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Antecedents of the Child Behavior Checklist--Dysregulation Profile in Children Born Extremely Preterm

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Abstract

Objective—Extremely preterm newborns are at heightened risk for emotional and behavioral dysregulation later in childhood. Our goal was to systematically evaluate the antenatal and early

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Ms. Allred served as the statistical expert for this research.

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postnatal antecedents that might mediate the association between extreme preterm birth and emotional and behavioral dysregulation at age 2 years (corrected age).

Method—In a multi-site, prospective study, the parents of 826 infants born before 28 weeks gestation completed a Child Behavior Checklist (CBCL) when the child was 2 years corrected age. We compared the maternal, pregnancy, placenta, delivery, and newborn characteristics**,** as well as early postnatal characteristics and exposures of those who satisfied criteria for the CBCL-dysregulation profile (CBCL-DP) to those of their peers. We then used time-oriented logistic regression models, starting first with antenatal variables that distinguished children with the CBCL-DP profile from their peers**,** and then added the distinguishing postnatal variables.

Results—Approximately 9% of the children had a CBCL-DP. In the time-oriented logistic regression model with antenatal variables only, low maternal education achievement, passive smoking, and recovery of Mycoplasma from the placenta were associated with increased risk, while histologic chorioamnionitis was associated with reduced risk. None of the postnatal variables added statistically significant discriminating information.

Conclusion—Very preterm newborns who later manifest the CBCL-DP at age two years differ in multiple ways from their preterm peers who do not develop the CBCL-DP, raising the possibility that potentially modifiable antenatal and early postnatal phenomena contribute to the risk of developing emotional and behavioral dysregulation.

Keywords

Antenatal; postnatal; antecedents; CBCL; premature

INTRODUCTION

Advances in neonatal intensive care have greatly increased the survival of extremely preterm infants.[1] These infants are at risk for a variety of neurodevelopmental outcomes, including emotional and behavioral dysregulation during school age. Some of these impairments continue into adolescence and adulthood, including higher rates of attention-deficit/hyperactivity disorder (ADHD), conduct, anxiety, emotional, and behavioral problems compared to youth born at term.[2–15]

Because emotional and behavioral dysregulation can result in difficulties in the classroom and impede learning, it is important to extend both research and clinical efforts downward in age to focus on the evaluation of infants and preschool children to identify those at risk for problematic behaviors so that intervention efforts can be implemented early. To date, only a few studies have evaluated preterm children during infancy or preschool for emotional and behavioral problems. Those studies have found increased emotion dysregulation, regulatory disorders, externalizing disorders, internalizing disorders, hyperactivity, anxious/depressed, aggression, and somatic problems.[16] Some studies of preschool children born preterm have used the well-known instrument the Child Behavior Checklist (CBCL),[17,18] which defines domains of dysfunction, and have reported increased CBCL Total Problem scores and Internalizing and Externalizing scores, but none of the studies has reported on the CBCL-Dysregulation Profile (CBCL-DP). [19–21] The CBCL-DP has been defined as representing a

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syndrome not defined by the *DSM* and is related to severe psychopathology and outcomes[22] in youth.

The Dysregulation Profile of the Child Behavior Checklist (CBCL-DP) is a combination of elevated scores on the attention problems, aggression, and anxious/depressed subscales of the CBCL.[23] The CBCL-DP phenotype is relatively common, with prevalence ranging from 1–5% in community samples[24,25] to 10–37% in referred samples.[25–28] One prior study evaluated a community sample of preschoolers and the rate of elevated CBCL-DP was 11%, but the investigators did not indicate how many youth in their sample were born prematurely. [29]

Multiple longitudinal studies document that elevated CBCL-DP scores in childhood predict the incidence of suicidal behavior, low psychosocial functioning, aggression, poor school performance, and psychiatric hospitalizations.[26,28,30,31] Thus, rather than representing a distinct and specific clinical diagnostic entity, the CBCL-DP is likely a set of non-specific dysfunctions associated with increased risks for a heterogeneous group of clinical outcomes. Although none of these studies indicate the percentage of youth who were born prematurely, an elevated score on the CBCL-DP across studies is stable over time, highly heritable (~67%), and genetic associations support its validity as a distinct phenotype.[24,25,32,33]

In addition to high heritability, the CBCL-DP is associated with familial and environmental adversity. Youth with CBCL-DP are more likely to have impairments in social, familial, and academic function.[29,34] In the study of preschool children in a community sample, children with the CBCL-DP had greater functional impairment and their parents had more psychopathology, personality difficulties, and marital difficulties than those without the CBCL-DP.[29] These studies highlight the complex interplay between genetic and environmental influences that appear to lead to the CBCL-DP.

While we do not know the relative stability and predictivity of the CBCL-DP in children born preterm, we know that compared to children born at term, extremely preterm and very preterm infants assessed at school age are at heightened risk of emotional and behavioral problems.[16,35–37] Unfortunately, no prior study has systematically evaluated and described extremely preterm children using the CBCL-DP during early childhood. Such information has the potential to help identify toddlers at risk. Moreover, no previous studies have examined antenatal and postnatal factors associated with emotional and behavioral dysregulation in toddlers born extremely preterm. The current study begins to fill that void.

METHOD

Participants

The ELGAN study was designed to identify characteristics and exposures that increase the risk of structural and functional neurologic disorders in extremely low gestational age newborns (ELGANs).[38] Between 2002 and 2004, women delivering before 28 weeks gestation across 14 participating institutions were asked to enroll in the study upon antenatal admission or shortly after delivery; 1,249 mothers of 1,506 infants consented. Of the 1,506 enrolled infants, 1,200 survived until age 2 years. Fully 92% (n=1,102) of these children

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were examined at age 2. Of those evaluated at age 2, a parent of 75% (n=826) completed a CBCL/1.5-5 either in English or Spanish.[17] Compared to the mothers who did not complete a CBCL, those who did were more likely to be college graduates (37% v. 28%) and less likely to have smoked during the pregnancy (12% v. 17%). Moreover, the included pregnancies were more likely to be multifetal (37% v. 28%). Each site's institutional review board approved enrollment and consent processes. At 12 of the 14 sites, a caregiver completed a CBCL when the child returned for the 2-year assessment. The mother was the informant for 92% of the children. Children for whom a CBCL was available differed minimally from those without a CBCL.[39] Of the 826 children, 764 had data on histologic examination of the placenta and 733 had culture of the placenta. All assessment procedures and data collection addressed below were standardized across sites, unless specifically noted otherwise.

Child Behavior Checklist

The child's primary caregiver completed the CBCL 1.5-5 questionnaire.[18] Respondents choose one of three responses to the 99 characteristics listed in the CBCL: "not true," "somewhat or sometimes true," and "very true or often true." [17,18] The CBCL-DP T scores were used in the analysis because they offer a clinical interpretation while the raw scores do not. Children were classified as having a significant dysregulation profile if the summed T scores of the attention problems, aggressive behavior, and anxious/depressed subscales were ≥180.[29]

Maternal characteristics, fetal characteristics, and addition predictors

Information on demographic, pregnancy, environmental exposure, and delivery variables were collected via interview with a trained research nurse. Gestational age (GA) estimates were based on the best information available; birth weight z score was calculated using the median birth weight in referent samples. We collected all the physiology, laboratory, and therapy data for the first 12 hours needed to calculate a Score for Neonatal Acute Physiology II (SNAP-II™).[40] Data were collected by trained study staff on placenta microbiology and histology, mode of ventilation, respiratory care, bacteremia, patent ductus arteriosis (PDA), medications used in the first 28 days postpartum, necrotizing enterocolitis, and retinopathy. Methods of data collection are described in greater detail in Supplement 1, available online.

Data analysis

We first compared the characteristics of children with and without the dysregulation profile using summary statistics, e.g., percent of mothers who conceived using birth control for each group. To evaluate risk factors in the presence of confounders, we constructed multivariable logistic regression models, evaluating the generalized null hypothesis that the risk of dysregulation is not associated with any pre- or postnatal exposure or characteristic. Because postnatal phenomena, such as the need for ventilation assistance, can be influenced by antepartum phenomena, we created logistic regression models in which risk factors are ordered in a temporal pattern, so that the earliest occurring predictors/covariates of CBCL-DP are entered first and are not displaced by later occurring covariates.[41,42] For these time-oriented risk models (TORMs), we categorize sets of antecedents/covariates by the time they occurred or are identified. We selected variables in each epoch using a manual backwards

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stepwise selection procedure, in which covariates were removed singly until all predictors in the model were statistically significant ($p<.05$).

RESULTS

Maternal characteristics (Table 1)

Seventy-three of 826 children (8.8%) were classified as having high dysregulation. Children with the CBCL-DP were twice as likely as their peers to have a mother who identified as a race other than white or black, and almost twice as likely to identify as Hispanic. The mothers of CBCL-DP children also tended to be younger, less educated, not married, and eligible for government-supported health care.

Pregnancy characteristics (Table 2)

The mothers of dysregulated children were more likely than the mothers of other children to have smoked during pregnancy and to have been exposed to the tobacco smoke of others. They were less likely to have planned the current pregnancy, have sought conception assistance, or had a previous pregnancy. During this pregnancy, mothers of dysregulated children were more likely than the mothers of other children to have had a vaginal/cervical infection, a urinary tract infection, been prescribed an antibiotic, and taken acetaminophen.

Placenta characteristics (Table 3)

The placentas of children with CBCL-DP were more likely than the placentas of other children to have harbored Mycoplasma species and less likely to have inflammation of the external membranes.

Delivery characteristics (Table S1, available online)

The delivery characteristics of children with CBCL-DP differed minimally from those of other children.

Newborn characteristics (Table S2, available online)

Children with CBCL-DP were more likely than their peers to be male, to have a birth weight Z score of < -1, and a birth head circumference Z score of < -1.

Early postnatal variables (Table 4)

Children with CBCL-DP were less likely than their peers to have had hypoxemia on two of the first three postnatal days, and more likely to have had hyperoxemia on these days. Although they were more likely to have harbored a pathogen in their trachea, they were not more likely to have been mechanically ventilated.

Medications and therapies (Table S3, available online)

Children with CBCL-DP were more likely than their peers to have received a sedative during the first postnatal month. No other drugs were given preferentially to either group.

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Diagnoses and dysfunctions (Table S4, available online)

Those with CBCL-DP were more likely than other children to have early and persistent pulmonary dysfunction, but did not differ appreciably in the occurrence of growth, bowel, or retinal disorders.

Multivariable analyses (Table 5)

The multivariable modeling process began by including antenatal variables that distinguished the children with CBCL-DP from their peers (see Tables 1–4 and Tables S1–4, available online). Variables from the antenatal period included: maternal education ≤ 12 years, maternal exposure to passive smoking, vaginal/cervical infection during pregnancy, Mycoplasma species cultured from the placenta, inflammation of the placenta chorion/decidua, and multifetal gestation. In the antenatal-only model, increased risk of the CBCL-DP was associated with the mother having no more than a high school education (OR =3.2; CI: 1.8, 5.6), maternal exposure to passive smoking (OR = 1.9; CI: 1.1, 3.2), and recovery of Mycoplasma from the placenta parenchyma (OR =2.5; CI: 1.2, 5.3). Decreased risk was associated with chorioamnionitis (OR = 0.4; CI: 0.2, 0.8). Indicators for missing data on placenta microbiology or histology were included as part of the multivariable model; sensitivity analyses limited to children for whom we had a complete data set produced similar results. Variables entered in the postnatal epoch were: highest P_aO_2 in the highest quartile on ≥ 2 of the first three postnatal days, culture proven tracheal infection, receipt of surfactant in the first week, any sedation in the first 28 days, and early respiratory group classification. None of these variables added significantly to the information provided by the antenatal variables.

DISCUSSION

In this prospective cohort study, the first to systematically evaluate the rate of elevated CBCL-DP in youth born extremely preterm, we observed an elevated CBCL-DP in approximately 9% of our youth. While this rate of the CBCL-DP is consistent with the rate (11%) described by Kim et al. in their community-based study of preschoolers,[29] these investigators did not identify how many of their youth were born prematurely. In addition, we observed several maternal, pregnancy, and microbiologic characteristics associated with high dysregulation in children, including low maternal education, exposure to passive tobacco smoke, and recovery of Mycoplasma species from the placenta. Reduced risk for dysregulation was associated with the presence of chorioamnionitis.

Maternal and sociodemographic characteristics

In our study, children with CBCL-DP were more likely than their peers to have a mother who identified as not white, was young, did not have any schooling beyond high school, was not married, was eligible for government provided health insurance (usually Medicaid), and was overweight or obese. In our multivariable model of dysregulation, we included low maternal education as a proxy for low socioeconomic status (SES).

The association between low SES and dysregulation in children is consistent with longstanding findings in the literature about outcomes in high-risk infants,[43–46] and may

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occur through multiple pathways. Low SES may be a marker for a long-term stress response to psychosocial stressors. Prior studies have suggested that psychosocial stressors experienced by low SES mothers can lead to epigenetic changes that are passed on to their offspring, reducing resilience to physiological and psychological stress in these children.[47,48] In addition, the infant's early developmental, social, and care experiences can result in epigenetic changes associated with later behaviors.[49]

Other maternal characteristics may have had an influence on child dysregulation. Mothers of children with CBCL-DP were more often obese, which may translate to a heightened inflammatory state in the developing fetus,[50] possibly contributing to epigenetic phenomena.[51-53] Maternal smoking and exposure to passive smoke were also associated with higher dysregulation; tobacco smoke exposure may have both direct effects on child development as well as indirect effects through epigenetic changes.[53] We included passive smoke exposure, rather than active maternal smoking, in the final multivariable model in light of research suggesting that passive smoke exposure is less often misclassified than active smoking, particularly in pregnant women.[54,55] In high-risk groups, pregnant women frequently under-report harmful exposures.[56] For example, the proportion of pregnant women who denied smoking yet whose cotinine levels were considered characteristic of smokers has sometimes exceeded 20%.[57–59] In addition to being independent risk factors for dysregulation, smoking and obesity are associated with low socioeconomic position and collectively might represent a cumulative or synergistic effect on fetal brain development. Importantly, information on family environment risk factors that may co-occur with low SES, such as maternal psychopathology, neglect, or abuse, were not available in this study.

Recovery of Mycoplasma from the placenta parenchyma

Mycoplasma hominis appears to serve as the stimulus for the production of inflammatory cytokines in vivo[60] which raises the possibility that Mycoplasma hominis in placenta parenchyma might increase inflammation in utero or in the newborn at risk of perinatal adversities.[61] Prior studies have noted that low SES is associated with presence of Mycoplasma hominis,[62] and as such this maternal characteristic might provide information about SES that supplements information provided by the maternal education variable.

Reduced risk associated with histologic chorioamnionitis

Although chorioamnionitis has been associated with adversities,[63] it appears to have the potential to reduce the risk of brain damage.[64] This has been attributed to preconditioning, which describes the diminished damage that follows a damaging exposure when it is preceded by a sub-injurious exposure.[65]

Nine percent of youth in our sample had developed significant dysregulation by age two years (corrected), twice the prevalence of CBCL-DP reported in community-based samples of slightly older youth and consistent with the CBCL-DP in a study of community-based preschoolers that did not indicate how many were born preterm.[24,25,29] In addition, the CBCL-DP was associated with several potentially modifiable antenatal risk factors including: low maternal education achievement, passive smoking, and recovery of Mycoplasma from the placenta. These findings add to a growing body of literature

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indicating that antenatal and perinatal risk factors are important targets for research into the origins of behavioral and emotional problems in children.

Our study has several strengths. First, we selected infants based on gestational age, not birth weight, to minimize confounding due to factors related to fetal growth restriction.[66] Second, we included a large number of infants who underwent very intensive assessment, making it unlikely that we have missed important associations due to lack of statistical power, or claimed associations that might reflect the instability of small numbers. Third, we collected all data prospectively, reducing the risk recall bias. Finally, although the CBCL-DP in slightly older youth is a known predictor of psychopathologies in adolescence, few studies have used the CBCL in preschoolers, and the stability of the profile from preschool to school age has not been well studied. Another limitation of our study is that while low SES is associated with maternal mental illness and substance abuse, we did not include assessments of maternal psychopathology. Perhaps the major limitation of the ELGAN Study is that it is observational and cannot provide information about causation.

Among children born before the 28th week of gestation, an increased risk of CBCL-DP was associated with mother's limited formal education, her exposure to the tobacco smoke of others, and recovery of Mycoplasma from the placenta. All three might reflect low SES. On the other hand, biologic explanations are readily available to explain how exposure to tobacco smoke and harboring Mycoplasma species can contribute to the newborn's risk of a CBCL-DP. Explanations for why chorioamnionitis might contribute to reduced risk most likely invoke preconditioning. All of these findings lend support to the contribution of antenatal exposures to the later development of CBCL-DP in very preterm newborns. No early postnatal variable added discriminating information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Guidance

- Approximately 9% of our sample of extremely low gestational age neonates had elevated dysregulation of emotion and behavior at two years of age.
- Preschool screening of extremely preterm infants may serve to identify those at greatest risk for emotional and behavioral problems so that early intervention and supports can be put into place prior to school entry in order to improve outcomes.
- Maternal education and exposure to passive cigarette smoke, as well as recovery of Mycoplasma from the placenta, were associated with elevated dysregulation. At least two of these variables (maternal education and exposure to passive cigarette smoke) are potentially modifiable.

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Table 1

Maternal Characteristics of Children With and Without the Child Behavior Checklist-Dysregulation Profile

		Dysregulation profile		Row
Maternal characteristic		**Yes (%)**	**No (%)**	**n**
Racial identity	White	44	61	483
	Black	34	29	240
	Other	23	10	89
Hispanic	Yes	18	10	89
Maternal age	< 21	22	12	110
	21–35	74	67	560
	> 35	4	20	156
Years of education	< 12	33	15	129
	12 (high school)	40	26	217
	> 12 to < 16	15	24	186
	16 (college)	5	20	150
	> 16	7	15	114
Married	Yes	33	60	477
Self supported?	Yes	56	68	538
Health insurance	Government	63	38	325
Prepregnancy BMI	< 18.5	5	7	55
	18.5 to < 25	44	51	400
	25 to < 30	23	22	174
	> 30	27	20	162
Maximum number of infants		73	753	826

Note: BMI = body mass index.

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Table 2

Pregnancy Characteristics of Children With and Without the Child Behavior Checklist-Dysregulation Profile

		Dysregulation profile		Row
Exposures and characteristics		**Yes (%)**	**No (%)**	**n**
Smoked during pregnancy	Yes	22	13	111
Passive smoke exposure	Yes	41	22	190
First pregnancy	Yes	30	43	338
Years since last pregnancy	< 1	22	19	89
	1–2	32	27	128
	2+	46	54	242
Conceived using birth control	Yes	19	15	126
Trying to get pregnant	Yes	37	57	443
Conception assistance	Yes	11	23	178
Due date changed	Yes	27	20	166
Illnesses this pregnancy				
Fever	Yes	8	5	41
Vaginal/cervical infection	Yes	23	14	117
Urinary tract infection	Yes	22	15	127
Peridontal	Yes	5	2	19
Medications				
Any medication	Yes	95	87	698
Aspirin [a]	Yes	4	6	47
Non-steroidal anti-inflammatory [a]	Yes	11	7	56
Acetaminophen [a]	Yes	55	42	392
Antibiotic [a]	Yes	38	31	251
Maximum number of infants		73	753	826

[a] Infants may be in more than one category.

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Table 3

Placenta Bacteriologic and Histologic Characteristics of Children With and Without the Child Behavior Checklist-Dysregulation Profile

		Dysregulation profile		Row
Placenta microbiology		**Yes (%)**	**No (%)**	**n**
Number of species isolated	1	29	22	167
	≥ 2	22	24	174
Aerobe	Yes	28	32	230
Anaerobe	Yes	25	26	192
Mycoplasma	Yes	17	8	66
Skin organisms [a]	Yes	20	19	143
Vaginal organisms [b]	Yes	15	14	106
Maximum number of infants		65	668	733
Placenta histology				
Chorionic plate inflammation [c]	Yes	15	18	136
Chorion/decidua inflammation [d]	Yes	24	37	266
Fetal stem vessel infiltration [e]	Yes	22	25	182
Umbilical cord vasculitis	Yes	14	18	131
Fetal stem vessel thrombosis	Yes	8	5	36
Infarct	Yes	18	15	117
Increased syncytial knots	Yes	15	21	153
Decidual hemorrhage/fibrin deposition	Yes	15	14	107
Maximum number of infants		70	694	764

[a] Corynebacterium sp, Propionebacterium sp, Staphylococcus sp

[b] Prevotella bivia, Lactobacillus sp, Peptostrep magnus, Gardnerella vaginalis

[c] Stage 3 and severity 3

[d] Grades 3 and 4

[e] Grades 3, 4, and 5

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Table 4

Characteristics of Children With and Without the Child Behavior Checklist-Dysregulation Profile

		Dysregulation profile		Row
Postnatal factors		**Yes (%)**	**No (%)**	**n**
SNAP-II	20–29	22	26	212
	≥ 30	25	22	181
Lowest MAP [a]	Lowest quartile	25	21	176
Vasopressor [b]	Given	27	26	218
MAP variability[c]	Highest quartile	25	24	196
Lowest P_aO_2[d]	Lowest quartile	17	25	164
Highest P_aO_2[d]	Highest quartile	33	22	159
Lowest PCO_2[d]	Lowest quartile	20	23	157
Highest PCO_2[d]	Highest quartile	19	22	151
Lowest pH [d]	Lowest quartile	19	22	150
P_aO_2, day 7	Lowest quartile	7	9	72
P_aO_2, day 14	Lowest quartile	7	6	52
Tracheal colonization	Definite	29	22	189
Early bacteremia, week 1	Definite	3	8	59
Late bacteremia, weeks 2–4	Definite	29	27	225
Mechanical ventilation [e]	Day 7	55	59	487
Mechanical ventilation [e]	Day 14	60	56	465
Mechanical ventilation [e]	Day 21	53	56	453
Mechanical ventilation [e]	Day 28	38	47	370
Maximum number of infants		73	753	826

Note: MAP = Mean Arterial Pressure; PCO_2 = partial pressure of carbon dioxide; PH = concentration of hydrogen in an aqueous solution; P_aO_2= partial pressure of oxygen; SNAP II = Score for Neonatal Acute Physiology-Version II.

[a] Lowest MAP recorded in the first 24 hours, in the lowest quartile for gestational age.

[b] Treatment for hypotension in the first 24 hours, using any vasopressor (dopamine, dobutamine, epinephrine).

[c] Labile blood pressure, defined as the upper quartile of the difference in the lowest and highest MAP.

[d] Extreme quartile for gestational age on two of the first three postnatal days.

[e] Includes conventional mechanical ventilation and high-frequency ventilation.

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Table 5

Multivariable-Adjusted Odds Ratios (Point Estimates and 95% CIs) for a Child Behavior Checklist-Dysregulation Profile Associated With Each Antenatal and Postnatal Risk Factor

Variables	Antenatal	Plus postnatal
Maternal education high school or less	**3.2 (1.8, 5.6)***	
Passive smoking	**1.9 (1.1, 3.2)***	
Mycoplasma cultured from placenta	**2.5 (1.2, 5.3)***	
No placenta microbiology [a]	1.2 (0.5, 2.6)	
Chorioamnionitis [b]	***0.4 (0.2, 0.8)****	
No placenta histology [c]	0.5 (0.2, 1.3)	
		nothing added

Note: Boldface data indicate p<0.05. Italicized data represent a decreased rather than increased risk associated with chorioamnionitis.

[a] No placenta available for microbiologic evaluation

[b] Histologic inflammation of the chorioamnion

[c] No placenta available for histologic evaluation