptomatic patients, such as hypertonia and spasticity and the impaired ability to perform routine daily tasks.[29] In our population, the motor deficit was defined as an abnormal early motor development or the need for physiotherapy in later life. In 21.6% of early infected children, mild motor deficit was observed, which is significantly more frequent than in the control group (p=0.005). No major motor deficits were found. Only 1.7% of infected children had a learning disability at school age. Pass *et al* found an IQ<70 in 17% after the first trimester of CMV transmission.[25] In addition, Noyola *et al* reported an IQ<70 in 46.2% of CMV-infected children symptomatic at birth.[29] Our data on the reduced prevalence of motor deficits and mental retardation can be related to the intensive ultrasound follow-up and the opportunity for late TOP. Intracranial abnormalities, such as microcephaly and intracerebral calcifications, are strongly related to poor neurodevelopmental outcomes.[29 30] However, the presence of motor deficits may be underestimated because it was not questioned in depth. Furthermore, mild mental retardation may become more obvious over time.[31] Since the median age of our infected population is 4 years, mental retardation and scholastic backwardness are probably underestimated.

Engman *et al* pointed out that congenital CMV infection might be an aetiological factor for autism.[19] No significant differences in behaviour scores were noted in our population. But for this parameter too, a mean follow-up of 4 years is too short to make the proper diagnosis.

A limitation of our study is the small number of children included in the late infection group. Another limitation is the response rate to the questionnaire. Not all participants responded, giving answer rates in group 1, 2 and 3 of 88%, 72.7% and 85.7%, respectively.

Most European countries do not routinely screen for CMV in pregnancy. This was also the case in most centres in Belgium because of restrictive global guidelines from the KCE (Kennis Centrum voor Epidemiologie). The relevance of this screening should be evaluated in each country, based on local epidemiology and cost-effectiveness. The policy of routinely proposing a CMV screening in the first trimester of pregnancy in our centre as well as in many other Belgian centres has been adapted after a recent French cost-effectiveness study showing that universal screening in conjunction with valaciclovir treatment would be cost-effective compared with current practice.[32]

CONCLUSION

From our results, we conclude that late CMV infection shows significantly fewer sequelae than previously reported, although mild audiological, visual and neurodevelopmental impairments have been reported.

Parents can be reassured on a negative PCR AF, however, it remains important to counsel correctly regarding the potential minor sequelae.

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