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Laryngoscope Investigative Otolaryngology

Impact of maternal cytomegalovirus seroconversion on newborn and childhood hearing loss

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[Correction added on Sept 14, 2022, after first online publication: Article title have been revised in this version.]

Abstract

Objectives/hypothesis: The objective of this study is to describe long-term hearing outcomes in infants born to mothers with a known cytomegalovirus (CMV) positivity who were not tested for congenital CMV.

Study type: Clinical research study.

Design: Retrospective cohort study.

Methods: Retrospective chart review was performed for mothers seropositive to CMV. Mother–infant dyads (130) were identified between January 1, 2013 and January 1, 2017. Outcomes data was collected through June 1, 2020. Demographics, risk factors for hearing loss, evidence of CMV infection, other causes of hearing loss, need for speech therapy services, and results of all hearing tests were collected.

Results: All 130 infants were asymptomatic and 5 were tested for congenital CMV. Five were negative for CMV and excluded from analyses. Of the remaining 125, only 1 had low-viral avidity IgG antibodies. None had IgM antibodies. Four children (3.2%) had hearing loss at last audiogram and one child had delayed onset SNHL due to an enlarged vestibular aqueduct. Speech therapy for communication was required for 33 children (26.4%).

Conclusions: Knowledge of maternal perinatal CMV status can allow for education about possible sequelae of cCMV, as well as trigger an alert for testing babies born to mothers with low-viral avidity IgG during the first trimester, when the risk of vertical transmission is highest. Also, babies born to CMV positive mothers may be more at risk for communication delays necessitating intervention. Studies focusing on the impact of maternal CMV related to childhood communication deficits could elucidate any direct relationships.

KEYWORDS

CMV, cytomegalovirus, maternal IgG, newborn hearing screening, viral avidity

1 | INTRODUCTION

Congenital cytomegalovirus (cCMV) infection is the leading cause of non-genetic pediatric sensorineural hearing loss (SNHL) in the United States.[1] Vertical transmission of CMV is possible during any trimester of pregnancy. Although third trimester transmission is most likely, transmission during the first trimester of pregnancy is associated with the highest risks of symptomatic infection in newborns.[2] SNHL was found in up to 80% of children where the primary CMV infection occurred in the first trimester and rare cases of hearing loss were identified when infection occurred in the third trimester.[3–7] Focusing on fetal transmission with primary versus non-primary infection, studies found that the highest risk is due to primary infection.[2,3,8]

Symptomatic cCMV is readily identifiable with findings of thrombocytopenia, hepatomegaly, SNHL, developmental delay, vision loss, microcephaly, and death.[1,4,5] cCMV without identifiable findings at birth is trickier to identify as only 10%–20% present with a failed newborn hearing screen. The remaining 80%–90% of cases are considered truly asymptomatic and indistinguishable from non-infected newborns at birth yet might develop SNHL later on in childhood due to cCMV.[1–3,8,9] To distinguish cCMV from acquired CMV, infection must be diagnosed within 3 weeks of birth. Without universal CMV screening it is very unlikely there would be testing done in the asymptomatic infant.[10] Distinguishing cCMV from acquired CMV is important because acquired CMV does not carry a risk of progressive SNHL.

One way of finding infants at risk for cCMV is to identify mothers with CMV infection during pregnancy. Primary CMV infection during pregnancy has the greatest risk of up to 40% fetal transmission; however, non-primary infection (re-activation or infection with a different strain) is more common and leads to a low vertical transmission rate of 1%–2%.[1,5,6] Figure 1 demonstrates these differences depending on whether the infection is primary or not. It is difficult to identify primary maternal CMV infections because symptoms are generally mild or even asymptomatic. Most expecting mothers have never heard of CMV and would not seek medical attention or ask for CMV testing to be done. In addition, many women of child-bearing age have had prior exposure to CMV and therefore test positive. Mothers of young children are at an increased risk of acquiring CMV during pregnancy, either due to reactivation or a de novo infection, resulting from exposure from their child's saliva or nasal secretions.[2,11]

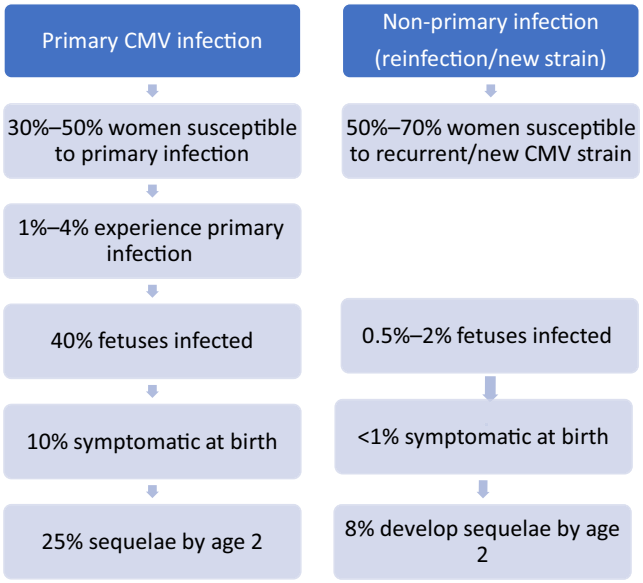

FIGURE 1 Maternal and neonatal risks for CMV infection.[2,10,13] CMV, cytomegalovirus

1.1 | Sensorineural hearing loss in congenital cytomegalovirus

SNHL in cCMV presents in a variety of ways including progression, fluctuation, asymmetry, and delayed onset. The association of cCMV with SNHL was identified in the 1960s and later population studies confirmed the rate of SNHL from cCMV around 10% with an overall prevalence of 0.58%.[8,12] cCMV hearing loss was further characterized by retrospective and prospective studies. These demonstrated more severe fluctuation, progression, asymmetry, and delayed onset in symptomatic cCMV. The reported incidence of SNHL in symptomatic babies is around 12%. Petechiae at birth and intrauterine growth restrictions were the only factors that correlated with SNHL in symptomatic babies.[8,13]

Comparing primary versus non-primary infection, studies demonstrated a higher incidence of profound hearing loss, delayed onset, and progression in infants born to mothers with primary CMV infection compared to mothers with non-primary CMV infection. Fowler et al. hypothesized that higher viral titers due to primary infection in asymptomatic babies were associated with a greater likelihood of SHNL. Inflammatory responses within the inner ear, injury to the stria vascularis, and viral reactivation are some proposed causes for delayed onset, progressive or fluctuating SNHL.[13] Regarding the newborn hearing screen failures, 58% of asymptomatic infants with confirmed cCMV passed their subsequent newborn hearing test and up to 15% demonstrated delayed onset SNHL as late as age 16.[13]

Table 1 summarizes the rates of unilateral SNHL, delayed onset SNHL, severity, fluctuation, and progression in asymptomatic cCMV.[8,12–15]

1.2 | Maternal cytomegalovirus testing

Maternal CMV testing has been investigated to predict cCMV infection in newborns. IgM antibodies are present during an acute infection and precede development of longer-term immunity from IgG antibodies. In CMV infections, IgM antibodies will persist and overlap with IgG antibodies for several months making it challenging to use as a direct marker for timing of infection.[1,2,9,16,17] IgM antibodies may also be detectible in non-primary infections despite having IgG antibodies.[2,16,17] IgM testing alone cannot be used to determine when the mother became infected.[1,2,10] In some cases, the presence of high IgM titers along with IgG may predict when infection occurred, but

TABLE 1 Comparison of hearing findings in asymptomatic cCMV by study

Author	Year	*N*	Asymptomatic SNHL (%)	Severe-profound (%)	Unilateral (%)	Progressive (%)	Fluctuating (%)	Delayed (%)
Goderis	2014	379	10	77	56.9	20.3	24	9
Foulon	2008	28	21	60	14	38	54	23
Ross[a]	2006	300	11	63	58	63	43	53
Fowler	2006	860	7.4	68	NR	50	NR	15
Williamson	1992	59	100[b]	77	11	62	11	9

Abbreviations: cCMV, congenital cytomegalovirus; NR, not reported; SNHL, sensorineural hearing loss.
[a]Data for primary maternal CMV infection.
[b]Only cCMV with SNHL included in study.

this is not always reliable especially in cases of non-primary infection.[1,4,5] If IgG antibodies are present, viral avidity testing can help determine the onset of a primary infection, but still cannot tell if it occurred during pregnancy, as the infection may have occurred just prior to conception.[1,2,7]

Viral avidity testing is a marker for how strongly the virus binds to circulating IgG. This method has been used to diagnose risk of fetal transmission for other maternal infections including toxoplasmosis, parvovirus and rubella. Viral avidity in CMV has been the most studied. Viral avidity testing uses maternal serum exposed to CMV antigens in vitro with an ELISA assay method.[17] In recent exposures (12–18 weeks) the viral specific IgG has low viral avidity due to the "novel" infection—either from a primary or a non-primary with a new strain.[17] Thus, there is more circulating virus in the bloodstream which can be transferred to the fetus. Conversely, in previous exposures, IgG will bind tightly to the virus (higher avidity), demonstrating a robust immune response.[2,11,17] Higher avidity is associated with lower vertical transmission and less circulating virus free to cross the placenta. Increased avidity is therefore associated with higher serum levels of virus-neutralizing antibodies.[1] In studies on women with primary CMV infection, high viral avidity IgG during the first trimester had decreased rates of intrauterine transmission.[1,7]

Low avidity IgG and IgM detection within the first trimester was found to be a reasonable indicator of predicting cCMV infection with 83% sensitivity and 84% specificity.[2,17–20] Yet, it is not routine for pregnant mothers to undergo serologic testing for CMV especially during the first trimester. Maternal immunity status (presence of IgG or IgM for CMV) cannot be reliably used to identify if exposure occurred during the current pregnancy and immunity prior to pregnancy does not guarantee protection because of possible re-activation or infection from a different CMV strain.[1,2,6,8,9] Studies looking at maternal immunity with active CMV infection noted preexisting immunity was not protective for development of SNHL and found no difference in the frequency of SNHL in these children. It did appear that the severity of hearing loss was lower in those whose mothers had pre-existing immunity.[3,5,16]

In this study, we sought to describe the long-term hearing outcomes of infants with an unknown CMV status at birth whose mothers had present IgG for CMV. If the incidence of hearing loss is elevated, this data could help determine whether these asymptomatic babies should undergo CMV testing as newborns.

2 | MATERIALS AND METHODS

The study included maternal–infant dyads with mothers who had CMV antibody and viral avidity testing. Mothers without seroconversion were excluded. A total of 130 dyads were identified between January 1, 2013 and January 1, 2017. Mother and infant demographics, maternal IgM, IgG and viral avidity status, newborn hearing screen results, results of infant CMV testing, follow-up audiologic tests, need for speech therapy services and any diagnostic information regarding hearing loss were collected. Hearing results were recorded until June 1, 2020, to capture delayed onset hearing loss. Patients without follow-up audiograms were also included. Infants were excluded if tested negative for cCMV.

Institutional Review Board approval (protocol Pro00103639) was obtained. All statistical analyses were performed using R 4.0.0 (R Core Team). Due to a small sample size of CMV positive mothers with low-viral avidity compared to high-viral avidity, no statistical tests were conducted. Descriptive statistics were used for demographic and clinical characteristics. Hearing results, need for speech therapy and use of augmentative communication methods were also recorded.

3 | RESULTS

3.1 | Demographic characteristics

One hundred and thirty infant dyads were identified. These dyads came from a different study looking at disease prevalence by zip code. Demographics are summarized in Table 2. Five infants were excluded due to a negative cCMV test. A total of 3 mothers demonstrated IgG with low-viral avidity and the remainder had high-viral avidity. Babies were tested for CMV due to failed newborn hearing screen (3) or detection of maternal IgG with low-viral avidity (2 of 3). One hundred and twenty-five infants were included in the study, slightly more than half were male ($n = 67$, 53.6%) and most identified as Black/African American ($n = 84$, 67.2%). The mean gestational age was 38.8 weeks

(SD 1.5 weeks) and the mean age at the time of the study was 61.1 months (SD 11.1 months) with a range of 42–87 months. Of the 125 mother–infant dyads analyzed, 124 mothers had IgG with high avidity, and 1 mother had IgG with low-viral avidity. None of the mothers had IgM present.

Fifty patients had hearing data up to the completion of the study. A total of 75 patients (60%) did not have any hearing tests performed after May 1, 2019 but were included in the analysis based on their most recent available audiometric data.

Figure 2 is a diagram of the maternal infant dyads analyzed.

TABLE 2 Demographic information

Infant sex	
Male	67 (53.6%)
Female	58 (46.4%)
Infant race	
Black/African American	84 (67.2%)
White/Caucasian	24 (19.2%)
Other/unknown	17 (13.6%)
Gestational age (weeks)	
Mean (SD)	38.8 (1.5)
Median (IQR)	39 (38–40)
Min–Max	34–42
Age at time of study (months)	
Mean (SD)	61.1 (11.1)
Median (IQR)	59.4 (52.4–70.8)
Min–Max	42.1–87.1
Maternal CMV status	
High avidity	124 (99.2%)
Low avidity	1 (0.8%)

Note: Total $n = 125$.
Abbreviations: CMV, cytomegalovirus; IQR, interquartile range; SD, standard deviation.

3.2 | Infant hearing outcomes

None of the 125 infants were tested for cCMV. One child was tested as a toddler due to an acute viral infection and was positive for IgG and IgM negative. This child was included in the analysis and has normal hearing.

Hearing outcomes for the 125 infants are shown in Table 3. All 125 patients had a newborn hearing test, done by aABR within 24 h of birth and repeated if there was a refer result. Of these infants, 80 (64%) passed the newborn hearing test and 45 (36%) failed and were referred for audiologic follow-up. The results of follow up screening Auditory Brainstem Response (ABR) testing were available for 44 of these infants. One infant moved shortly after birth and passed hearing screen at an outside hospital. He was classified as lost to follow-up with normal hearing. Of the 44 infants with ABR data, 37 (84.1%) passed bilaterally, 4 failed unilaterally, and 3 failed bilaterally. All of these ultimately passed subsequent diagnostic ABR testing.

3.3 | Longer-term hearing testing results

Of the 125 infants, 4 (3.2%) had evidence of hearing loss at their most recent audiologic study. One had unilateral SNHL, two had unresolved conductive hearing loss (CHL), and one failed a screening at a primary care visit without any follow up. The one infant with SNHL was diagnosed at 62.2 months and imaging found an enlarged vestibular aqueduct. A total of 5 patients (4%) had CHL on at least one audiologic exam detected at a mean age of 14.1 months (SD 11.9 months). Three

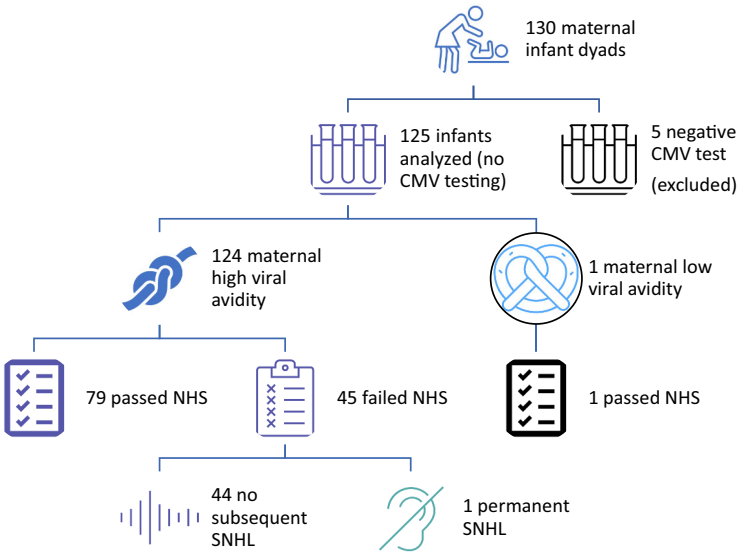

FIGURE 2 Cohort of maternal infant dyads and outcomes

TABLE 3 Hearing outcomes

Hearing loss on most recent exam	4 (3.2%)
Lost to follow-up	1 (25.0%)
No hearing loss on most recent exam	121 (96.8%)
Lost to follow-up	74 (61.1%)
Newborn hearing screen performed	125 (100.0%)
Pass bilaterally	80 (64.0%)
Fail unilaterally	34 (27.2%)
Fail bilaterally	11 (8.8%)
Follow-up screening ABR performed	44 (35.2%)
Pass bilaterally	37 (29.6%)
Fail unilaterally	4 (3.2%)
Fail bilaterally	3 (2.4%)
Presence of CHL on any formal exam	5 (4.0%)
Age when CHL first detected (months)	
Mean (SD)	14.1 (11.9)
Median (IQR)	16.4 (3.4–21.6)
Min–Max	0.7–28.5
Presence of SNHL on any formal exam	1 (0.8%)
Age when SNHL detected (months)	62.2
Use of hearing aids	2 (1.6%)
Use of cochlear implant	0 (0.0%)
Use of sign language	2 (1.6%)
Use of augmentative communication	2 (1.6%)
Need for speech therapy	33 (26.4%)
Age at speech therapy referral (years)	
Mean (SD)	2.5 (1.1)
Median (IQR)	2 (2–3)
Min–Max	0–5

Note: Total $n = 125$.
Abbreviations: ABR, auditory brainstem response; CHL, conductive hearing loss; IQR, interquartile range; SD, standard deviation; SNHL, sensorineural hearing loss.

of the infants with CHL resolved at their most recent audiogram. Age-appropriate audiometric testing was performed in a sound booth by pediatric audiologists.

3.4 | Speech and communication outcomes

Two children (1.6%) used hearing aids, sign language and augmentative communication. Use of sign language and augmentative communication in these children was due to developmental delay, not SNHL. One child had severe speech delay from Bardet-Beidl syndrome and used augmentative communication. He had normal hearing. The other patient had Down syndrome and mild bilateral CHL.

Thirty-three children (26.4%) required speech therapy. The mean age at referral for speech therapy was 2.5 years (SD 1.1 years). The majority ($n = 30$, 90.9%) of the subjects requiring speech therapy did not have evidence of hearing loss. The one patient with late onset SNHL did not require speech therapy and had normal hearing up until identified at age 4. The need for speech therapy with respect to hearing findings is summarized in Table 4.

TABLE 4 Need for speech therapy

Speech therapy	
Required speech therapy	33 (26.4%)
With hearing loss	3 (9.1%)
Without hearing loss	30 (90.9%)
Did not require speech therapy	92 (73.6%)
With hearing loss[a]	1 (1.1%)
Without hearing loss	91 (98.9%)

Note: Total $n = 125$.
[a]This patient passed the newborn hearing screening and did not have an abnormal hearing test until a clinic screen at age 4 that has not yet had follow-up.

4 | DISCUSSION

Given the risk of SNHL in undiagnosed cCMV, we sought to identify if maternal testing alone can identify which infants may be at-risk for delayed onset SNHL. Our study did not find the hearing loss expected if infants born to CMV positive mothers had asymptomatic cCMV. This is likely due to the predominantly high-viral avidity maternal cohort. Viral avidity has been proposed as a possible predictor to identify either a recent or past infection, thereby only screening asymptomatic babies born to mothers whose IgG and viral avidity status are known. Even in those with low-viral avidity, there has not been a clear correlation to delayed onset SNHL.[2,17–19] In our study, two infants were tested because of maternal IgG with low-viral avidity and were negative. One maternal–infant dyad who had low-viral avidity was not tested for cCMV, passed the newborn hearing screen and follow up audiograms. The remaining cohort had mothers with positive IgG and high-viral avidity indicating initial infection prior to the pregnancy. Of these, only one had SNHL (0.8%) and that was due to an anatomic inner ear anomaly.

Congenital CMV is the most common cause of non-hereditary SNHL, yet identification of asymptomatic infants is still challenging. Concerns about deciding which infants are at-risk or how to manage asymptomatic positive cases also influence the decision to test.[21–23] Several states have enacted hearing targeted CMV screening (HT–CMV) legislation in an effort to capture at-risk children, however currently there are no states that have implemented universal CMV screening.[24] Since cCMV is time-sensitive for detection, this raised the question of other options to identify children that may be at a higher risk for late onset SNHL due to asymptomatic cCMV.

Dried blood spot analysis has been used but until recently was not felt to be a very effective way to identify cCMV. A recent study of cCMV confirmed newborns showed a reported sensitivity range of 73%–77% with 100% specificity. Prior population based studies had a much lower range of sensitivity (40%–60%).[25] One challenge is that many states do not keep the Guthrie cards for more than 5 years

making retrospective diagnosis difficult. Asymptomatic cCMV is particularly challenging as up to 15% of those will progress to have communication-limiting SNHL by the time they reach 5 years old.[26,27] Since there is no reliable way to retrospectively identify cCMV as a cause, it is difficult to predict the risk of progression. This may lead to delay in diagnosis of hearing loss, speech and language delay, and poor cognitive performance. These problems can be mitigated by early identification and parental education for children with asymptomatic cCMV.[22,27]

Other studies noted that while maternal pre-existing immunity was not protective for development of delayed onset SNHL, the severity of hearing loss was lower in these children.[3,5,16] A study of 300 cCMV children found that primary maternal infection had more severe or progressive hearing loss yet delayed onset or fluctuating SNHL was similar when compared to those who had non-primary infection. Maternal antibodies were analyzed prior to pregnancy, during the first trimester and at delivery. All subjects were confirmed to have cCMV within 2 weeks of life.[16] Their findings demonstrated that CMV transmission is possible with non-primary infection even in mothers who have high-viral avidity IgG levels.

Conductive hearing loss is common in young children due to middle ear effusion or infections. This can be problematic in children with an underlying SNHL, worsening communication delay. Although not related to CMV, it helps to identify children who had CHL and resolved. Some studies that looked at longitudinal hearing results attempted to adjust for hearing loss unrelated to cCMV including middle ear disease.[3,5,16,26,28]

5 | COMMUNICATION DISORDERS

Our study demonstrated 26% of the children needed speech therapy for communication. While there were two children who used hearing aids for CHL and another two with developmental delay, all requiring speech services; the remaining children did not have hearing loss. It is clear that SNHL adversely affects speech and language development, and that early intervention is imperative to mitigate long-term delays. Very early identification of hearing loss and providing appropriate amplification is a stated goal of the JCIH 2019 position statement.[21] Interventions include speech therapy, sign language, parent support services, and individualized educational plans.

Speech delay in cCMV is common with children with SNHL, but has not been studied outside of a hearing impairment. A study in 2017 evaluated 92 asymptomatic cCMV children for neurocognitive delay, speech-language development and IQ. They did not find differences in academic achievement or IQ compared to uninfected controls. They looked at language development in cCMV children with normal hearing versus controls and the findings were again similar. Children with cCMV and SNHL scored 13% lower in receptive language than controls. There was no difference amongst the groups in expressive language; however, they stated a limitation was the small control group and above average maternal socioeconomic and educational status. They concluded that if there are no delays by age 2, there would not be any longer-term effects. The study did not take into account the possibility of delayed onset SNHL and did not document if any had speech therapy.[28] Speech language delay has a reported prevalence from 6% to 11% in children up to age 5 with higher numbers in preterm children or those from lower socioeconomic or ethnically diverse backgrounds. Despite the risk of communication delays, only about 30% of children who meet criteria for language impairment receive speech services.[29,30] Although we do not know the cCMV status of our cohort in this study, 26% needing speech therapy for communication deserves additional investigation. Our cohort was 71% non-white which may in part account for this. There is overlap in the risk of acquiring cCMV and the need for speech language services in populations from lower socio-economic areas. Some purported explanations include crowded living conditions, lack of reliable preschool education, single parent homes and access to services.[29,31–34] Recognition and early intervention of these social determinants of health may mitigate longer term communication deficits in this at-risk population. This would include early speech screening and implementation of preschool educational programs.

The impact of congenital CMV is recognized in the newest JCIH position statement highlighting the need for CMV education and awareness.[21] Even though CMV has a higher incidence than other common prenatal conditions, up to 90% of pregnant women have never heard of it.[22] This stresses the importance of public education regarding prevention and early identification. The CMV and hearing multicenter screening (CHIMES) study, looked at over 100,000 children from 2007 to 2012 and determined that even at a rate of 0.5%, many children in the United States are at risk for development of significant hearing loss due to cCMV.[22,23]

In 2019, the American Academy of Pediatrics approved a resolution advocating for CMV education. Providing education to expectant mothers about cCMV risks and sequela will help them be informed advocates for their children. Educating primary care providers and obstetricians about transmission and prevention of CMV can reduce the overall burden of disease.[31] cCMV and hearing loss is more prevalent in lower SES communities, communities of color, or with large Hispanic populations.[1,32–34] These vulnerable populations should be educated on preventing CMV infection during pregnancy.

6 | STUDY LIMITATIONS

This study is limited by the lack of mothers with low avidity IgG to CMV as well as its small sample size. We are also limited by lack of information regarding any earlier pregnancies, other CMV testing, characterization of the CMV species and whether these mothers had other children with cCMV. By the age of 6, most children who will develop delayed SNHL due to cCMV would be identified, although a few may not present until adolescence. Since most of our cohort had high-viral avidity, the potential for intrauterine transmission of CMV was quite low. Eighty-three percentage (5 out of 6) of the infants born to mothers with low-viral avidity were tested for cCMV and found to be negative, further diluting the pool for comparison.

7 | CONCLUSION

Of 125 children born to CMV positive mothers, 4 (3.2%) had hearing loss with only 1 (0.8%) being SNHL. Theoretically, knowing the maternal CMV status promotes discussion regarding the risks of cCMV and the need for audiologic follow up even if their infants are asymptomatic at birth. Also, identifying CMV within the first trimester by the presence of IgM and IgG low avidity antibodies could trigger an alert to test for cCMV. It is important since diagnosing cCMV is so time-sensitive that if there are other ways to identify at risk children, they can be captured and monitored.

It was interesting that 26% of this cohort required speech therapy for communication. Controlling for socioeconomic status and race could elucidate the role of cCMV in communication disorders especially in those with normal hearing.

Providing families information about potential delays with cCMV infection, can allow them to be better advocates for their children and improve outcomes in the future.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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