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Prenatal predictors of adverse perinatal outcome in congenital cytomegalovirus infection: a retrospective multicenter study

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Abstract

Objectives: To identify predictors of adverse perinatal outcome in congenital cytomegalovirus (CMV) infection.
Methods: In a multicenter study fetuses with congenital CMV infection diagnosed by PCR on amniotic fluid and normal prenatal imaging at the time of diagnosis were included. Primary outcome was the occurrence of structural anomalies at follow-up ultrasound or prenatal magnetic resonance imaging (MRI). Secondary outcomes were the occurrence of anomalies detected exclusively postnatally and the rate of symptomatic infection.
Results: One hundred and four fetuses with congenital CMV were included in the study. Anomalies were detected at follow-up ultrasound or MRI in 18.3% (19/104) cases. Additional anomalies were found after birth in 11.9% (10/84) of cases and 15.5% (13/85) of newborns showed clinical symptoms related to CMV infection. There was no difference in either maternal age (p=0.3), trimester (p=0.4) of infection and prenatal therapy (p=0.4) between fetuses with or whiteout anomalies at follow-up. Conversely, median viral load in the amniotic fluid was higher in fetuses with additional anomalies at follow-up (p=0.02) compared to those without. At multivariate logistic regression analysis, high viral load in the amniotic fluid, defined as ≥100,000 copies/mL was the only independent predictor for the occurrence of anomalies detected exclusively at follow-up ultrasound assessment or MRI, with an OR of 3.12.
Conclusions: Viral load in the amniotic fluid is a strong predictor of adverse perinatal outcome in congenital CMV infection. The results of this study emphasize the importance of adequate follow up even in case of negative neurosonography to better predict postnatal adverse outcomes of infected newborns, especially in amniotic fluid high viral load.

Keywords: cytomegalovirus (CMV); infection; outcome.

Introduction

Cytomegalovirus (CMV) is a DNA virus of the Herpesviridae family [1] and is the most frequent cause of congenital viral infection, with a prevalence of around 0.5 and 1.3% of all live births [2–4]. CMV is the leading cause of neurosensorial hearing loss and mental retardation in children without genetic diseases worldwide [5].

Timing and type of maternal infection are the primary determinants of perinatal outcome in fetuses with CMV infection [6–8]. Although the risk of vertical transmission increases with gestational age, the magnitude of fetal damage is higher when the infection is acquired in early pregnancy. Likewise, the risk of vertical transmission is higher in primary compared to non-primary maternal infection [9].

The gold standard for the diagnosis of congenital CMV infection is the identification of CMV DNA in the amniotic fluid, confirmed at polymerase chain reaction (PCR) at amniocentesis at approximately 20 weeks' gestation [10]. Once CMV infection is diagnosed on amniotic fluid, longitudinal imaging assessment of the fetus should be undertaken to identify structural anomalies potentially impacting the short- and long-term outcome of the newborn [11]. CMV is associated with a. multitude of nonspecific fetal anomalies, mainly, affecting the central nervous system, including ventriculomegaly, periventricular calcification, microcephaly and altered cortical development [12]. Ultrasound is the

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primary imaging technique for assessing fetuses with CMV infection, although recent evidence suggests that fetal magnetic resonance imaging can detect additional structural anomalies not identified at ultrasound in about 7–8% of cases [12, 13].

Prenatal prediction of post-natal outcome in fetuses with congenital CMV infection is challenging, especially when no structural anomaly is identified at the time of diagnosis [14]. The published literature is highly heterogenous and the previously published studies are affected by small sample size, retrospective design, lack of longitudinal imaging assessment and heterogeneity in the definition of the adverse outcomes explored [15–17]. We hypothesized that variables such timing of the infection, prenatal treatment on viral load in the amniotic may affect the prevalence of poor perinatal outcome.

The primary aim of the present study is to identify possible predictors of adverse outcome in fetuses with congenital CMV infection, especially when no anomalies are detected at the time of diagnosis.

Materials and methods

Study design and participants

This was a multicenter, retrospective, cohort study involving 11 referral centers in Italy from 2012 to 2021 (Brescia, Chieti, Foggia, Modena, Naples, Padova, Rome–Catholic University of Sacred Heart, Rome; Sapienza University, Rome; University Tor Vergata, Treviso and Trieste). The study included pregnant women with primary or non-primary CMV infection confirmed by PCR analysis of amniotic fluid. Approval of the local Ethical Committees of the participating centers was obtained.

Inclusion criteria were fetuses with congenital CMV infection diagnosed by PCR analysis of amniotic fluid obtained by amniocentesis performed after 20 weeks of gestation or after 6–8 weeks after maternal seroconversion as recommended by national and international guidelines [10]. And normal karyotype, Exclusion criteria were the presence of CNS and extra-CNS anomalies detected at the time of the diagnosis.

The outcomes observed were:

- Additional CNS or extra-CNS anomalies detected either at ultrasound or fetal MRI.
- Additional anomalies detected exclusively post-natally.
- Post-natal clinical symptoms related to congenital CMV infection, including microcephaly, neurological symptoms, hearing and ocular anomalies.

Longitudinal, detailed ultrasound follow-up after diagnosis of fetal infection was performed every 2–4 weeks, according to each local protocol, including a comprehensive evaluation of fetal growth, placenta, amniotic fluid volume, fetal Doppler and the assessment of potential ultrasound markers of fetal disease. Fetal MRI was performed according to the standardized planes for fetal brain examination according to ISUOG guidelines for fetal MRI [18].

Cases with ultrasound anomalies at diagnosis and chromosomal anomalies or genetic syndromes detected either before or after birth were excluded. The clinical records were examined, and data collected in a dedicated merged database. STROBE guidelines were followed [19].

Data analysis

The potential association between the recorded demographic and clinical characteristics and each of the three outcomes were initially evaluated using chi-squared test for categorical variables, t-test and Kruskal-Wallis test for normally distributed and non-normally distributed continuous variables (Shapiro-Wilk test), respectively. The potential independent predictors of each outcome were then evaluated using stepwise forward logistic regression. All covariates were tested for inclusion in the final model, in which only those significant at either univariate or adjusted analysis were retained. To reduce potential overfitting, the overall number of covariates was limited to 1/10 of the anomalies in all phases of model fitting. The goodness-of-fit was checked using Hosmer-Lemeshow test, and the predictive power assessed through C-statistics (area under the receiving operator curve). Given the low number of women with additional anomalies detected only on postnatal imaging (n=10) and with postnatal clinical symptoms (n=13), no multivariate analysis could be performed for these two outcomes, and raw ORs and 95% CIs were reported. Missing values were less than 1% for all variables, thus no missing imputation technique was adopted.

Statistical significance was defined as a two-sided p-value<0.05, and all analyses were carried out using Stata, version 13.1 (Stata Corp., College Station, Texas, USA, 2013).

Results

Maternal characteristics

One hundred and four fetuses with congenital CMV were included in the study. General characteristics of the study population are reported in Table 1. Mean maternal age was 31.3 ± 5.8 years while mean BMI was 25.9 ± 3.9 years. 85.6% of women acquired infection in the first while 14.4% in the second trimester. 96.2% of congenital CMV infections were primary and only 3.8% secondary.

Additional anomalies were detected at follow-up ultrasound or prenatal imaging in 18.3% (19/104) cases. Table 2 reported the results of the univariate analysis comparing fetuses with and those without additional anomalies detected at prenatal imaging (either MRI or ultrasound). There was no difference in either maternal age (p=0.3), type (p=0.12) and trimester (p=0.4) of infection and prenatal therapy with either Immunoglobulin or Valacyclovir (p=0.4) between fetuses who compared to those who did not show additional anomalies at follow-up ultrasound or MRI. Conversely, median

Table 1: Selected demographic and clinical characteristics, and outcomes of the sample.

Variables	(n=104)
Mean age at diagnosis, years (SD)	31.3 (5.8)
Mean body mass index, kg/m^2 (SD)	25.9 (3.9)
Year of scan	
2010–2015	25.0
2016–2017	32.7
2018–2021	42.3
Trimester of infection, %	
First	85.6
Second	14.4
Type of infection, %	
Primary	96.2
Secondary	3.8
Mean gestational age at 1st US assessment, weeks (SD)	17.5 (4.2)
Mean gestational age at amniocentesis, weeks (SD)	20.5 (1.4)
Mean gestational age at MRI, weeks (SD)	26.1 (5.1)
Mean interval between last US and MRI, days (SD)	6.1 (8.2)
Detected viral load at PCR	
Median value, copies/mL (IQR)	58,791 (1,058,465)
High viral load, %[a]	41.7
Therapy	
Prenatal therapy, %	24.0
Type of therapy, %	(n=25)
Immunoglobulin	64.0
Valaciclovir	36.0
Mean gestational age at therapy start, weeks (SD)	19.7 (4.0)
Mean gestational age at therapy end, weeks (SD)	26.7 (7.4)
Mean therapy length, weeks (SD)	7.0 (9.0)
Pregnancy outcome, %	
Livebirth	90.4
Termination of pregnancy	9.6
Outcomes	
Additional anomalies detected only at follow-up US or prenatal MRI, %	18.3
Livebirth only	(n=94)
Additional anomalies detected only on post-natal imaging, %	10.6
Post-natal symptoms, %	13.8
Hearing anomalies, %	7.5

[a]Defined as ≥ 100,000 copies/mL. SD, standard deviation; IQR, interquartile range; US, ultrasound; MRI, magnetic resonance imaging; PCR, polymerase chain reaction.

viral load in the amniotic fluid was higher in fetuses with compared to those without additional anomalies at follow-up (p=0.02). The rate of termination of pregnancy was significantly higher in fetuses with anomalies (0.012). Additional anomalies were found after birth in 11.9% (10/84) of cases. There was no significant difference in any of the main prenatal characteristics explored between fetuses with compared to those without additional anomalies detected exclusively after birth (Table 3).

After birth 15.5% (13/85) of newborns showed clinical symptoms related to CMV infection. At univariate analysis (Table 4), the presence of associated anomalies detected prenatally (p=<0.001) and postnatally, were the only predictors of symptomatic infection, while viral load in the amniotic fluid (p=0.05), type and timing at infection were not.

At multivariate logistic regression analysis, high viral load in the amniotic fluid, defined as a 100,000 copies/mL was the only independent predictor for the occurrence of anomalies

Table 2: Selected demographic and clinical characteristics, stratified by fetal anomalies detected only at follow-up US or prenatal MRI.

Variables	Additional fetal anomalies					
	No (n=85)	Yes (n=19)	Raw OR (95% CI)	p[a]	Adjusted OR (95% CI)	p[b]
Mean maternal age, years (SD)	31.6 (5.7)	29.9 (6.2)	0.95 (0.87–1.04)	0.3	–	–
Mean maternal BMI, kg/m^2 (SD)	25.9 (3.9)	26.2 (3.9)	1.02 (0.90–1.16)	0.8	–	–
Year of scan						
2010–2015	23.5	31.6	1 (Ref. cat.)	–	–	–
2016–2017	30.6	42.1	1.03 (0.31–3.43)	0.9	–	–
2018–2021	45.9	26.3	0.43 (0.12–1.47)	0.2	–	–
Trimester of infection, %						
First	87.1	79.0	1 (Ref. cat.)	–	–	–
Second	12.9	21.0	1.79 (0.50–6.40)	0.4	–	
Type of infection, %						
Primary	97.6	89.5	1 (Ref. cat.)	–	–	–
Secondary	2.4	10.5	4.88 (0.64–37.1)	0.12	–	–
Mean gestational age in weeks at 1st US assessment (SD)	18.0 (4.1)	15.4 (4.1)	0.87 (0.78–0.98)	0.022	0.87 (0.77–0.98)	0.02
Mean gestational age in weeks at amniocentesis (SD)	20.5 (1.4)	20.6 (1.1)	1.07 (0.77–1.49)	0.7	–	–
Mean gestational age in weeks at MRI (SD)	26.0 (5.1)	26.3 (4.8)	1.01 (0.92–1.12)	0.8	–	–
Mean interval between last US and MRI in days (SD)	5.9 (8.7)	7.1 (5.5)	1.11 (0.77–1.61)	0.6	–	–
Detected viral load at PCR						
Median value, copies/mL (IQR)	40,500 (514,772)	1,650,000 (5,022,204)	1.02 (1.00–1.04)	0.02	–	–
High viral load, %[c]	42.3	68.4	2.95 (1.02–8.50)	0.045	3.12 (1.04–9.39)	0.042
Therapy						
Prenatal therapy, %	22.4	31.6	1.60 (0.54–4.69)	0.4	–	–
Type of therapy, %	(n=19)	(n=6)				
Immunoglobulin	57.9	83.3	–	–	–	–
Valaciclovir	42.1	16.7	–	–	–	–
Mean gestational age in weeks at therapy start (SD)	18.9 (4.3)	21.9 (1.0)	–	–	–	–
Mean gestational age in weeks at therapy end (SD)	26.6 (7.8)	26.9 (6.5)	–	–	–	–
Mean therapy length in weeks (SD)	7.7 (9.8)	5.0 (6.1)	–	–	–	–
Pregnancy outcome, %						
Livebirth	94.1	73.7	1 (Ref. cat.)	–	–	–
Termination of pregnancy	5.9	26.3	5.71 (1.46–22.3)	0.012	–	–
Livebirth only (n=94)	(n=80)	(n=14)				
Additional anomalies detected only on post-natal imaging, %	7.5	28.6	4.93 (1.18–20.5)	0.03	–	–
Post-natal clinical symptoms, %	7.5	50.0	12.3 (3.24–47.0)	<0.001	–	–
Hearing anomalies, %	5.0	21.4	5.18 (1.02–26.3)	0.047	–	–

OR, odds ratio; CI, confidence interval; Ref. cat., reference category; SD, standard deviation; IQR, interquartile range; PCR, polymerase chain reaction; US, ultrasound; MRI, magnetic resonance imaging. [a]Chi-squared test for categorical variables; t-test and Kruskal-Wallis test for normally distributed and non-normally distributed continuous variables, respectively. [b]Logistic regression model including 104 observations; area under the ROC curve=0.77; Hosmer-Lemeshow test for the goodness-of-fit p=0.3. [c]Defined as ≥ 100,000 copies/mL.

Table 3: Selected demographic and clinical characteristics, stratified by additional anomalies detected only on postnatal imaging.

Variables	Additional postnatal anomalies			
	No (n=84)	Yes (n=10)	Raw OR (95% CI)	p[a]
Mean maternal age, years (SD)	31.5 (5.9)	30.3 (5.5)	0.96 (0.86–1.08)	0.5
Mean maternal BMI, kg/m^2 (SD)	25.7 (4.0)	27.5 (4.3)	1.12 (0.95–1.31)	0.2
Year of scan				
2010–2015	23.8	20.0	1 (Ref. cat.)	–
2016–2017	29.8	70.0	2.80 (0.52–15.0)	0.2
2018–2021	46.3	10.0	0.26 (0.02–3.00)	0.2
Trimester of infection, %				
First	83.3	90.0	1 (Ref. cat.)	–
Second	16.7	10.0	0.56 (0.07–4.74)	0.6
Type of infection, %				
Primary	98.8	90.0	1 (Ref. cat.)	–
Secondary	1.2	10.0	9.22 (0.53–160)	0.12
Mean gestational age in weeks at 1st US assessment (SD)	18.2 (3.9)	15.6 (5.2)	0.88 (0.76–1.01)	0.07
Mean gestational age in weeks at amniocentesis (SD)	20.5 (1.5)	20.5 (1.0)	1.00 (0.63–1.59)	0.9
Mean gestational age in weeks at MRI (SD)	27.0 (5.0)	23.9 (4.6)	0.88 (0.76–1.02)	0.08
Mean interval between last US and MRI in days (SD)	6.4 (9.0)	5.8 (4.7)	0.99 (0.91–1.08)	0.8
Detected viral load at PCR				
Median value, copies/mL (IQR)	49,202 (840,127)	259,000 (1,684,500)	1.00 (0.98–1.02)	0.7
High viral load, %[a]	46.4	50.0	1.15 (0.31–4.38)	0.8
Therapy				
Prenatal therapy, %	15.5	80.0	21.9 (4.16–115)	<0.001
Type of therapy, %	(n=13)	(n=8)		
Immunoglobulin	76.9	50.0	–	–
Valaciclovir	23.1	50.0	–	–
Mean gestational age in weeks at therapy start (SD)	19.4 (4.9)	21.1 (1.5)	–	–
Mean gestational age in weeks at therapy end (SD)	22.9 (4.5)	31.4 (7.2)	–	–
Mean therapy length in weeks (SD)	3.5 (7.3)	10.3 (7.6)	–	–
Fetal anomalies detected only at follow-up US or prenatal MRI, %	11.9	40.0	4.93 (1.18–20.5)	0.03
Post-natal clinical symptoms, %	8.3	60.0	16.5 (3.74–72.7)	<0.001
Hearing anomalies, %	6.0	20.0	3.95 (0.66–23.8)	0.13

OR, odds ratio; CI, confidence interval; Ref. cat., reference category; SD, standard deviation; IQR, interquartile range; PCR, polymerase chain reaction; US, Ultrasound; MRI, magnetic resonance imaging. [a]Chi-squared test for categorical variables; t-test and Kruskal-Wallis test for normally distributed and non-normally distributed continuous variables, respectively.

detected exclusively at follow-up ultrasound assessment or MRI, with an OR of 3.12 (95% CI 1.0–9.4), while it was not possible to carry multivariate analysis for the other explored outcomes in view of the small number of events detected.

Discussion

Summary of the main findings

The findings from this study show that, in fetuses with congenital CMV infection and normal ultrasound assessment at the time of diagnosis, additional anomalies at follow-up or after birth are detected in 18% and 11.9% of cases respectively, while 16% of newborns showed clinical symptoms related to the infection. Viral load in the amniotic fluid was independently associated with adverse fetal and post-natal outcome, irrespective of the presence of normal prenatal imaging, thus confirming the prognostic role of PCR in predicting the prognosis of fetuses with congenital CMV infection.

Strengths and limitations

The relatively large sample size, longitudinal assessment of fetal anatomy through ultrasound and MRI in each of the

Table 4: Selected demographic and clinical characteristics, stratified by postnatal clinical symptoms.

Variables	Postnatal clinical symptoms			
	No (n=81)	Yes (n=13)	Raw OR (95% CI)	p[a]
Mean maternal age, years (SD)	31.6 (5.8)	29.9 (5.6)	0.95 (0.86–1.05)	0.3
Mean maternal BMI, kg/m^2 (SD)	25.8 (4.0)	26.8 (6.4)	1.04 (0.90–1.20)	0.6
Year of scan				
2010–2015	21.0	38.5	1 (Ref. cat.)	–
2016–2017	32.1	46.1	0.79 (0.21–2.98)	0.7
2018–2021	46.9	15.4	0.18 (0.03–1.02)	0.052
Trimester of infection, %				
First	84.0	84.6	1 (Ref. cat.)	–
Second	16.0	15.4	0.95 (0.19–4.90)	0.9
Type of infection, %				
Primary	100	84.6	–	–
Secondary	0.0	15.4	–	–
Mean gestational age in weeks at 1st US assessment (SD)	18.1 (4.0)	16.5 (4.6)	0.92 (0.82–1.05)	0.2
Mean gestational age in weeks at amniocentesis (SD)	20.5 (1.5)	20.5 (1.0)	0.97 (0.53–1.62)	0.9
Mean gestational age in weeks at MRI (SD)	27.0 (5.2)	27.0 (4.0)	1.01 (0.90–1.14)	0.8
Mean interval between last US and MRI in days (SD)	6.4 (9.0)	6.1 (5.8)	0.99 (0.92–1.07)	0.9
Detected viral load at PCR				
Median value, copies/mL (IQR)	48,403 (539,500)	1,695,000 (2,465,306)	1.02 (0.99–1.03)	0.05
High viral load, %[a]	45.7	53.9	1.39 (0.43–4.49)	0.6
Therapy				
Prenatal therapy, %	19.8	38.5	2.54 (0.73–8.81)	0.14
Type of therapy, %	(n=16)	(n=5)		
Immunoglobulin	75.0	40.0	–	–
Valaciclovir	25.0	60.0	–	–
Mean gestational age in weeks at therapy start (SD)	19.7 (4.4)	21.2 (1.9)	–	–
Mean gestational age in weeks at therapy end (SD)	23.7 (5.8)	34.0 (3.5)	–	–
Mean therapy length in weeks (SD)	4.0 (7.6)	12.8 (5.0)	–	–
Fetal anomalies detected only at follow-up US or prenatal MRI, %	8.6	53.9	12.3 (3.24–47.0)	<0.001
Additional anomalies detected only on postnatal imaging, %	4.9	46.2	16.5 (3.74–72.7)	<0.001
Hearing anomalies, %	6.2	15.4	2.76 (0.48–16.0)	0.3

OR, odds ratio; CI, confidence interval; Ref. cat., reference category; SD, standard deviation; IQR, Interquartile range; PCR, polymerase chain reaction; US, ultrasound; MRI, magnetic resonance imaging. [a]Chi-squared test for categorical variables; t-test and Kruskal-Wallis test for normally distributed and non-normally distributed continuous variables, respectively.

included cases and the multitude of pre and post-natal outcomes explored represents the main strengths of the present study.

The retrospective non-randomized design represents the main weakness of the present study. Furthermore, we could not elucidate the potential role of prenatal medical therapy because not all the included cases received valacyclovir at the time of maternal seroconversion. Finally, we could not assess the individual components of post-natal clinical symptoms in view of the small number of events reported for this outcome.

Implications for clinical practice and research

Prenatal prediction of adverse outcome in fetuses with congenital CMV infection is challenging [14]. CMV is associated with a multitude of adverse neurological and neurosensorial outcome, including epilepsy, mental retardation, hearing, and visual problems [20]. The presence of associated anomalies, mainly those involving the CNS, is among the main determinants of post-natal outcomes in fetuses with CMV infection. However, prenatal

counselling in case no associated anomaly is detected prenatally is difficult [10].

CMV has a peculiar tropism for the neurons in the periventricular zone, thus potentially affecting neuronal migration and proliferation [21]. However, anomalies involving the cortical surface of the brain, including lissencephaly and microcephaly can be detected only later in gestation [22–26]. In the present study, additional anomalies detected only at follow-up imaging, either ultrasound or MRI, 18% and 11.9% of the cases respectively. These findings highlight the need for a thorough longitudinal imaging follow-up in fetuses with congenital CMV infection. Likewise, parents should be counselled on the high risk of detecting associated anomalies only later in pregnancy or after birth. High viral laod in the amniotic fluid has been anecdotally reported to predict the outcome of fetuses with CMV infection. However, previous studies did not differentiate between cases presenting compared to those not presenting with additional structural ultrasound [12]. This is crucial as the presence of a CNS anomaly is likely to be associated with a high risk of adverse neurological outcome. In the present study, mean viral load in the amniotic fluid was higher in fetuses with additional anomalies detected exclusively at follow-up or at birth, confirming the predictive role of viral load in identifying fetuses at risk of adverse outcome. Importantly, at multivariate logistic regression analysis, viral load was independently associated with the risk of associated anomalies, irrespective of type and gestational age at infection. In this scenario, parental counselling of pregnant women with congenital CMV infection should mention that the risk of anomalies detected only in the third trimester or after birth and potentially not identified with either ultrasound or MRI.

Despite its prevalence and morbidity among the neonatal population, there is not yet a standardized diagnostic test and therapeutic approach for congenital CMV infection. Literature analysis shows that preventive interventions other than behavioral measures during pregnancy are still lacking, although many clinical trials are currently ongoing to formulate a vaccination for women before pregnancy [27, 28]. Some evidence in literature describes attempts to use CMV hyperimmune globulin in order to decrease the incidence of congenital CMV infection or fetal or neonatal death among the offspring of women with primary CMV infection in pregnancy, without significant success [28, 29]. Secondary prevention of congenital cytomegalovirus infection with valacyclovir following maternal primary infection in early pregnancy seems to show some benefit in reducing vertical transmission [29, 30].

The burden of congenital CMV infection is an unmet public issue [30], for this reason the attention towards this infection must be destined to grow. The lack of evidence in the literature on any prenatal predictors of adverse outcomes in congenital CMV infections should be a pretext for new future studies focused on this aspect, in parallel with the attention for new therapeutic strategies in the case of confirmed infection. This study identifies the high viral load in the amniotic fluid as the only predictor of abnormalities at follow-up ultrasound assessment or MRI that were the only predictors of symptomatic infection ($p=<0.001$). This finding indicates that therapeutic strategies should focus on viral load reduction and that in the future viral load can be a useful tool for risk prediction and prenatal follow up of these fetuses.

Conclusions

High viral load in the amniotic fluid is a strong predictor of pre and postnatal adverse outcome in fetuses with congenital CMV infection and normal ultrasound assessment at the time of diagnosis. The findings from this study emphasize the importance of a proper integration between imaging and laboratory findings to more accurately counsel parents whose pregnancy is complicated by congenital CMV infection. Further studies are needed to validate these findings and construct an objective prediction model for adverse outcome in fetuses with congenital CMV infection.

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Ethical approval: The research has complied all the relevant national regulation institutional policies and in accordance with the tenets of the Helsinki Declaration and has been approved by all centers Institutional Review Board

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