ORIGINAL ARTICLE

A Trial of Hyperimmune Globulin to Prevent Congenital Cytomegalovirus Infection

B.L. Hughes, R.G. Clifton, D.J. Rouse, G.R. Saade, M.J. Dinsmoor, U.M. Reddy, R. Pass, D. Allard, G. Mallett, L.M. Fette, C. Gyamfi-Bannerman, M.W. Varner, W.H. Goodnight, A.T.N. Tita, M.M. Costantine, G.K. Swamy, R.S. Gibbs, E.K. Chien, S.P. Chauhan, Y.Y. El-Sayed, B.M. Casey, S. Parry, H.N. Simhan, P.G. Napolitano, and G.A. Macones, for the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network*

ABSTRACT

BACKGROUND

Primary cytomegalovirus (CMV) infection during pregnancy carries a risk of congenital infection and possible severe sequelae. There is no established intervention for preventing congenital CMV infection.

METHODS

In this multicenter, double-blind trial, pregnant women with primary CMV infection diagnosed before 24 weeks' gestation were randomly assigned to receive a monthly infusion of CMV hyperimmune globulin (at a dose of 100 mg per kilogram of body weight) or matching placebo until delivery. The primary outcome was a composite of congenital CMV infection or fetal or neonatal death if CMV testing of the fetus or neonate was not performed.

RESULTS

From 2012 to 2018, a total of 206,082 pregnant women were screened for primary CMV infection before 23 weeks of gestation; of the 712 participants (0.35%) who tested positive, 399 (56%) underwent randomization. The trial was stopped early for futility. Data on the primary outcome were available for 394 participants; a primary outcome event occurred in the fetus or neonate of 46 of 203 women (22.7%) in the group that received hyperimmune globulin and of 37 of 191 women (19.4%) in the placebo group (relative risk, 1.17; 95% confidence interval [CI], 0.80 to 1.72; P=0.42). Death occurred in 4.9% of fetuses or neonates in the hyperimmune globulin group and in 2.6% in the placebo group (relative risk, 1.88; 95% CI, 0.66 to 5.41), preterm birth occurred in 12.2% and 8.3%, respectively (relative risk, 1.47; 95% CI, 0.81 to 2.67), and birth weight below the 5th percentile occurred in 10.3% and 5.4% (relative risk, 1.92; 95% CI, 0.92 to 3.99). One participant in the hyperimmune globulin group had a severe allergic reaction to the first infusion. Participants who received hyperimmune globulin had a higher incidence of headaches and shaking chills while receiving infusions than participants who received placebo.

CONCLUSIONS

Among pregnant women, administration of CMV hyperimmune globulin starting before 24 weeks' gestation did not result in a lower incidence of a composite of congenital CMV infection or perinatal death than placebo. (Funded by the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Center for Advancing Translational Sciences; ClinicalTrials.gov number, NCT01376778.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Hughes at Duke University School of Medicine, 2608 Erwin Rd., Suite 200, Durham, NC 27710, or at brenna.hughes@duke.edu.

*A list of the members of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal–Fetal Medicine Units Network is provided in the Supplementary Appendix, available at NEJM.org.

N Engl J Med 2021;385:436-44.
DOI: 10.1056/NEJMoa1913569

Congenital cytomegalovirus (CMV) infection affects as many as 40,000 infants in the United States annually and is associated with stillbirth, neonatal death, deafness, and cognitive and motor delay among symptomatic infants and children. Among pregnant women with primary CMV infection, the incidence of fetal infection is estimated to be 35 to 40%, with approximately 10% of infected fetuses having symptoms at birth.[1-3] Moreover, in approximately 20% of infants who have no evidence of infection at birth, neurologic deficits (most commonly deafness) that are attributable to CMV develop later in life.[3-5]

In small observational studies, CMV hyperimmune globulin was evaluated for both treatment and prevention of congenital infection among women with primary CMV infection during pregnancy.[6-8] The results of these studies were neither consistent nor conclusive. Therefore, the objective of the present trial was to assess whether CMV hyperimmune globulin prevents congenital CMV among women with evidence of primary infection early in pregnancy.

Methods

Overview

We conducted this multicenter, randomized, double-blind trial at 16 centers in the Maternal–Fetal Medicine Units Network of the Eunice Kennedy Shriver National Institute of Child Health and Human Development and at one military medical center (a list of sites is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org). The protocol (available at NEJM.org) was approved by the institutional review board at each site. The investigators have adhered to the policies for protection of human subjects according to Health and Human Services regulations. Oral or written informed consent was obtained from all participants before serologic screening, and written consent was obtained before randomization. The authors take responsibility for the accuracy and completeness of the data and the fidelity of the trial to the protocol. An Investigational New Drug application was approved by the Food and Drug Administration for CMV hyperimmune globulin to be studied as part of this trial. The trial drug and placebo were provided by CSL Behring free of charge. The company had no involvement in the management or analysis of the data or in the preparation of the manuscript.

Screening and Recruitment

Pregnant women with a singleton pregnancy of less than 23 weeks' gestation were eligible for serologic screening for primary CMV infection. CMV IgG and IgM antibodies were measured by the Department of Microbiology at Mount Sinai Hospital, Toronto, with the use of a commercially available chemiluminescent microparticle immunoassay (Architect platform, Abbott).[9-11] Women who underwent screening were considered eligible if they had evidence of primary infection. We defined primary infection as meeting either of these sets of criteria: presence of CMV IgM antibody of at least 1.00 index, IgG antibody of at least 6.0 AU per milliliter, and IgG avidity less than 50%; or a positive CMV IgG screening result after an initial negative screen earlier in pregnancy (i.e., seroconversion).[9-11] Low-avidity IgG in addition to positive IgM and IgG has been shown to be similar to seroconversion in predicting congenital CMV infection.[12] Positive screening results were confirmed in duplicate by the laboratory.

Pregnant women who were confirmed to have a primary CMV infection, who had had their initial screening within the previous 6 weeks, and were at no more than 23 weeks 6 days of gestation (27 weeks 6 days for those who were eligible owing to seroconversion) met inclusion criteria. Before randomization, a serum creatinine test and ultrasonography to rule out sonographic signs of fetal CMV infection (i.e., cerebral ventriculomegaly, microcephaly, cerebral or intraabdominal calcifications, abnormalities of amniotic fluid volume, echogenic bowel, or ascites) were performed in all participants. Women with renal disease (serum creatinine >1.4 mg per deciliter), immune impairment, or hypersensitivity to plasma products were excluded, as were those with evidence on ultrasonography of fetal infection, fetal anomalies, or fetal death. Full eligibility criteria are provided in the Supplementary Appendix and protocol.

Randomization and Treatment

Participants were randomly assigned in a 1:1 ratio to receive CMV hyperimmune globulin (Cytogam, CSL Behring) or placebo. The independent data

coordinating center provided a secure website for performing randomization and also prepared the randomization sequences using the simple urn method.[13] CMV hyperimmune globulin was administered by intravenous infusion at a dose of 100 mg per kilogram of body weight in a concentration of 50 mg per milliliter. CSL Behring data showing the antibody titers in Cytogam CMV hyperimmune globulin have been published previously.[14] The placebo was albumin (AlbuRx), chosen to mimic the "foamy" appearance of CMV hyperimmune globulin, mixed in a 1:9 ratio with a solution of 5% dextrose in water to match the volume required for CMV hyperimmune globulin. Neither the participants nor the clinical investigators were aware of the group assignments.

Participants received hyperimmune globulin or placebo in monthly infusions until delivery. Infusions were administered in a clinical setting. Each infusion was administered at a rate of 0.3 ml per kilogram per hour; if there were no adverse reactions, the dose was increased in increments. (If no adverse reaction occurred after 30 minutes, the rate could be increased to 0.6 ml per kilogram per hour; if no adverse reaction was observed after a subsequent 30 minutes, the rate could be increased again to a maximum of 1.2 ml per kilogram per hour or 75 ml per hour, whichever was lower.) Trial-trained medical staff members monitored the participants throughout the duration of the infusion, which took 2 to 6 hours. At each visit, clinical center staff assessed whether the participant had any adverse events and whether she had received interval ganciclovir, valganciclovir, or open-label immune globulin. If the monthly infusion was declined at any time after randomization, follow-up data were collected at monthly visits. After delivery, trial-trained research staff certified by the data coordinating center abstracted maternal and neonatal outcome data from the medical records.

Trial-trained and certified pediatric audiologists who were unaware of the treatment assignments conducted screenings for otoacoustic emission, auditory brain-stem response, and acoustic immittance in infants born to trial participants to determine whether the infants had hearing loss; testing was conducted at 4 weeks of age. If screening revealed evidence of hearing loss, testing was performed to distinguish between sensorineural and conductive hearing loss.

STUDY OUTCOMES

The primary outcome was a composite of confirmed fetal infection or congenital infection diagnosed by 3 weeks of age or fetal or neonatal death (including pregnancy termination) without CMV testing of samples from neonates or samples of amniotic fluid, placenta, or other fetal tissues. Fetal and neonatal deaths without confirmatory testing were included as potentially competing outcomes that, if not assessed, could introduce bias. Neonatal urine and saliva were tested by culture and polymerase chain reaction (PCR) at the University of Alabama, Birmingham. Congenital infection was confirmed if both culture and PCR assay were positive for CMV in either specimen. If the cultures of both urine and saliva were negative, but the PCR assay was positive for either, specimens were collected from infants again before 3 weeks of age for confirmatory testing. In this case, neonatal congenital CMV infection was diagnosed if culture or repeat PCR assay of either urine or saliva was positive for CMV. Confirmation of infection was also made by analysis of amniotic fluid (if an amniocentesis was performed after randomization) or, in cases of fetal and neonatal deaths, from tissue, if available. Neonatal secondary outcomes included fetal or neonatal death, gestational age at delivery, preterm delivery before 34 and before 37 weeks, birth weight below the 5th percentile for gestational age according to race and sex,[15] and symptomatic CMV infection. We defined CMV infection as a composite of CMV isolated from amniotic fluid obtained during amniocentesis, from placental tissue, or from urine or saliva samples during the first 3 weeks of life and at least one of the following: hearing loss, jaundice (direct bilirubin exceeding 20% of the total bilirubin), hepatomegaly, splenomegaly, birth weight below the 5th percentile, intracerebral calcifications, microcephaly (head circumference below the 3rd percentile),[16] hypotonia, seizures, petechial rash, interstitial pneumonitis, thrombocytopenia (defined as platelet count <100,000 per cubic millimeter), anemia (defined as a hematocrit <35%), hepatitis (defined as an aspartate aminotransferase or alanine aminotransferase level ≥100 U per liter), chorioretinitis, or CMV found in the cerebrospinal fluid. In the event of a fetal or neonatal death, symptomatic CMV infection was defined as CMV isolated from amniotic fluid obtained during amniocentesis or CMV detected in fetal or placental samples.

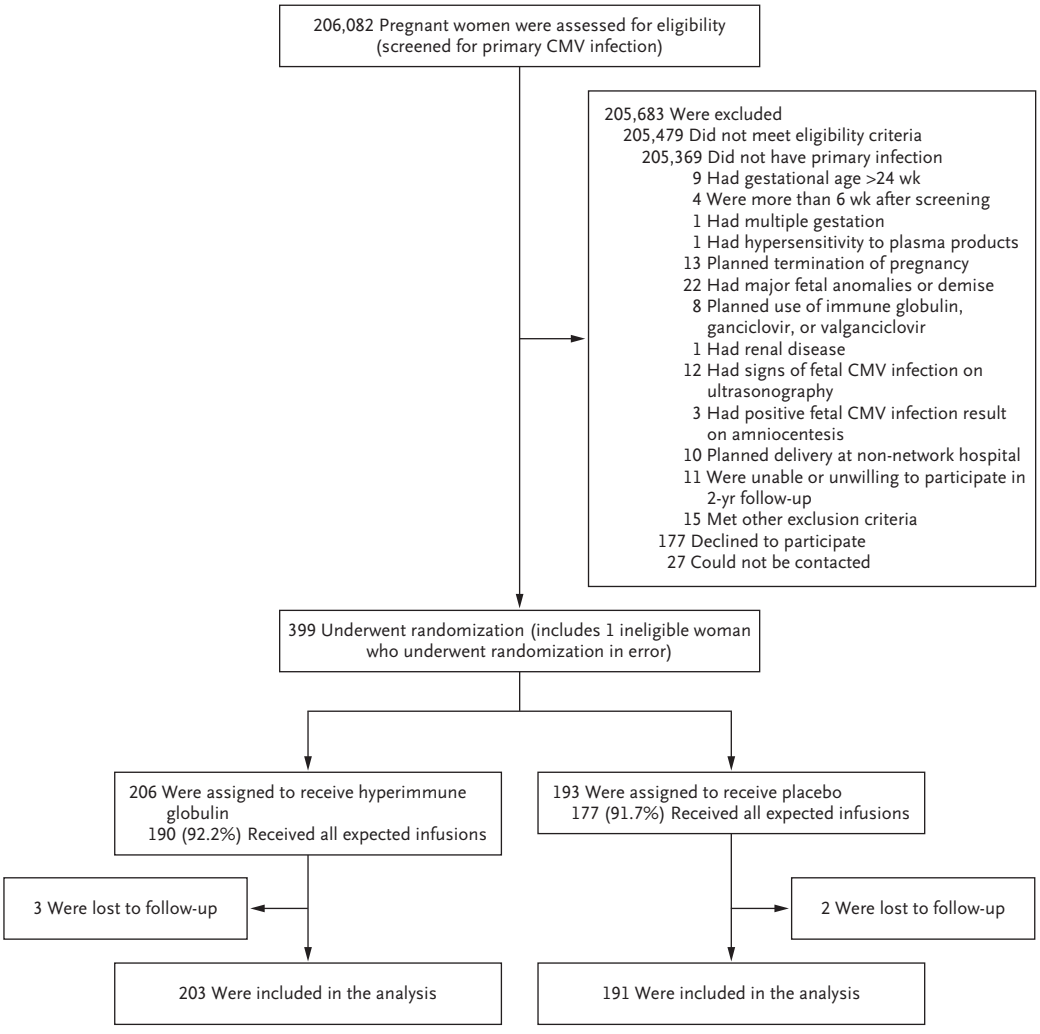

Figure 1. Screening, Enrollment, Randomization, and Follow-up.
CMV denotes cytomegalovirus.

Maternal secondary outcomes included hypertensive disorders of pregnancy and placental abruption, as well as adverse events (anaphylaxis, hypotension, pulmonary embolism, deep venous thrombosis, or stroke) potentially associated with administration of hyperimmune globulin. Maternal death, anaphylaxis, pulmonary embolism, and deep venous thrombosis that occurred during the treatment period were reported as serious adverse events of special interest.

STATISTICAL ANALYSIS

We estimated that 10% of the participants in the placebo group would have fetal losses or undergo termination of pregnancy and that the incidence of neonatal congenital infection would be 32% (estimated on the basis of previous studies) in the remaining sample,[4,6] resulting in a projected incidence of a primary outcome event of 38% in the placebo group. We estimated that a total sample size of 800 women (400 per group) would give the trial at least 90% power to detect a 30% lower incidence of the primary outcome (26.6%) in the hyperimmune globulin group, at a type I error rate (two-sided) of 5%.

An independent data and safety monitoring committee monitored the trial. We used a group sequential method to control the type I error,

Table 1. Maternal Characteristics at Baseline.*

Characteristic	Hyperimmune Globulin (N=206)	Placebo (N=193)
Age — yr	27.2±6.3	28.5±6.0
Race and ethnic group — no. (%)†		
Non-Hispanic White	135 (65.5)	124 (64.2)
Non-Hispanic Black	35 (17.0)	30 (15.5)
Hispanic	30 (14.6)	33 (17.1)
Other, unknown, or more than one race or ethnic group	6 (2.9)	6 (3.1)
Married or living with partner — no. (%)	145 (70.4)	142 (73.6)
Education — yr	14.1±2.1	14.2±2.3
Occupational exposure — no./total no. (%)‡	78/195 (40.0)	63/174 (36.2)
≥1 Child living at home — no. (%)	150 (72.8)	140 (72.5)
≥1 Child in day care — no. (%)	83 (40.3)	78 (40.4)
Nulliparous — no. (%)	75 (36.4)	62 (32.1)
Tobacco use — no. (%)	22 (10.7)	23 (11.9)
Alcohol use — no. (%)	21 (10.2)	24 (12.4)
CMV infection at screening — no. (%)§		
IgM+, IgG+, low avidity¶	200 (97.1)	183 (94.8)
IgM+, IgG seroconversion	5 (2.4)	10 (5.2)
Weeks' gestation at randomization		
Mean	16.2±3.9	15.6±4.1
Distribution — no. (%)		
≤11 wk 6 days	26 (12.6)	36 (18.7)
12 wk 0 days to 19 wk 6 days	142 (68.9)	126 (65.3)
≥20 wk 0 days	38 (18.4)	31 (16.1)
Body-mass index at randomization‖	27.2±7.0	26.9±7.0
Avidity index at randomization**	29.7±14.6	29.9±13.6
Days from screening to randomization	25.5±9.1	25.2±8.2

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Race and ethnic group were reported by the patient.
‡ Includes teacher, student, babysitter or nanny, health care worker, or day-care worker.
§ One participant in the hyperimmune globulin group did not have primary cytomegalovirus (CMV) infection and underwent randomization in error.
¶ Low avidity is defined as less than 50%.
‖ The body-mass index is the weight in kilograms divided by the square of the height in meters.
** Data are not included for 4 participants (1 in the hyperimmune globulin group and 3 in the placebo group) who underwent seroconversion.

with the Lan–DeMets characterization of the O'Brien–Fleming boundary providing the stopping rule for benefit.[17] We also used conditional power analysis as a stopping guideline for futility. If the conditional power was low (<10%) given the observed data and assuming the alternative hypothesis for the remainder of the trial, termination for futility could be considered. In addition, the data coordinating center continuously monitored the outcomes of infusions for serious adverse events of special interest that occurred during the treatment period (defined above) in the hyperimmune globulin group. If the percentage of women in the hyperimmune globulin group who had one of these events within 72 hours after an infusion was not consistent with the assumed percentage among pregnant women in the general population (≤0.5%), the trial would be halted until the data and safety monitoring committee determined whether the trial should

continue. Five interim analyses were performed for the primary outcome.

Analyses were performed according to the intention-to-treat principle. We compared the primary outcome using the chi-square test and estimated relative risks for the primary and other dichotomous outcomes. For continuous variables, we calculated differences between means except for length of hospital stay, for which we calculated the difference between medians using Hodges–Lehmann estimators. Since the type I error adjustment for the multiple interim analyses was minimal, 95% confidence intervals are reported throughout. The statistical analysis plan is provided in the protocol.

In addition, we report ad hoc secondary outcomes (gestational diabetes, clinical chorioamnionitis, oligohydramnios, polyhydramnios, and cesarean delivery) requested by the data and safety monitoring committee for interim analyses.

RESULTS

ENROLLMENT, ADHERENCE, AND PATIENT CHARACTERISTICS

From April 2012 to June 6, 2018, a total of 206,082 pregnant women at less than 23 weeks of gestation were screened with CMV antibody testing; of those, 205,479 did not meet eligibility criteria. A total of 712 women (0.35%) had primary CMV infection; of those, 398 (56%) underwent randomization. In addition, one person whose CMV antibody test was negative underwent randomization in error (Fig. 1) and is included in the analysis cohort. At the fifth interim analysis, which included data from 356 participants (45% of the planned sample size), a conditional power analysis showed that given the data to date and assuming a 30% lower incidence in the hyperimmune globulin group than the observed incidence in the placebo group for the remainder of the trial, the conditional power to show a benefit was 7%, less than the prespecified cutoff of 10%. The data and safety monitoring committee recommended trial termination in June 2018.

A total of 24 women still receiving infusions when the study was stopped were given the option of continuing infusions; 14 received all their remaining infusions and 10 did not. In all, 92.2% of participants in the hyperimmune globulin group and 91.7% in the placebo group received infusions as scheduled until delivery. The characteristics of the treatment groups at baseline were similar except that the hyperimmune globulin group was younger on average (27 vs. 29 years of age) (Table 1).

Table 2. Primary and Related Outcomes.

Outcome	Hyperimmune Globulin (N=203)	Placebo (N=191)
Primary outcome — no. (%)*	46 (22.7)	37 (19.4)
Fetus or neonate with CMV infection	36 (17.7)	32 (16.8)
Neonatal death without CMV infection	0	0
Fetal or neonatal death with proven CMV infection	7 (3.4)	3 (1.6)
Fetal death without proven CMV infection	3 (1.5)	2 (1.0)
CMV infection		
None — no. (%)	160 (78.8)	156 (81.7)
Asymptomatic CMV infection — no. (%)	20 (9.9)	20 (10.5)
Symptomatic CMV infection — no. (%)	23 (11.3)	15 (7.9)
Jaundice	3	1
Hepatomegaly	1	1
Splenomegaly	1	0
Birth weight <5th percentile	8	2
Intracerebral calcifications	1	0
Head circumference <3rd percentile	4	2
Hypotonia	1	1
Seizures	0	0
Petechial rash	1	5
Hearing loss	1	1
Interstitial pneumonitis	0	0
Thrombocytopenia	2	2
Anemia	2	1
Hepatitis	5	5
Chorioretinitis	0	0

* For the primary outcome, the relative risk was 1.17 (95% confidence interval, 0.80 to 1.72; P=0.42).

OUTCOMES

The fetus or neonate of 22.7% of the participants in the hyperimmune globulin group and of 19.4% in the placebo group had a primary outcome event (relative risk, 1.17; 95% confidence interval [CI], 0.80 to 1.72; P=0.42) (Table 2). This association did not change after adjustment for maternal age. Of the 83 pregnancies that met primary outcome criteria, 67 (81%) did so on the basis of detection of neonatal infection (35 in the hyperimmune globulin group and 32

Table 3. Other Neonatal Secondary Outcomes.*

Outcome	Hyperimmune Globulin (N=203)	Placebo (N=191)	Difference	Relative Risk (95% CI)
All neonates				
Gestational age at delivery — wk	38.2±4.1	38.6±3.6	−0.41 (−1.17 to 0.35)	
Preterm birth at <37 wk gestation — no. (%)	25 (12.3)	16 (8.4)		1.47 (0.81 to 2.67)
Preterm birth at <34 wk gestation — no. (%)	12 (5.9)	7 (3.7)		1.61 (0.65 to 4.01)
Fetal or neonatal death — no. (%)	10 (4.9)	5 (2.6)		1.88 (0.66 to 5.41)
Termination of pregnancy — no. (%)†	5 (2.5)	2 (1.0)		2.35 (0.47 to 21.95)
Live-born infants				
Head circumference — cm	33.9±2.1	34.1±1.9	−0.25 (−0.66 to 0.15)	
Birth weight — g	3268±657	3303±548	−35 (−157 to 87)	
Birth weight <5th percentile — no./total no. (%)	20/194 (10.3)	10/186 (5.4)		1.92 (0.92 to 3.99)
Head circumference <3rd percentile — no./total no. (%)	6/193 (3.1)	5/186 (2.7)		1.16 (0.36 to 3.72)
Grade 3 or 4 intraventricular hemorrhage — no./total no. (%)	1/193 (0.5)	0/186		
Ventriculomegaly — no./total no. (%)	1/194 (0.5)	0/186		
Retinopathy of prematurity — no./total no. (%)†	1/193 (0.5)	1/186 (0.5)		0.94 (0.03 to 31.5)
Respiratory distress syndrome — no./total no. (%)	5/193 (2.6)	10/186 (5.4)		0.48 (0.17 to 1.38)
Chronic lung disease — no./total no.	0/193	0/186		
Necrotizing enterocolitis (stage 2 or 3) — no./total no.	0/193	0/186		
Hyperbilirubinemia — no./total no. (%)	13/150 (8.7)	19/138 (13.8)		0.63 (0.32 to 1.23)
Suspected sepsis — no./total no. (%)	14/193 (7.3)	16/186 (8.6)		0.84 (0.42 to 1.68)
Confirmed sepsis — no./total no.	0/193	0/186		
Pneumonia — no./total no. (%)†	1/193 (0.5)	2/186 (1.1)		0.47 (0.17 to 5.23)
Seizures or encephalopathy — no./total no.	0/193	0/186		
Median hospital stay (95% CI) — days	2 (2 to 2)	2 (2 to 2)	0	
Admission to intermediate or intensive care nursery				
Admission — no./total no. (%)	33/193 (17.1)	25/186 (13.4)		1.27 (0.79 to 2.05)
Median stay (95% CI) — days	7 (4 to 12)	5 (3 to 10)	1 (−1 to 5)	

* Plus–minus values are means ±SD. Confidence intervals (CI) were not adjusted for multiplicity, so the intervals should not be used to infer definitive treatment effects.
† Exact confidence intervals were calculated for rare outcomes with the use of StatXact software (Cytel).

in the placebo group). There were 15 fetal or neonatal deaths (10 in the hyperimmune globulin group and 5 in the placebo group, including 5 and 2 pregnancy terminations, respectively). A total of 20 infants (10.3%) in the hyperimmune globulin group and 10 infants (5.4%) in the placebo group had birth weight below the 5th percentile (relative risk, 1.92; 95% CI, 0.92 to 3.99). The percentage of preterm births at less than 37 weeks was 12.3% in the hyperimmune globulin group and 8.4% in the placebo group (relative risk, 1.47; 95% CI, 0.81 to 2.67) (Table 3). A number of maternal secondary outcomes were evaluated, as prespecified in the protocol. There were no differences in any of the maternal outcomes between the groups (Table 4).

Because there was no significant difference between the groups for the primary outcome, we did not conduct interaction tests by subgroups. The 95% confidence intervals for secondary neonatal outcomes revealed no indication of meaningful differences between the two groups.

There was one case of a possible type 1 hypersensitivity reaction in the hyperimmune globulin

group and two cases of hypotension in the placebo group, but no thromboembolic or ischemic events. There was no significant difference between the groups in the overall proportion of participants with minor side effects; however, a greater percentage of those receiving hyperimmune globulin had headaches (28.6% vs. 19.9%; relative risk, 1.44; 95% CI, 1.00 to 2.05) and shaking chills (6 women in the hyperimmune globulin group vs. none in the placebo group) during infusion.

Table 4. Maternal Secondary Outcomes.*

Outcome	Hyperimmune Globulin (N=205)	Placebo (N=193)	Relative Risk (95% CI)
	no. (%)		
Gestational diabetes	5 (2.4)	7 (3.6)	0.67 (0.22–2.08)
Clinical chorioamnionitis	7 (3.4)	7 (3.6)	0.94 (0.34–2.63)
Oligohydramnios†	10 (4.9)	3 (1.6)	3.14 (0.93–15.10)
Polyhydramnios†	6 (2.9)	3 (1.6)	1.88 (0.45–14.06)
Gestational hypertension or preeclampsia	24 (11.7)	14(7.3)	1.61 (0.86–3.03)
Placental abruption†	3 (1.5)	1 (0.5)	2.82 (0.29–72.42)
Cesarean delivery	51 (24.9)	49 (25.4)	0.98 (0.70–1.38)

* All available maternal data are shown; values are missing for one participant in the hyperimmune globulin group. The 95% confidence intervals are not adjusted for multiplicity, so these values should not be used to infer definitive treatment effects.

† Exact confidence limits were calculated for rare outcomes with the use of StatXact software (Cytel).

DISCUSSION

In this placebo-controlled, randomized trial involving women with primary CMV infection during early pregnancy, monthly infusions of CMV hyperimmune globulin did not prevent congenital CMV infection in their offspring. These findings contradict the conclusions of observational studies that suggested significant improvement in outcomes with the administration of CMV hyperimmune globulin.[6-8] The prospective observational study reported by Nigro et al., which suggested benefit, was limited by lack of randomization and by assignment to treatment that was unblinded and therefore probably biased.[6] A recent observational study in Spain showed no benefit of hyperimmune globulin administration.[18] The results of the study in Spain are consistent with those of a smaller randomized trial by Revello et al., which showed no lower risk of congenital CMV with administration of hyperimmune globulin but a slightly higher (but not statistically significant) risk of a composite of adverse obstetrical outcomes, including preterm delivery, preeclampsia, and fetal growth below the 5th percentile (13% vs. 2%, P=0.06).[19] This trial similarly shows increases in some of these outcomes, although the 95% confidence intervals include 1.

One potential limitation of the trial is that most women were screened only once during pregnancy and that most participants qualified for enrollment because of low-avidity IgG with IgM. CMV avidity testing can detect primary infection within approximately 3 to 4 months after occurrence. Thus, it is possible that CMV hyperimmune globulin was given to some women after their fetuses were already infected. Positive IgM, IgG, and low-avidity IgG screening are similar to seroconversion in predicting congenital CMV infection. In a large cohort study, Lazzarotto et al. showed that this method was associated with detection of 25% of congenital CMV infections, as compared with 30% detection with seroconversion.[12] In addition, on a pragmatic level, the screening approach in this trial was similar to the approach that would most likely be performed if universal CMV screening were to be adopted in the United States. Monthly serial testing throughout pregnancy is impractical from a cost and logistic standpoint. This trial evaluated only neonatal outcomes. In a continuation of this trial, a 2-year follow-up study to assess motor, cognitive, and hearing outcomes among the infants is ongoing. Longer-term outcomes and severity of infection will be assessed in that follow-up study.

The percentage of women in the placebo group whose fetus or neonate had a primary outcome event (19.4%) was lower than we anticipated, as was the frequency of primary CMV infection among pregnant women screened for the trial. These findings are probably related to the fact that women with evidence of fetal infection at the time of randomization were not eligible for the trial. Recent attention has been given to an observational study that suggested the efficacy of hyperimmune globulin administered twice monthly in reducing the risk of congenital CMV infection.[20] The study was neither

blinded nor randomized and the comparison group was a historical cohort, so drawing conclusions about efficacy is difficult.

We found that CMV hyperimmune globulin did not decrease the incidence of congenital CMV infection or fetal or neonatal death among the offspring of women with primary CMV infection in pregnancy.

The content of this article does not necessarily reflect the views or policies of the National Institutes of Health, the Department of the Army, the Department of Defense, or the U.S. government.

Supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (grants HD40500, HD36801, HD53097, HD40512, HD40485, HD34208, HD40560, HD27869, HD27915, HD68258, HD68282, HD40544, HD40545, HD68268, HD34116, HD87192, and HD87230) and the National Center for Advancing Translational Sciences (grants UL1TR001873 and UL1TR000040). CSL Behring provided the Cytogam and AlbuRx but had no other role in the trial.

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

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank Elizabeth A. Thom, Ph.D., for study design, study management, oversight, and statistical analysis; Catherine Y. Spong, M.D., for protocol development; Sallie Permar, M.D., for sample analysis; and Tony Mazzulli, M.D., F.R.C.P., and his staff at Mount Sinai Hospital for expert advice and assistance.

APPENDIX

The authors' full names and academic degrees are as follows: Brenna L. Hughes, M.D., Rebecca G. Clifton, Ph.D., Dwight J. Rouse, M.D., George R. Saade, M.D., Mara J. Dinsmoor, M.D., M.P.H., Uma M. Reddy, M.D., Robert Pass, M.D., Donna Allard, R.N., Gail Mallett, R.N., Lida M. Fette, M.S., Cynthia Gyamfi-Bannerman, M.D., Michael W. Varner, M.D., William H. Goodnight, M.D., Alan T.N. Tita, M.D., Ph.D., Maged M. Costantine, M.D., Geeta K. Swamy, M.D., Ronald S. Gibbs, M.D., Edward K. Chien, M.D., Suneet P. Chauhan, M.D., Yasser Y. El-Sayed, M.D., Brian M. Casey, M.D., Samuel Parry, M.D., Hyagriv N. Simhan, M.D., Peter G. Napolitano, M.D., and George A. Macones, M.D.

The authors' affiliations are as follows: the Department of Obstetrics and Gynecology, Brown University, Providence, RI (B.L.H., D.J.R., D.A.); George Washington University Biostatistics Center, Washington, DC (R.G.C., L.M.F.); the University of Texas Medical Branch, Galveston (G.R.S.), the University of Texas Health Science Center at Houston, Children's Memorial Hermann Hospital, Houston (S.P.C.), and the University of Texas Southwestern Medical Center, Dallas (B.M.C.); Northwestern University, Chicago (M.J.D., G.M.); Eunice Kennedy Shriver National Institute of Child Health and Human Development, Bethesda, MD (U.M.R.); Columbia University, New York (C.G.-B.); the University of Utah Health Sciences Center, Salt Lake City (M.W.V.); the University of North Carolina at Chapel Hill, Chapel Hill (W.H.G.), and Duke University, Durham (G.K.S.) — both in North Carolina; the Department of Pediatrics (R.P.), University of Alabama at Birmingham (A.T.N.T.), Birmingham; Ohio State University, Columbus (M.M.C.), the University of Colorado School of Medicine, Anschutz Medical Campus, Aurora (R.S.G.); Case Western Reserve University, Cleveland (E.K.C.); Stanford University, Stanford, CA (Y.Y.E.-S.); the University of Pennsylvania, Philadelphia (S.P.), and the University of Pittsburgh, Pittsburgh (H.N.S.); Madigan Army Medical Center, Joint Base Lewis–McChord, WA (P.G.N.); and Washington University, St. Louis (G.A.M.).

REFERENCES

1. Stagno S, Pass RF, Dworsky ME, Alford CA Jr. Maternal cytomegalovirus infection and perinatal transmission. Clin Obstet Gynecol 1982;25:563-76.
2. Stagno S, Pass RF, Cloud G, et al. Primary cytomegalovirus infection in pregnancy; incidence, transmission to fetus, and clinical outcome. JAMA 1986;256:1904-8.
3. Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. N Engl J Med 1992;326:663-7.
4. Kenneson A, Cannon MJ. Review and meta-analysis of the epidemiology of congenital cytomegalovirus (CMV) infection. Rev Med Virol 2007;17:253-76.
5. Dollard SC, Grosse SD, Ross DS. New estimates of the prevalence of neurological and sensory sequelae and mortality associated with congenital cytomegalovirus infection. Rev Med Virol 2007;17:355-63.
6. Nigro G, Adler SP, La Torre R, Best AM. Passive immunization during pregnancy for congenital cytomegalovirus infection. N Engl J Med 2005;353:1350-62.
7. Nigro G, La Torre R, Pentimalli H, et al. Regression of fetal cerebral abnormalities by primary cytomegalovirus infection following hyperimmunoglobulin therapy. Prenat Diagn 2008;28:512-7.
8. La Torre R, Nigro G, Mazzocco M, Best AM, Adler SP. Placental enlargement in women with primary maternal cytomegalovirus infection is associated with fetal and neonatal disease. Clin Infect Dis 2006;43:994-1000.
9. Diagnostics Division. ARCHITECT CMV IgM. Sligo, Ireland: Abbott Ireland, January 2007 (package insert) (https://www.ilexmedical.com/files/PDF/CMVIgM_ARC.pdf).
10. Diagnostics Division. ARCHITECT CMV IgG. Sligo, Ireland: Abbott Ireland, 2015 (package insert).
11. Diagnostics Division. ARCHITECT CMV IgG avidity. Sligo, Ireland: Abbott Ireland, December 2008 (package insert) (https://www.ilexmedical.com/files/PDF/CMVIgG.pdf).
12. Lazzarotto T, Guerra B, Lanari M, Gabrielli L, Landini MP. New advances in the diagnosis of congenital cytomegalovirus infection. J Clin Virol 2008;41:192-7.
13. Rosenberger WF, Lachin JM. Randomization in clinical trials: theory and practice. New York: John Wiley, 2002.
14. Miescher SM, Huber TM, Kühne M, et al. In vitro evaluation of cytomegalovirus-specific hyperimmune globulins vs. standard intravenous immunoglobulins. Vox Sang 2015;109:71-8.
15. Alexander GR, Kogan MD, Himes JH. 1994-1996 U.S. singleton birth weight percentiles for gestational age by race, Hispanic origin, and gender. Matern Child Health J 1999;3:225-31.
16. Olsen IE, Groveman SA, Lawson ML, Clark RH, Zemel BS. New intrauterine growth curves based on United States data. Pediatrics 2010;125(2):e214-e224.
17. Lan KKG, Demets DL. Discrete sequential boundaries for clinical trials. Biometrika 1983;70:659-63.
18. Blázquez-Gamero D, Galindo Izquierdo A, Del Rosal T, et al. Prevention and treatment of fetal cytomegalovirus infection with cytomegalovirus hyperimmune globulin: a multicenter study in Madrid. J Matern Fetal Neonatal Med 2019;32:617-25.
19. Revello MG, Lazzarotto T, Guerra B, et al. A randomized trial of hyperimmune globulin to prevent congenital cytomegalovirus. N Engl J Med 2014;370:1316-26.
20. Kagan KO, Enders M, Schampera MS, et al. Prevention of maternal-fetal transmission of cytomegalovirus after primary maternal infection in the first trimester by biweekly hyperimmunoglobulin administration. Ultrasound Obstet Gynecol 2019;53:383-9.