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Randomized Trial of Hyperimmune Globulin for Congenital CMV Infection — 2-Year Outcomes

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

The data set will be made available through the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Data and Specimen Hub (https://dash.nichd.nih.gov/).

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TO THE EDITOR:

The prevalence of congenital cytomegalovirus (CMV) infection at birth ranges from 0.2 to 2.2% and is higher in low-income communities. Approximately 10% of affected infants are symptomatic at birth, and disability develops in up to 25% by the age of 2 years[1-3]; sensorineural hearing loss and neurologic impairment are well-recognized sequelae among fetuses infected in early gestation.[2] There are no in utero treatments recommended in the United States to improve outcomes of pregnancies in persons with primary CMV infection.[4]

We previously reported the results of a multicenter, randomized, placebo-controlled trial of CMV hyperimmune globulin (Cytogam, CSL Behring) involving 399 pregnant women who had primary CMV infection in pregnancy (ClinicalTrials.gov number, NCT01376778). The trial showed no benefit associated with CMV hyperimmune globulin with respect to the incidence of congenital CMV infection or fetal or neonatal death.[5] Here, we report the results of a planned 2-year follow-up study involving the children of mothers who were enrolled at 17 centers to evaluate whether CMV hyperimmune globulin improves childhood outcomes. The trial protocol is available with the full text of this letter at NEJM.org. Participants were randomly assigned to receive monthly infusions of CMV hyperimmune globulin or placebo until delivery. After delivery, follow-up of the children was performed by certified research staff for 2 years. Participants and trial personnel were unaware of the treatment assignments throughout follow-up. The outcomes assessed at 24 months (prespecified as secondary trial outcomes) included a composite of death (fetal loss or death during infancy or childhood) or CMV infection with severe disability (defined as sensorineural hearing loss, developmental delay [a cognitive score or motor score of <70 on the Bayley Scales of Infant and Toddler Development, third edition, which is >2 SD below the standardized mean score of 100; higher scores on the scale indicate better performance], chorioretinitis, or seizure disorder from CMV infection); measures of otoacoustic emission; findings on visual reinforcement audiometry; findings on acoustic immittance testing; and cognitive and motor scores on the Bayley Scales of Infant and Toddler Development, third edition (performed by centrally certified examiners).

At least partial data on 2-year outcomes were available for 360 children (90%). Death or CMV infection with severe disability occurred in 20 of the 149 children (13.4%) in the hyperimmune-globulin group and in 15 of the 149 children (10.1%) in the placebo group (relative risk, 1.33; 95% confidence interval, 0.71 to 2.50). No material differences were found between the groups in the incidence of any component of the composite outcome or in any other outcome at 24 months, including severe disability with or without congenital CMV infection (Table 1). No deaths occurred after the delivery hospitalization. Results obtained by multiple imputation were consistent with those in the complete case analysis (Table S2 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). Limitations of this study include low event rates and missing data.

In this multicenter trial, CMV hyperimmune globulin did not improve 2-year hearing or developmental outcomes. These results, along with those previously reported, do not support the use of maternal CMV hyperimmune globulin to improve outcomes in the children of women with primary CMV infection in early pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Outcomes among Children at 24 Months.[*]

Outcome	Hyperimmune Globulin	Placebo	Relative Risk or Difference (95% CI)[†]
Composite outcome: death or CMV infection with severe disability — no./total no. (%)	20/149 (13.4)	15/149 (10.1)	1.33 (0.71 to 2.50)
Death or fetal loss[‡]	10/184 (5.4)	5/176 (2.8)	—
Sensorineural hearing loss, unilateral or bilateral	2/138 (1.4)	7/146 (4.8)	—
Chorioretinitis	0/173 (0)	1/171 (0.6)	—
Seizure disorder	2/173 (1.2)	0/171 (0)	—
Bayley-III cognitive score of <70	4/155 (2.6)	4/160 (2.5)	—
Bayley-III motor score of <70	6/155 (3.9)	1/158 (0.6)	—
Overall status — no./total no. (%)			
Death or fetal loss[§]	10/148 (6.8)	5/149 (3.4)	—
Congenital CMV infection with severe disability	6/148 (4.1)	7/149 (4.7)	—
Congenital CMV infection without severe disability	21/148 (14.2)	19/149 (12.8)	—
Not infected with CMV with severe disability	4/148 (2.7)	3/149 (2.0)	—
Not infected with CMV with no disabilities	107/148 (72.3)	115/149 (77.2)	—
Other outcomes			
Bayley-III cognitive score	96.2±15.1	97.1±13.5	−0.9 (−4.1 to 2.3)
Bayley-III motor score	98.7±16.4	101.9±14.9	−3.2 (−6.7 to 0.3)
Birth weight <10th percentile — no./total no. (%)	20/169 (11.8)	21/167 (12.6)	0.94 (0.53 to 1.67)

[*]Plus–minus data are means ±SD. Severe disability was defined as any sensorineural hearing loss, developmental delay (a cognitive or motor score of less than 70 on the Bayley Scales of Infant and Toddler Development, third edition [Bayley-III], which is >2 SD below the standardized mean score of 100; higher scores on the scale indicate better performance), chorioretinitis, or seizure disorder.

[†]Relative risk is provided for the composite outcome and for <10th percentile weight, and the between-group difference is provided for the mean Bayley-III scores. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing.

[‡]No deaths occurred after the delivery hospitalization.

[§]Data from the cohort of participants with information on death or fetal loss plus information on CMV infection and disability status are included here.