Is mode of delivery associated with the risk of necrotizing enterocolitis?

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BACKGROUND: The pathogenesis of necrotizing enterocolitis remains poorly understood. Different newborn bacterial colonization due to cesarean delivery as opposed to vaginal delivery has been implicated as one potential contributing factor.

OBJECTIVE: We sought to determine whether mode of delivery is associated with the risk of necrotizing enterocolitis in neonates of women who were at imminent risk of delivery <32 weeks' gestational age.

STUDY DESIGN: This is a secondary analysis of data from a randomized controlled trial of magnesium sulfate for the prevention of cerebral palsy. The parent trial included women with pregnancies at 24 to 31 6/7 weeks of gestation who were considered at imminent risk for preterm delivery. Women with a viable singleton gestation and data available on mode of delivery and development of necrotizing enterocolitis were included. Neonates delivered by vaginal delivery were compared to those delivered by cesarean delivery in bivariable analyses. Multivariable analysis was used to adjust for potential confounders.

RESULTS: A total of 2012 mother-neonate pairs were analyzed. Of these, 731 (36%) women delivered by cesarean delivery and 170 neonates (8.4%) developed necrotizing enterocolitis. In bivariable analyses, women who delivered by cesarean delivery were older (27 [interquartile range, 22-32] vs 24 [interquartile range, 20-29] years, $P < .001$) and had a higher frequency of chorioamnionitis (14.0% vs 10.5%, $P = .021$) compared to those who delivered vaginally. Neonates delivered by cesarean delivery were more premature (29.3 [interquartile range, 27.1-31.4] vs 30.3 [interquartile range, 27.9-31.9] weeks, $P < .001$), were smaller (1266 [interquartile range, 920-1643] vs 1465 [interquartile range, 1067-1850] g, $P < .001$), were more likely to be small for gestational age (4.4% vs 1.9%, $P = .001$), and had a higher frequency of proven sepsis (20.1% vs 14.7%, $P = .002$) compared to those who delivered vaginally. Rates of necrotizing enterocolitis (8.1% vs 8.7%, $P = .65$) and stage 2 or 3 necrotizing enterocolitis (4.4% vs 4.7%, $P = .75$) did not differ by mode of delivery. After adjusting for potential confounders, cesarean delivery continued to have no association with the frequency of necrotizing enterocolitis (adjusted odds ratio, 0.74; 95% confidence interval, 0.52—1.04) or stage 2 or 3 necrotizing enterocolitis (adjusted odds ratio, 0.73; 95% confidence interval, 0.46—1.16). This study was powered to detect a minimum relative risk of 1.5 for necrotizing enterocolitis associated with mode of delivery.

CONCLUSION: Mode of delivery was not significantly associated with necrotizing enterocolitis in neonates born to a cohort of women who were considered at imminent risk of extreme preterm delivery.

Key words: cesarean, microbial colonization, mode of delivery, necrotizing enterocolitis

Introduction

Necrotizing enterocolitis (NEC), characterized by severe intestinal inflammation and necrosis, is the most common gastrointestinal emergency affecting neonates and primarily occurs in those who deliver preterm. NEC is associated with significant short-term and long-term morbidities, as well as a mortality rate of at least 20% in those requiring surgical intervention.[1] Unfortunately, the pathogenesis of the disease process remains poorly understood, but likely involves a complex interplay among bacterial colonization, initiation of enteral nutrition, and hypoxia-related intestinal injury.[2]

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Neonates born by cesarean delivery (CD) were shown to have significantly altered bacterial flora of the newborn intestine compared to those born vaginally, with increased colonization by bacteria such as *Klebsiella*, *Enterobacter*, and *Clostridium*.[3-6] Thus, it has been speculated that CD may be an important contributor to the development of NEC, although this association has not been well evaluated. Therefore, our objective was to examine whether neonates delivered by CD are at an increased risk of developing NEC compared to neonates delivered vaginally.

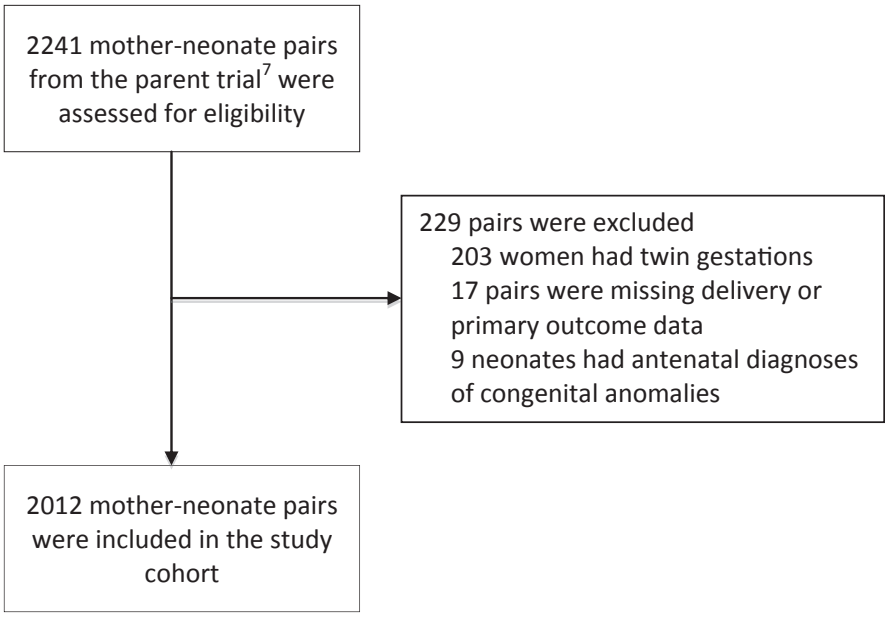
Materials and Methods

This was a secondary analysis of data from the randomized controlled trial of magnesium sulfate for the prevention of cerebral palsy that was conducted by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. The parent trial[7] enrolled women who presented at 24 to 31 6/7 weeks of gestation and were considered at very high risk for spontaneous (advanced preterm labor with cervical dilatation of 4-8 cm or premature rupture of membranes) or indicated (eg, fetal growth restriction) preterm delivery at 20 centers across the United States from 1997 through 2004. Women were randomly assigned to intrapartum magnesium sulfate or placebo.

In the current analysis, we included all women from the clinical trial who delivered viable singleton gestations and had data available on mode of delivery and diagnosis of NEC. Women with fetuses who were antenatally diagnosed with congenital anomalies were excluded from the study. Eligible women were divided into 2 comparison groups based on their mode of delivery: those who underwent vaginal delivery and those who underwent CD.

Maternal and neonatal demographic and clinical characteristics were assessed.

FIGURE
Flow chart detailing exclusion criteria applied to the present analysis



Study cohort sample.

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In the parent trial,[7] chorioamnionitis was defined as a body temperature of ≥100°F (or ≥37.8°C) with at least 1 additional clinical sign of chorioamnionitis (persistent maternal or fetal tachycardia for at least 20 minutes, malodorous fluid, uterine tenderness, or maternal leukocytosis with white blood cell count at >20,000 cells/mm^3) and no other defined infection. Proven neonatal sepsis was defined as positive cultures of neonatal blood, cerebrospinal fluid, or urine in conjunction with clinical findings suggestive of infection on physical examination, or in the absence of positive cultures, clinical evidence of cardiovascular collapse, or an unequivocal X-ray confirming infection in a neonate who was believed to be clinically septic. A woman was defined as having a small-for-gestational-age (SGA) neonate based on a birthweight <10th percentile of normative birthweights for singletons at the time of the original trial.[8]

The primary outcome of our study was the diagnosis of NEC. NEC (comprising 3 stages) was defined by the clinical staging system of Bell et al[9] based on systemic, intestinal, and radiographic findings. The secondary outcome was the diagnosis of stage 2 or 3 NEC. Stage 2 NEC represented definite NEC with mild to moderate illness and stage 3 NEC represented advanced NEC with severe illness with intact or perforated bowel.

Bivariable comparisons were performed using the Mann-Whitney *U* tests or χ^2 analyses for continuous and categorical variables, respectively. Multivariable logistic regression analyses were performed to assess whether mode of delivery was independently associated with the odds of NEC or stage 2 or 3 NEC. Variables that significantly differed by exposure ($P < .05$) in the bivariable analyses were included in the multivariable logistic regression equations. All hypotheses tests were 2-tailed and $P < .05$ was used to define statistical significance. All statistical analyses were performed using software (Stata, Version 13.1; StataCorp, College Station, TX). This study was considered exempt by the Northwestern University Institutional Review Board because only deidentified data were used.

TABLE 1
Characteristics of study sample, stratified by mode of delivery

Characteristic	Vaginal delivery, n = 1281	Cesarean delivery, n = 731	*P* value
Maternal age, y	24 (20–29)	27 (22–32)	<.001
Race/ethnicity			.064
Non-Hispanic black	582 (45.5)	306 (41.9)	
Non-Hispanic white	434 (33.9)	290 (39.7)	
Hispanic	235 (18.3)	119 (16.3)	
Asian	14 (1.1)	4 (0.5)	
Other	16 (1.2)	12 (1.6)	
Tobacco use	354 (27.6)	209 (28.6)	.646
Illicit drug use	133 (10.4)	65 (8.9)	.280
Pregestational diabetes	66 (5.2)	40 (5.5)	.761
Preeclampsia	9 (0.7)	11 (1.5)	.081
Chorioamnionitis	136 (10.6)	102 (14.0)	.012

Data are presented as median (interquartile range) or n (%).

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Results

Of the 2012 mother-neonate pairs who were eligible for analysis (Figure), 731 (36%) underwent CD and 1281 (64%) underwent vaginal delivery. Women who underwent CD were older and had a higher frequency of chorioamnionitis compared to those who delivered