Tara M. Randis*, Madeline Murguia Rice, Leslie Myatt, Alan T.N. Tita, Kenneth J. Leveno, Uma M. Reddy, Michael W. Varner, John M. Thorp Jr., Brian M. Mercer, Mara J. Dinsmoor, Susan M. Ramin, Marshall W. Carpenter, Philip Samuels, Anthony Sciscione, Jorge E. Tolosa, George Saade and Yoram Sorokin, for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network[a]

Incidence of early-onset sepsis in infants born to women with clinical chorioamnionitis

https://doi.org/10.1515/jpm-2017-0192
Received June 12, 2017. Accepted March 6, 2018.

Abstract

Objective: To determine the frequency of sepsis and other adverse neonatal outcomes in women with a clinical diagnosis of chorioamnionitis.

Methods: We performed a secondary analysis of a multicenter placebo-controlled trial of vitamins C/E to prevent preeclampsia in low risk nulliparous women. Clinical chorioamnionitis was defined as either the "clinical diagnosis" of chorioamnionitis or antibiotic administration during labor because of an elevated temperature or uterine tenderness in the absence of another cause. Early-onset neonatal sepsis was categorized as "suspected" or "confirmed" based on a clinical diagnosis with negative or positive blood, urine or cerebral spinal fluid cultures, respectively, within 72 h of birth. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by logistic regression.

Results: Data from 9391 mother-infant pairs were analyzed. The frequency of chorioamnionitis was 10.3%. Overall, 6.6% of the neonates were diagnosed with confirmed (0.2%) or suspected (6.4%) early-onset sepsis. Only 0.7% of infants born in the setting of chorioamnionitis had culture-proven early-onset sepsis versus 0.1% if chorioamnionitis was not present. Clinical chorioamnionitis was associated with both suspected [OR 4.01 (3.16–5.08)] and confirmed [OR 4.93 (1.65–14.74)] early-onset neonatal sepsis, a need for resuscitation within the first 30 min after birth [OR 2.10 (1.70–2.61)], respiratory distress [OR 3.14 (2.16–4.56)], 1 min Apgar score of ≤3 [OR 2.69 (2.01–3.60)] and 4–7 [OR 1.71 (1.43–2.04)] and 5 min Apgar score of 4–7 [OR 1.67 (1.17–2.37)] (vs. 8–10).

Conclusion: Clinical chorioamnionitis is common and is associated with neonatal morbidities. However, the vast

[a]See Appendix for a list of other members of the NICHD MFMU Network.

***Corresponding author: Tara M. Randis,** MD, MS, Department of Pediatrics, Vagelos College of Physicians and Surgeons, Columbia University, New York, NY, USA; and Department of Pediatrics and Microbiology, New York University School of Medicine, 317 East 34th St, Suite 902, New York, NY 10016, USA, Tel.: 646-754-1041, E-mail: Tara.Randis@NYUMC.org

Madeline Murguia Rice: George Washington University Biostatistics Center, Washington, DC, USA

Leslie Myatt: Department of Obstetrics and Gynecology, University of Cincinnati, Cincinnati, OH, USA

Alan T.N. Tita: Department of Obstetrics and Gynecology, University of Alabama at Birmingham, Birmingham, AL, USA

Kenneth J. Leveno: Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Uma M. Reddy: Pregnancy and Perinatology Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, Bethesda, MD, USA

Michael W. Varner: Department of Obstetrics and Gynecology, University of Utah, Salt Lake City, UT, USA

John M. Thorp Jr.: Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Brian M. Mercer: Department of Obstetrics and Gynecology, Case Western Reserve University-MetroHealth Medical Center, Cleveland, OH, USA

Mara J. Dinsmoor: Department of Obstetrics and Gynecology, Northwestern University, Chicago, IL, USA

Susan M. Ramin: Department of Obstetrics and Gynecology, University of Texas Health Science Center at Houston, Houston, TX, USA

Marshall W. Carpenter: Department of Obstetrics and Gynecology, Brown University, Providence, RI, USA

Philip Samuels: Department of Obstetrics and Gynecology, The Ohio State University, Columbus, OH, USA

Anthony Sciscione: Department of Obstetrics and Gynecology, Drexel University, Philadelphia, PA, USA

Jorge E. Tolosa: Department of Obstetrics and Gynecology, Oregon Health and Science University, Portland, OR, USA

George Saade: Department of Obstetrics and Gynecology, University of Texas Medical Branch, Galveston, TX, USA

Yoram Sorokin: Department of Obstetrics and Gynecology, Wayne State University, Detroit, MI, USA

majority of exposed infants (99.3%) do not have confirmed early-onset sepsis.

Keywords: Chorioamnionitis; early-onset sepsis; intrapartum fever.

Introduction

Current obstetric interventions to reduce early-onset newborn infections, including intrapartum antibiotic prophylaxis for mothers colonized with group B *Streptococcus* (GBS) and treatment of clinically diagnosed chorioamnionitis, are effective [1, 2]. However, accurate identification of newborns who will develop early-onset sepsis despite these interventions remains a major challenge. For this reason, the American Academy of Pediatrics and the Centers for Disease Control recommend treating asymptomatic infants born to mothers with clinically diagnosed chorioamnionitis with broad-spectrum antibiotics for at least 48 h until infection can be ruled out [3, 4]. As a result of these guidelines, many healthy infants are ultimately treated with empiric antibiotics in order to prevent a single case of sepsis [5–8].

Emerging data regarding the adverse consequences of early antibiotic exposure on the developing infant microbiome are worrisome [9], as is the growing problem of antimicrobial resistance among neonatal pathogens [10]. Furthermore, sepsis evaluations often require neonatal intensive care unit (NICU) admission and/or separation of the mother and infant dyad, potentially disrupting the early establishment of breastfeeding [11]. For these reasons, many experts in the field have called for a re-evaluation of the approach to the newborn exposed to maternal chorioamnionitis [5, 12].

Our objective was to determine, within the current paradigm of intrapartum treatment of clinical chorioamnionitis and empiric newborn treatment after delivery, the associations between clinical chorioamnionitis and early-onset sepsis and other adverse neonatal outcomes.

Patients and methods

We performed a secondary analysis of a multi-center placebo-controlled randomized trial of vitamins C/E to prevent serious complications associated with pregnancy-associated hypertension in low-risk nulliparous women. The trial, conducted from 2003 to 2008 at 16 clinical centers in the *Eunice Kennedy Shriver* National Institute of Child and Human Development (NICHD) Maternal-Fetal Medicine Units Network (ClinicalTrials.gov number NCT00135707), has been previously described [13]. Pregnant women who were nulliparous and had a singleton gestation less than 16 weeks 0 days at the time of screening were eligible for inclusion in the trial. A total of 10,154 women underwent randomization to receive capsules containing a combination of 1000 mg of vitamin C (ascorbic acid) and 400 IU of vitamin E (RRR-alpha-tocopherol acetate) or matching placebo (mineral oil). Data were collected by trained and certified research personnel. The study was approved by the Institutional Review Board at each clinical site and the data-coordinating center, and all participants provided written informed consent before enrollment.

A total of 10,154 women were enrolled in the trial. This secondary analysis was restricted to women with outcome data (n = 9969, 98%) who labored (n = 9585, 94.4%). Excluded from the analysis were those with missing data regarding chorioamnionitis status (n = 87, 0.86%) or neonatal sepsis status (n = 9, 0.09%). Also excluded were fetal deaths that occurred prior to the intrapartum period (n = 98, 0.97%). Clinical chorioamnionitis was defined as either the "clinical diagnosis" of chorioamnionitis or the administration of antibiotics during labor because of either an elevated temperature or uterine tenderness in the absence of another cause. Maternal fever during labor was defined as a temperature ≥38.0°C. Early-onset neonatal sepsis (within the first 72 h after birth) was categorized as suspected or confirmed. Confirmed early-onset sepsis included those infants with positive cultures of blood, cerebrospinal fluid or urine from the first 72 h after birth with or without suspicious clinical findings of infection on physical examination or (in the absence of positive cultures) there is clinical evidence of cardiovascular collapse or an unequivocal X-ray confirming infection in an infant who is believed to be clinically septic. Suspected sepsis included those infants who developed clinical findings suspicious for infection on physical examination within the first 72 h after birth with negative cultures and non-confirmatory X-rays. Simply being at risk for sepsis did not meet the necessary criteria for suspected sepsis. Late-onset neonatal sepsis was suspected or confirmed beyond the first 72 h after birth. Bronchopulmonary dysplasia (BPD) was diagnosed when an infant received oxygen therapy [with or without mechanical ventilation/continuous positive airway pressure (CPAP)] and had an oxygen requirement ($FiO_2 > 0.21$) for the first 28 days of life. A clinical diagnosis of necrotizing enterocolitis (NEC) was made, regardless of the stage, by any of the following findings being observed at surgery or autopsy: (1) the unequivocal presence of intramural air on abdominal X-ray, (2) perforation seen on abdominal X-ray, clinical evidence as suggested by erythema and induration of the abdominal wall, or intra-abdominal abscess formation or (3) stricture formation following an episode of suspected NEC. The presence of seizures was per the diagnosis of seizures in medical record.

Statistical analysis

Descriptive analyses used the chi-squared (χ^2) test or Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables to compare characteristics by maternal chorioamnionitis status. We also conducted analyses to describe the frequency of early-onset sepsis by gestational age at delivery and by chorioamnionitis status with and without fever. Early-onset sepsis was evaluated as a dichotomous outcome (combined suspected and confirmed, none) and as a multinomial outcome (confirmed, suspected, none). Due to small numbers, late-onset sepsis was only evaluated as a dichotomous outcome (combined suspected and confirmed, none) without further separation of confirmed and suspected. One and 5 min Apgar scores were evaluated as multinomial outcomes (≤3, 4–7,

8–10); all other secondary outcomes were evaluated as dichotomous outcomes. The association between each dichotomous neonatal outcome and chorioamnionitis status was evaluated using multivariable logistic regression yielding odds ratios (ORs) and 95% confidence intervals (CIs) after adjusting for years of education, time from membrane rupture to delivery, gestational age at delivery, vitamin C, E or placebo treatment group, race/ethnicity, smoking, type of labor and delivery mode. Multinomial multivariable logistic regression was used for the outcomes with more than two categories. Because deaths that occur prior to NICU admission (intrapartum stillbirths and deaths in the delivery room) are competing outcomes with neonatal sepsis, we conducted a sensitivity analysis in which the outcome was neonatal sepsis or death before NICU admission. Finally, we evaluated the association between sepsis and maximum maternal temperature during labor using multivariable logistic regression. SAS software (SAS Institute, Cary, NC, USA) was used for the analyses. All tests were two-tailed and $P < 0.05$ was used to define statistical significance. No imputation for missing data was performed. Adjustment for multiple comparisons was not performed.

Results

Data from 9391 mother-infant pairs were analyzed. The frequency of clinical chorioamnionitis was 10.3% (970 women), and ranged from 15.5% with delivery before 34 weeks' gestation to 6.2% in women delivering $34^{0/7}$–$36^{6/7}$ weeks, 9.5% in women delivering $37^{0/7}$–$40^{6/7}$ weeks and 15.7% at ≥41 weeks of gestation. In a univariable analysis, several maternal characteristics were associated with chorioamnionitis including race, uninsured or government-assisted insurance, education level, duration of membrane rupture and advanced gestational age (Table 1).

Overall, 620 infants were diagnosed with early-onset sepsis (6.6%). Sixteen infants (0.2%) had confirmed sepsis and 604 (6.4%) were diagnosed with suspected sepsis. The frequency of confirmed or suspected early-onset sepsis

Table 1: Maternal characteristics by chorioamnionitis status.

Characteristic	Chorioamnionitis		P-value[a]
	Yes n=970	No n=8421	
Vitamin C/E treatment group	488 (50.3)	4228 (50.2)	0.95
Maternal age (years)	22 (19–26)	22 (19–27)	0.009
Race/ethnicity			<0.001
Non-Hispanic Black	224 (23.1)	2133 (25.3)	
Non-Hispanic White	227 (23.4)	3693 (43.9)	
Other	519 (53.5)	2595 (30.8)	
Private insurance	212 (21.9)	3174 (37.7)	<0.001
Education (years)	12 (10–14)	13 (11–16)	<0.001
Smoking	118 (12.2)	1306 (15.5)	0.006
GBS any time since randomization	132 (13.6)	1697 (20.2)	<0.001
Induced labor	360 (37.2)	3133 (37.2)	0.96
Duration of ROM (time from rupture to delivery) (min)	779 (555–1097)	431 (238–695)	<0.001
Highest temperature in labor[b]			<0.001
Low <36.5°C	5 (0.5)	669 (8.3)	
Normal 36.5–37.5°C	56 (5.9)	5768 (71.8)	
Normal high 37.5–37.9°C	117 (12.4)	1308 (16.3)	
Low grade fever 38.0–38.23°C	411 (43.4)	178 (2.2)	
High fever ≥38.3°C	358 (37.8)	110 (1.4)	
Gestational age at delivery (weeks)	40.0 (39.0–40.9)	39.6 (38.6–40.4)	<0.001
A priori stratification variable: gestational age at delivery categories			<0.001
<34 0/7	33 (3.4)	180 (2.1)	
34 0/7–36 6/7	35 (3.6)	527 (6.3)	
37 0/7–38 6/7	146 (15.1)	2002 (23.8)	
39 0/7–40 6/7	546 (56.3)	4588 (54.5)	
≥41 0/7	210 (21.6)	1124 (13.3)	
Cesarean delivery	376 (38.8)	1740 (20.7)	<0.001
Birth weight	3420 (3119–3728)	3270 (2953–3590)	<0.001
Male fetal sex, n (%)	537 (55.4)	4364 (51.8)	0.04

BMI = Body mass index, GBS = group B *Streptococcus*, ROM = rupture of membranes.

Data are n (%) or median (interquartile range) unless otherwise specified.

[a]Based on the χ^2 test or Fisher's exact test for categorical variables and the Wilcoxon rank sum test for continuous variables.

[b]Missing in 411.

decreased with increasing gestational age, affecting 30.2% of preterm neonates and 4.5% of those ≥37 weeks of gestation (Table 2). The most commonly isolated organisms in confirmed cases of sepsis were GBS in term infants and *Escherichia coli* in preterm infants, regardless of maternal chorioamnionitis status (Table S1).

Maternal fever during labor (temperature ≥38°C) was observed in 11.8% of the women (81.2% in the women with chorioamnionitis and 3.6% in the women without chorioamnionitis). Unadjusted infectious outcomes by chorioamnionitis and fever status showed the highest OR for confirmed early-onset sepsis in infants born to mothers with both chorioamnionitis and fever during labor (Table 3). An increased odds of confirmed early-onset sepsis was observed with increasing maternal temperature; adjusted OR (95% CI) 0.98 (0.65–1.46) for maximum maternal temperature below 36.5°C, 1.69 (1.32–2.16); for 37.5–37.9°C, 3.30 (2.43–4.48) and for 38.0–38.23°C, 5.40 (3.99–7.31) for maximum maternal temperature of 38.3°C or more, compared with a normal temperature (36.5–37.5°C).

Unadjusted frequencies of neonatal sepsis and other adverse outcomes according to the chorioamnionitis status are presented in Table 4. The frequency of suspected early-onset sepsis was 15.2% (95% CI 12.9%–17.4%) in infants born to mothers with clinical chorioamnionitis vs. 5.4% (95% CI 4.9%–5.9%) in absence of chorioamnionitis. The frequency of culture-proven early-onset sepsis was 0.7% (95% CI 0.2%–1.3%) in infants born to mothers with clinical chorioamnionitis vs. 0.1% (95% CI 0.0%–0.2%) in those not exposed to maternal chorioamnionitis. The frequency of early-onset sepsis by chorioamnionitis status and gestational age is shown in Table S2. In multivariable analysis, chorioamnionitis was associated with the following neonatal morbidities: suspected [OR 4.01 (CI 3.16–5.08)] and confirmed [OR 4.93 (CI 1.65–14.74)] early onset-sepsis, resuscitation within the first 30 min after birth [OR 2.10 (CI 1.70–2.61)], respiratory distress [OR 3.14 (CI 2.16–4.56)], 1 min Apgar score of ≤3 [OR 2.69 (CI 2.01–3.60)] and 4–7 [OR 1.71 (CI 1.43–2.04)] and 5 min Apgar score of 4–7 [OR 1.67 (CI 1.17–2.37)] (vs. 8–10) (Table 3). Seizures, BPD, late-onset sepsis, NEC and intraventricular hemorrhage were not significantly associated with maternal chorioamnionitis. The multivariable analysis results were similar in the sensitivity analyses that considered intrapartum stillbirth

Table 2: Confirmed or suspected early-onset sepsis by gestational age.

Outcome (%)	Gestational age at delivery n (%)				
	<34.0 n=213	34.0–36.6 n=562	37.0–38.6 n=2148	39.0–40.6 n=5134	≥41.0 n=1334
Early-onset sepsis (combined suspected and confirmed)	120 (56.3)	114 (20.3)	99 (4.6)	232 (4.5)	55 (4.1)
Confirmed early-onset sepsis	2 (0.9)	2 (0.4)	1 (0.0)	6 (0.1)	5 (0.4)
Suspected early-onset sepsis	118 (55.4)	112 (19.9)	98 (4.6)	226 (4.4)	50 (3.7)

Table 3: Early-onset sepsis by chorioamnionitis and fever status (unadjusted).

Outcome	Chorioamnionitis with fever during labor			Chorioamnionitis without fever during labor			Fever during labor without chorioamnionitis			No fever during labor and no chorioamnionitis
	n (%)	Unadjusted odds ratios (95% CI)	P-value	n (%)	Unadjusted odds ratios (95% CI)	P-value	n (%)	Unadjusted odds ratios (95% CI)	P-value	n (%) (referent)
Early-onset sepsis (combined suspected and confirmed)	121 (15.7)	3.29 (2.65–4.09)	<0.001	29 (16.3)	3.43 (2.28–5.17)	<0.001	27 (9.4)	1.82 (1.21–2.74)	0.004	416 (5.4)
Early-onset sepsis categorized										
Confirmed early-onset sepsis	6 (0.8)	8.49 (2.94–24.54)	<0.001	1 (0.6)	6.15 (0.76–49.47)	0.09	1 (0.4)	3.51 (0.44–28.17)	0.24	8 (0.1)
Suspected early-onset sepsis	115 (15.0)	3.19 (2.55–3.98)	<0.001	28 (15.7)	3.38 (2.23–5.12)	<0.001	26 (9.0)	1.79 (1.18–2.71)	0.006	408 (5.3)
No early-onset sepsis	648 (84.3)	Referent		149 (83.7)	Referent		261 (90.6)	Referent		7329 (94.6)

Table 4: Neonatal outcome by chorioamnionitis status.

Outcome	Chorioamnionitis, n (%)		Unadjusted odds ratios (95% CI)	P-value	Adjusted odds ratios (95% CI)[a]	P-value[a]
	Yes	No				
Early-onset sepsis (combined suspected and confirmed)	154 (15.9)	466 (5.5)	3.22 (2.65–3.92)	<0.001	4.05 (3.21–5.11)	<0.001
Early onset sepsis categorized						
Confirmed early-onset sepsis	7 (0.7)	9 (0.1)	7.59 (2.82–20.42)	<0.001	4.93 (1.65–14.74)	0.004
Suspected early-onset sepsis	147 (15.2)	457 (5.4)	3.14 (2.57–3.83)	<0.001	4.01 (3.16–5.08)	<0.001
No early-onset sepsis	816 (84.2)	7955 (94.5)	Referent		Referent	
Resuscitation within first 30 min after birth[b]	153 (15.8)	625 (7.4)	2.33 (1.93–2.83)	<0.001	2.10 (1.70–2.61)	<0.001
Seizures	6 (0.6)	12 (0.1)	4.36 (1.63–11.65)	0.003	[c]	
Respiratory distress	56 (5.8)	196 (2.3)	2.57 (1.90–3.49)	<0.001	3.14 (2.16–4.56)	<0.001
BPD	3 (0.3)	26 (0.3)	1.00 (0.30–3.32)	1.00	0.73 (0.17–3.14)	0.67
Confirmed or suspected late-onset sepsis	6 (0.6)	57 (0.7)	0.91 (0.39–2.12)	0.83	0.72 (0.25–2.08)	0.54
Necrotizing enterocolitis	4 (0.4)	13 (0.2)	2.68 (0.87–8.23)	0.09	1.57 (0.38–6.52)	0.53
IVH (any grade)	6 (0.6)	26 (0.3)	2.01 (0.83–4.90)	0.12	1.53 (0.45–5.17)	0.49
IVH (grade III or IV)	2 (0.2)	8 (0.1)	2.17 (0.46–10.25)	0.33	[c]	
1 min Apgar						
≤3	89 (9.2)	290 (3.5)	3.14 (2.44–4.03)	<0.001	2.69 (2.01–3.60)	<0.001
4–7	214 (22.1)	1299 (15.5)	1.69 (1.43–1.99)	<0.001	1.71 (1.43–2.04)	<0.001
8–10	666 (68.7)	6810 (81.1)	Referent		Referent	
5 min Apgar						
≤3	13 (1.3)	40 (0.5)	2.91 (1.55–5.46)	<0.001	2.45 (0.93–6.47)	0.07
4–7	50 (5.2)	255 (3.0)	1.75 (1.29–2.39)	<0.001	1.67 (1.17–2.37)	0.005
8–10	906 (93.5)	8103 (96.5)	Referent		Referent	

CPAP = continuous positive airway pressure, BPD = bronchopulmonary dysplasia, IVH = intraventricular hemorrhage.
[a]Adjusted for years of education, time from membrane rupture to delivery (log), gestational age at delivery (linear and quadratic terms), treatment group, race/ethnicity, smoking, type of labor and delivery mode; a total of 194 patients had missing data on one or more of the adjustment variables.
[b]Includes bag and mask with oxygen, CPAP, intubation, chest compression, cardiac medication.
[c]Not computed due to small cell sizes and lack of model fit.

and newborn death before NICU admission. For example, the OR for the association between confirmed or suspected early-onset sepsis and chorioamnionitis were 4.05 (95% CI 3.21–5.11) in the main analysis and 4.09 (95% CI 3.24–5.17) in the sensitivity analysis.

Discussion

The diagnosis of clinical chorioamnionitis is common, and infants born to women with chorioamnionitis are at risk for sepsis and other neonatal morbidities. While the overall incidence of early-onset sepsis (both confirmed and suspected) in our study population is higher than previously reported [6, 14], the incidence of confirmed early-onset sepsis in chorioamnionitis-exposed infants is very low (0.7%) and is consistent with the recent literature [5, 15–18]. Of note, the association between confirmed early-onset sepsis and chorioamnionitis was statistically significant only if maternal fever was present, which could be partially explained by the importance of precise diagnostic criteria, or may be explained by the small sample size when stratifying chorioamnionitis by the presence or absence of maternal fever.

Infants born to mothers with chorioamnionitis were nearly 3 times as likely to be diagnosed with suspected sepsis (a diagnosis that required the presence of suspicious clinical findings) compared with those who were unexposed. Commonly used blood culture media may be inadequate to detect fastidious microbes or obligate anaerobic organisms, as demonstrated in a recent study by Mukhopadhyay and Puopolo [19]. Another possible contributing factor is clinicians' lower threshold to diagnose suspected newborn sepsis in the setting of ambiguous/equivocal physical examination findings or abnormal screening laboratory values with antenatal risk factors such as chorioamnionitis, intrapartum fever, inadequate antibiotic therapy for GBS colonization or prolonged membrane rupture. There is considerable heterogeneity in the literature regarding the definition of culture-negative sepsis and the lack of a neonatal-specific consensus

definition renders the study of this condition and its associated risk factors problematic [20, 21].

Despite current practices regarding intrapartum antibiotic treatment, gestational age at delivery remains an important consideration when assessing risk for early-onset sepsis, particularly in the setting of chorioamnionitis [22, 23]. Chorioamnionitis was more commonly diagnosed in those mothers who delivered <34 weeks' gestation and at ≥41 weeks' gestation. As expected, the frequency of confirmed or suspected early-onset sepsis was highest in the preterm neonates (30.2%) and was substantially lower (4.5%) in those born at term.

In this study, BPD and NEC were not significantly associated with a diagnosis of maternal chorioamnionitis; however, our sample size limited our ability to adequately evaluate rare outcomes. Previous reports investigating the association between these specific morbidities and chorioamnionitis have yielded conflicting results [24–27]. This may reflect inconsistent case definitions as well as variability of fetal exposure with regard to extent, severity and timing of infectious insult [28–30].

Another limitation of this study is that we cannot determine the true risk of culture-negative sepsis in infants born to women with a diagnosis of chorioamnionitis given the current standard of care to treat all exposed newborns with empiric antibiotics. It is possible that a brief course of antimicrobial therapy (48–72 h) may effectively treat some infants who would have otherwise developed sepsis.

A major strength of this study is its generalizability, as these data were derived from a large, ethnically diverse, multicenter patient population. The definition of chorioamnionitis used for this study (a clinical diagnosis of chorioamnionitis by the obstetric provider or if antibiotics were administered during labor due to an elevated body temperature or uterine tenderness with no other defined infection) is reflective of current practice in most US hospitals. Greenberg et al. [31] examined variation in US obstetrical management of patients with chorioamnionitis and noted that the diagnosis of clinical chorioamnionitis is frequently made in the presence of maternal fever alone (26%) or with the presence of only one additional criterion (61%). This lack of precision in the diagnosis of chorioamnionitis remains a challenge for clinicians and investigators alike. The term was initially intended to describe the histopathologic changes in the chorion and/or amnion observed in the presence of inflammation [32]. It has become increasingly apparent that histologic inflammation and clinical signs of infection do not always overlap [33–37]. In 1980, a clinical definition for chorioamnionitis was proposed [38]. This definition required the presence of maternal fever and two additional clinical findings suggestive of intrauterine infection. The initial epidemiologic studies linking maternal chorioamnionitis with neonatal sepsis utilized these strict diagnostic criteria. In 2015, a NICHD workshop was convened in order to provide evidence-based guidelines for the diagnosis and management of pregnant women with chorioamnionitis [12]. This expert panel acknowledged the imprecise and heterogeneous nature of the term chorioamnionitis and recommended it be replaced with "intrauterine inflammation or infection or both (Triple I)" [12]. The use of this more descriptive term may assist clinicians in accurately identifying those neonates most at risk for sepsis. Data collected for this study do not allow us to determine what proportion of women diagnosed with chorioamnionitis would meet the proposed Triple I criteria.

Emerging data suggest that reliance on serial physical examinations rather than screening laboratory tests may better identify infected neonates [39–41]. Recently proposed strategies that combine a rigorous assessment of maternal risk factors together with the neonate's clinical presentation, such as that described by Escobar et al. [42] may provide the most accurate estimate of the probability of sepsis in at-risk newborns. Because the likelihood of sepsis in well-appearing term newborns is exceedingly low, incorporation of the infant's physical examination into their risk assessment algorithm significantly reduced the number of healthy newborns exposed to empiric antibiotics therapy [42]. Such an approach may be preferable given our findings that the vast majority of term infants delivered in the setting of maternal chorioamnionitis do not have culture-proven infection. Finally, the discovery and validation of novel biomarkers to assess the risk of newborn sepsis remains an important research initiative [12].

Conclusion

The diagnosis of clinical chorioamnionitis is common and is associated with neonatal morbidities. However, the vast majority of exposed infants (99.3%) do not have confirmed early-onset sepsis. Identification of those infants most at risk remains a diagnostic challenge.

Acknowledgments: Presented in part at the Pediatric Academic Societies' 2015 Annual Meeting. The authors thank Richard A. Polin, MD (Columbia University College of Physicians and Surgeons) for contributions to the design of this secondary analysis and review and editing of the manuscript; Sabine Bousleiman, RNC, MSN, and Margaret Cotroneo, RN for protocol development and coordination between clinical research centers; Rebecca Clifton, PhD

for protocol/data management; Vinay Bhandaru, MS for statistical analysis; and Gail D. Pearson, MD, ScD, Elizabeth Thom, PhD, James M. Roberts, MD, and Catherine Y. Spong, MD for protocol development and oversight.

Author's statement

Conflict of interest: The authors have no conflicts of interest relevant to this article to disclose.

Material and methods: Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research related to human subject use has complied with all the relevant national regulations, and institutional policies, and is in accordance with the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee.

Financial disclosure: The authors have no financial relationships relevant to this article to disclose.

Funding source: The project described was supported by grants from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) [HD34208, HD27869, HD40485, HD40560, HD40544, HD34116, HD40512, HD21410, HD40545, HD40500, HD27915, HD34136, HD27860, HD53118, HD53097, HD27917, and HD36801]; the National Heart, Lung, and Blood Institute; and the National Center for Research Resources [M01 RR00080, UL1 RR024153, UL1 RR024989]. Comments and views of the authors do not necessarily represent the views of the NIH.

Source of the work or study: Combined Antioxidants and Preeclampsia Prediction Studies, Clinical Trial.gov Identifier NCT00135707.

References

[1] Gilstrap LC 3rd, Leveno KJ, Cox SM, Burris JS, Mashburn M, Rosenfeld CR. Intrapartum treatment of acute chorioamnionitis: impact on neonatal sepsis. Am J Obstet Gynecol. 1988;159: 579–83.

[2] Gibbs RS, Dinsmoor MJ, Newton ER, Ramamurthy RS. A randomized trial of intrapartum versus immediate postpartum treatment of women with intra-amniotic infection. Obstet Gynecol. 1988;72:823–8.

[3] Verani JR, McGee L, Schrag SJ, Division of Bacterial Diseases National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention. Prevention of perinatal group B streptococcal disease – revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010;59:1–36.

[4] Polin RA, Committee on Fetus and Newborn. Management of neonates with suspected or proven early-onset bacterial sepsis. Pediatrics. 2012;129:1006–15.

[5] Benitz WE, Wynn JL, Polin RA. Reappraisal of guidelines for management of neonates with suspected early-onset sepsis. J Pediatr. 2015;166:1070–4.

[6] Lukacs SL, Schrag SJ. Clinical sepsis in neonates and young infants, United States, 1988–2006. J Pediatr. 2012;160: 960–5 e1.

[7] Stoll BJ, Hansen NI, Sanchez PJ, Faix RG, Poindexter BB, Van Meurs KP, et al. Early onset neonatal sepsis: the burden of group B streptococcal and E. coli disease continues. Pediatrics. 2011;127:817–26.

[8] Wortham JM, Hansen NI, Schrag SJ, Hale E, Van Meurs K, Sanchez PJ, et al. Chorioamnionitis and culture-confirmed, early-onset neonatal infections. Pediatrics. 2016;137:1–11.

[9] Gibson MK, Crofts TS, Dantas G. Antibiotics and the developing infant gut microbiota and resistome. Curr Opin Microbiol. 2015;27:51–6.

[10] Thaver D, Ali SA, Zaidi AK. Antimicrobial resistance among neonatal pathogens in developing countries. Pediatr Infect Dis J. 2009;28:S19–21.

[11] Mukhopadhyay S, Lieberman ES, Puopolo KM, Riley LE, Johnson LC. Effect of early-onset sepsis evaluations on in-hospital breastfeeding practices among asymptomatic term neonates. Hosp Pediatr. 2015;5:203–10.

[12] Higgins RD, Saade G, Polin RA, Grobman WA, Buhimschi IA, Watterberg K, et al. Evaluation and management of women and newborns with a maternal diagnosis of chorioamnionitis: summary of a workshop. Obstet Gynecol. 2016;127:426–36.

[13] Roberts JM, Myatt L, Spong CY, Thom EA, Hauth JC, Leveno KJ, et al. Vitamins C and E to prevent complications of pregnancy-associated hypertension. N Engl J Med. 2010;362:1282–91.

[14] Weston EJ, Pondo T, Lewis MM, Martell-Cleary P, Morin C, Jewell B, et al. The burden of invasive early-onset neonatal sepsis in the United States, 2005–2008. Pediatr Infect Dis J. 2011;30:937–41.

[15] Braun D, Bromberger P, Ho NJ, Getahun D. Low rate of perinatal sepsis in term infants of mothers with chorioamnionitis. Am J Perinat. 2016;33:143–50.

[16] Jackson GL, Engle WD, Sendelbach DM, Vedro DA, Josey S, Vinson J, et al. Are complete blood cell counts useful in the evaluation of asymptomatic neonates exposed to suspected chorioamnionitis? Pediatrics. 2004;113:1173–80.

[17] Jackson GL, Rawiki P, Sendelbach D, Manning MD, Engle WD. Hospital course and short-term outcomes of term and late preterm neonates following exposure to prolonged rupture of membranes and/or chorioamnionitis. Pediatr Infect Dis J. 2012;31:89–90.

[18] Kiser C, Nawab U, McKenna K, Aghai ZH. Role of guidelines on length of therapy in chorioamnionitis and neonatal sepsis. Pediatrics. 2014;133:992–8.

[19] Mukhopadhyay S, Puopolo KM. Clinical and microbiologic characteristics of early-onset sepsis among very low birth weight infants: opportunities for antibiotic stewardship. Pediatr Infect Dis J. 2017;36:477–81.

[20] Wynn JL, Wong HR, Shanley TP, Bizzarro MJ, Saiman L, Polin RA. Time for a neonatal-specific consensus definition for sepsis. Pediatr Crit Care Med. 2014;15:523–8.

[21] Cantey JB, Baird SD. Ending the culture of culture-negative sepsis in the neonatal ICU. Pediatrics. 2017;140:e20170044.

[22] Pappas A, Kendrick DE, Shankaran S, Stoll BJ, Bell EF, Laptook AR, et al. Chorioamnionitis and early childhood outcomes

among extremely low-gestational-age neonates. JAMA Pediatr. 2014;168:137–47.
[23] Soraisham AS, Singhal N, McMillan DD, Sauve RS, Lee SK, Canadian Neonatal N. A multicenter study on the clinical outcome of chorioamnionitis in preterm infants. Am J Obstet Gynecol. 2009;200:372.e1–6.
[24] Been JV, Lievense S, Zimmermann LJ, Kramer BW, Wolfs TG. Chorioamnionitis as a risk factor for necrotizing enterocolitis: a systematic review and meta-analysis. J Pediatr. 2013;162:236–42.e2.
[25] Watterberg KL, Demers LM, Scott SM, Murphy S. Chorioamnionitis and early lung inflammation in infants in whom bronchopulmonary dysplasia develops. Pediatrics. 1996;97:210–5.
[26] Hartling L, Liang Y, Lacaze-Masmonteil T. Chorioamnionitis as a risk factor for bronchopulmonary dysplasia: a systematic review and meta-analysis. Arch Dis Child Fetal Neonatal Ed. 2012;97:F8–17.
[27] Shankaran S, Lin A, Maller-Kesselman J, Zhang H, O'Shea TM, Bada HS, et al. Maternal race, demography, and health care disparities impact risk for intraventricular hemorrhage in preterm neonates. J Pediatr. 2014;164:1005–11.e3.
[28] Lee Y, Kim HJ, Choi SJ, Oh SY, Kim JS, Roh CR, et al. Is there a stepwise increase in neonatal morbidities according to histological stage (or grade) of acute chorioamnionitis and funisitis?: effect of gestational age at delivery. J Perinat Med. 2015;43:259–67.
[29] Park CW, Moon KC, Park JS, Jun JK, Romero R, Yoon BH. The involvement of human amnion in histologic chorioamnionitis is an indicator that a fetal and an intra-amniotic inflammatory response is more likely and severe: clinical implications. Placenta. 2009;30:56–61.
[30] Thomas W, Speer CP. Chorioamnionitis: important risk factor or innocent bystander for neonatal outcome? Neonatology. 2011;99:177–87.
[31] Greenberg MB, Anderson BL, Schulkin J, Norton ME, Aziz N. A first look at chorioamnionitis management practice variation among US obstetricians. Infect Dis Obstet Gynecol. 2012;2012:628362.
[32] Blanc WA. Pathways of fetal and early neonatal infection. Viral placentitis, bacterial and fungal chorioamnionitis. J Pediatr. 1961;59:473–96.
[33] Romero R, Chaemsaithong P, Korzeniewski SJ, Kusanovic JP, Docheva N, Martinez-Varea A, et al. Clinical chorioamnionitis at term III: how well do clinical criteria perform in the identification of proven intra-amniotic infection? J Perinat Med. 2016;44:23–32.
[34] Martinez-Varea A, Romero R, Xu Y, Miller D, Ahmed AI, Chaemsaithong P, et al. Clinical chorioamnionitis at term VII: the amniotic fluid cellular immune response. J Perinat Med. 2017;45:523–38.
[35] Romero R, Chaemsaithong P, Docheva N, Korzeniewski SJ, Tarca AL, Bhatti G, et al. Clinical chorioamnionitis at term IV: the maternal plasma cytokine profile. J Perinat Med. 2016;44:77–98.
[36] Chaiyasit N, Romero R, Chaemsaithong P, Docheva N, Bhatti G, Kusanovic JP, et al. Clinical chorioamnionitis at term VIII: a rapid MMP-8 test for the identification of intra-amniotic inflammation. J Perinat Med. 2017;45:539–50.
[37] Romero R, Chaemsaithong P, Korzeniewski SJ, Tarca AL, Bhatti G, Xu Z, et al. Clinical chorioamnionitis at term II: the intra-amniotic inflammatory response. J Perinat Med. 2016;44:5–22.
[38] Gibbs RS, Castillo MS, Rodgers PJ. Management of acute chorioamnionitis. Am J Obstet Gynecol. 1980;136:709–13.
[39] Berardi A, Fornaciari S, Rossi C, Patianna V, Bacchi Reggiani ML, Ferrari F, et al. Safety of physical examination alone for managing well-appearing neonates >/= 35 weeks' gestation at risk for early-onset sepsis. J Mat Fetal Med. 2015;28:1123–7.
[40] Cantoni L, Ronfani L, Da Riol R, Demarini S, Perinatal Study Group of the Region Friuli-Venezia G. Physical examination instead of laboratory tests for most infants born to mothers colonized with group B Streptococcus: support for the Centers for Disease Control and Prevention's 2010 recommendations. J Pediatr. 2013;163:568–73.
[41] Flidel-Rimon O, Galstyan S, Juster-Reicher A, Rozin I, Shinwell ES. Limitations of the risk factor based approach in early neonatal sepsis evaluations. Acta Paediatr. 2012;101:e540–4.
[42] Escobar GJ, Puopolo KM, Wi S, Turk BJ, Kuzniewicz MW, Walsh EM, et al. Stratification of risk of early-onset sepsis in newborns >/= 34 weeks' gestation. Pediatrics. 2014;133:30–6.

Supplemental Material: The online version of this article offers supplementary material (https://doi.org/10.1515/jpm-2017-0192).