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Antenatal antecedents of a small head circumference at age 24-months post-term equivalent in a sample of infants born before the 28th post-menstrual week

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Abstract

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Background—Little is known about the antecedents of microcephaly in early childhood among children born at extremely low gestational age.

Aim—To identify some of the antecedents of microcephaly at age two years among children born before the 28th week of gestation.

Study design—Observational cohort study.

Subjects—1004 infants born before the 28th week of gestation.

Outcome measures—Head circumference Z-scores of <-2 and ≥-2 , <-1 .

Results—Risk of microcephaly and a less severely restricted head circumference decreased monotonically with increasing gestational age. After adjusting for gestational age and other potential confounders, the risk of microcephaly at age 2 years was increased if microcephaly was present at birth [odds ratio: 8.8 (95% confidence interval: 3.7, 21)], alpha hemolytic Streptococci were recovered from the placenta parenchyma [2.9 (1.2, 6.9)], the child was a boy [2.8 (1.6, 4.9)], and the child's mother was not married [2.5 (1.5, 4.3)]. Antecedents associated not with microcephaly, but with a less extreme reduction in head circumference were recovery of *Propionibacterium* sp from the placenta parenchyma [2.9 (1.5, 5.5)], tobacco exposure [2.0 (1.4, 3.0)], and increased syncytial knots in the placenta [2.0 (1.2, 3.2)].

Conclusions—Although microcephaly at birth predicts a small head circumference at 2 years among children born much before term, pregnancy and maternal characteristics provide supplemental information about the risk of a small head circumference years later. Two findings appear to be novel. Tobacco exposure during pregnancy, and organisms recovered from the placenta predict reduced head circumference at age two years.

Keywords

Microcephaly; Epidemiology

1. Introduction

Head circumference usually parallels brain volume [7–14] and its presence in childhood predicts cognition and perception better than does head circumference at birth [1–6]. Previous studies of the antecedents of a small head circumference in childhood have evaluated individual or only a small number of possible antecedents [7–12].

In this paper we describe the results of our efforts to identify potentially modifiable antenatal antecedents of microcephaly as well as a less severe reduction in head circumference among children born at an extremely low gestational age.

2. Methods

The ELGAN study was designed to identify characteristics and exposures that increase the risk of structural and functional neurologic disorders in ELGANs (the acronym for *Extremely Low Gestational Age Newborns*) [13]. During the years 2002–2004, women delivering before 28 weeks gestation at one of 14 participating institutions in 11 cities in 5 states were asked to enroll in the study. The enrollment and consent processes were approved by the individual institutional review boards.

Mothers were approached for consent either upon antenatal admission or shortly after delivery, depending on clinical circumstance and institutional preference. 1249 mothers of 1506 infants consented. Approximately 260 women were either missed or did not consent to participate. Of the 1155 children who had their head circumference measured at birth, had a protocol brain

ultrasound scan, and survived to age 24 months post-term equivalent, 1019 (88%) returned for a neurodevelopmental assessment. Head circumference was measured then on all but 15 of these children (N=1004).

2.1. Demographic and pregnancy variables

After the infant's delivery, a trained research nurse interviewed each mother in her native language using a structured data collection form and following procedures documented in a manual. The mother's report of her own characteristics and exposures, as well as the sequence of events leading to preterm delivery, was taken as truth, even when her medical record provided discrepant information.

Shortly after the mother's discharge, the research nurse reviewed the maternal chart using a second structured data collection form. The medical record was reviewed for information about events following admission. The clinical circumstances that led to each maternal admission and ultimately to each preterm delivery were operationally defined [14].

2.2. Placentas

Delivered placentas were placed in a sterile exam basin and transported to a sampling room, where they were biopsied under sterile conditions. Eighty-two percent of the samples were obtained within 1 h of delivery.

The microbiologic procedures are described in detail elsewhere [15,16]. Briefly, the frozen samples were allowed to thaw at room temperature, a portion approximately 1 cm² was removed and weighed, then diluted 1:10 with sterile phosphate buffered saline (PBS), homogenized and aliquots plated on selective and non-selective media, including pre-reduced brucella-base agar with 5% sheep blood enriched with hemin and vitamin K₁, tryptic soy agar with 5% sheep blood, chocolate agar, and A-7 agar. After incubation, the various colony types were enumerated, isolated and identified by established criteria [17].

In keeping with the guidelines of the 1991 CAP Conference [18], representative sections were taken from all abnormal areas as well as routine sections of the umbilical cord and a membrane roll, and full thickness sections from the center and a paracentral zone of the placental disc. After training to minimize observer variability, study pathologists examined the slides for histologic characteristics listed on a standardized data form they helped create [19,20]. Briefly, infarcts and inter-villous fibrin, fetal stem vessel thrombosis, and decidual hemorrhage and fibrin deposition consistent with abruption were coded as present or absent. Chorionic villi were scored for syncytial knots (no, occasional, and increased).

At the chorionic plate of the disc, grade 3 acute inflammation was defined as neutrophils up to amnionic epithelium and stage 3 was defined as >20 neutrophils/20×). Grade 3 inflammation of the external membranes, as well as of the chorion/decidua required numerous large or confluent foci of neutrophils.

Inflammation in the umbilical cord was graded from 0 to 5. Grade 3 required neutrophils in perivascular Wharton's jelly, grade 4 required panvasculitis and umbilical cord vasculitis extending deep into Wharton's jelly, and grade 5 required a 'Halo lesion' (ring of precipitate in Wharton's jelly encircling each vessel). Neutrophilic infiltration into fetal stem vessels in the chorionic plate required that neutrophils appeared to have migrated towards the amnionic cavity.

2.3. Newborn variables

The gestational age estimates were based on a hierarchy of the quality of available information. Most desirable were estimates based on the dates of embryo retrieval or intrauterine insemination or fetal ultrasound before the 14th week (62%). When these were not available, reliance was placed sequentially on a fetal ultrasound at 14 or more weeks (29%), LMP without fetal ultrasound (7%), and gestational age recorded in the log of the neonatal intensive care unit (1%).

The birth weight Z-score is the number of standard deviations the infant's birth weight is above or below the median weight of infants at the same gestational age in a standard data set [21].

2.4. Head circumference Z-scores

Families were invited to bring their child for a developmental assessment close to the time when s/he would be 24-month corrected age. Fully 92% of surviving children had some portion of this developmental assessment, which included a measurement of the head circumference.

The head circumference was measured by an ELGAN Study trained examiner as the largest possible occipital–frontal circumference. Measurements were rounded to the closest 0.1 cm when taken at birth, and when examined at 24-month corrected age. All head circumferences are presented as Z-scores because newborns were assessed at different gestational ages at birth (23–27 weeks) and at different approximations of 24 months corrected age (range: 16–44 months corrected age, with 68% assessed at 23–25 weeks corrected age). Z-scores of head circumference at birth were based on standards in the Yudkin et al. data set [21]. Z-scores of head circumference at approximately 24 months were based on standards in the CDC data sets [22].

We limit the use of the term microcephaly to the 108 children whose head circumference was more than two standard deviations below the median ($HCZ < -2$). These 108 represent 10% of our sample (108/1039), whereas only 2.2% would be expected in a normal sample to have such an extremely small head circumference. While 16% of children in a normally distributed sample would be expected to have a head circumference between one and two standard deviations below the median, 18.6% (193/1039) in our sample had a head circumference in this range. We use the term small head or small head circumference to include these children whose head circumference is between one and two standard deviations below the median ($N = 193$).

2.5. Data analysis

We evaluated the generalized null hypothesis that the occurrence of a head circumference at 2 years of age more than two standard deviations below the expected median or between one and two standard deviations below the expected median is NOT associated with maternal demographic characteristics, pregnancy exposures and characteristics, organism recovery from the placenta parenchyma, placenta histologic features, or characteristics of the newborn.

We adjusted for gestational age with three groups (23–24, 25–26, and 27), which gave results similar to when adjustment was made with five individual weeks.

Because our outcomes of interest are mutually exclusive (head circumference < -2 and head circumference ≥ -2 , < -1) and each is appropriately compared to the same referent group (head circumference ≥ -1), we used multinomial logistic regression to identify the contribution of relevant characteristics and exposures to the risk of each level of head circumference [23,24]. Variables were *not* selected for the multivariable models on the basis of their p values on univariate analyses. Rather, all variables from Tables 1–4 were considered in a step-down

logistic regression procedure that sought a parsimonious solution without interaction terms for each of the two head circumference entities. We then entered variables related to each entity into the maximum-likelihood multinomial logistic regression. The contribution of each antecedent is presented as a risk ratio with the 95% confidence interval.

3. Results

Children born to Black, Hispanic, single, and/or low-income mothers were at increased risk of microcephaly, and to a lesser extent of a small head (Table 1). The younger the mother and/or the lower her educational achievement, the higher the likelihood of microcephaly. A child was at increased risk of microcephaly if her mother was exposed to tobacco smoke.

The risk of microcephaly, but not a less extreme reduction in head circumference was increased if the mother ingested medication during the pregnancy, especially a non-steroidal anti-inflammatory drug (NSAID) (Table 2). The risk of microcephaly was not increased among children whose mother ingested aspirin or acetaminophen.

Those delivered for preeclampsia or fetal indications were at increased risk years later of microcephaly and a small head (Table 3). A correlate of preeclampsia, receipt of magnesium for seizure prophylaxis, was also associated with microcephaly, but not a small head. Children whose mother presented in preterm labor were at low risk of microcephaly, even if given magnesium for tocolysis. Antenatal corticosteroid exposure, route of delivery, duration of labor, and duration of membrane rupture were not associated with the risk of microcephaly or a head circumference Z-score in the -2 to -1 range.

Boys tended to have a smaller head circumference than girls (Table 4). The risk of microcephaly and a less extremely small head circumference decreased monotonically with increasing gestational age, birth weight, birth weight Z-score, and birth head circumference Z-score. Within gestational age and birth weight strata, the risk of a small head is more clearly associated with lower birth weight and lower birth weight Z-score than with gestational age (data not shown). The risk of microcephaly varied more prominently with head circumference at birth than with indication for delivery (data not shown).

No organism or group of organisms was associated with microcephaly in the entire sample (Table 5). Alpha hemolytic *Streptococcus* was the only organism associated with microcephaly among placentas delivered by Cesarean section. *Propionibacterium* was the only species associated with a small head in the total sample and in the sample of placentas delivered by Cesarean section. As a group, colonizers of skin (including *Propionibacterium* sp) were associated with a small head in the sample of placentas delivered by Cesarean section.

Reduced risk of a small head, but not microcephaly, was associated with neutrophilic infiltration of the fetal stem vessels, while increased syncytial knots was associated with increased risk of a small head (Table 6).

The variables that contributed significantly in a multivariable model to the risk of microcephaly and the risk of small head circumference at 24 months were microcephaly at birth, low gestational age, and male sex. Variables that contributed only to the risk of microcephaly were recovery of alpha hemolytic *Streptococci* from the placenta, and birth to an unmarried mother (Table 7); while variables that contributed only to the risk of a small head circumference were tobacco smoke exposure, and recovery of *Propionibacterium* sp from the placenta.

4. Discussion

Our major finding is that antenatal phenomena influence postnatal head growth. By and large, the findings we report here for microcephaly (Z-score <-2) apply also to a smaller reduction in head circumference (Z-score ≥-2 , <-1). This similarity in risk profile suggests what limits brain volume growth can do so with varying intensity, sometimes resulting in microcephaly and sometimes less severely.

We begin the discussion with comments about phenomena common to both of the head circumference classifications (Z-score <-2 and Z-score ≥-2 , <-1). Then we discuss phenomena restricted to each classification.

The three antecedents common to both head circumference classifications are microcephaly at birth, low gestational age, and male sex. None of these findings is a surprise. Others have found that a small head in childhood is predicted by a small head at birth [7], low gestational age [10,11], and low weight at birth [8,12]. Boys, too, have been found by others to be at increased risk of a small head in childhood [9].

Infants with the most extremely small head circumference at 24 months were also more likely than others to have been born to an unmarried mother, and to have had a placenta that harbored alpha hemolytic *Streptococci*. We doubt that marriage influences a child's head circumference directly. We view marriage as a surrogate for many phenomena that might influence head growth. In our sample, maternal correlates of marriage, including racial and ethnic identity, age at delivery, level of education, financial well-being, and social support were associated with the child's head circumference at age 24-months (Table 1). These are only the correlates we identified. Obviously, others might have been important in conveying information about the child's risk of microcephaly. Low maternal education has been associated with congenital microcephaly [25].

Recovery of alpha hemolytic *Streptococci* from the placenta predicted microcephaly, and recovery of *Propionibacterium* sp from the placenta predicted a less extremely small head circumference (i.e., Z-score ≥-2 , <-1). We offer the view that the individual organism might be much less important than the pro-inflammatory environment likely when any of these organisms is present. For example, *Propionibacterium* is one of three normal skin flora species, along with *Corynebacterium* species and *Staphylococcus* species, which as a group, but only inconstantly as individual organisms recovered from the placenta, predicted white matter damage (i.e., ventriculomegaly and an echolucent lesion) in this sample [26]. Others, too, have reported that inflammatory stimuli influence the risk of cerebral white matter damage [27–30].

Early cerebral white matter damage can result in limited brain volume growth [31].

Thus, it should not be surprising that the inflammatory stimuli associated with early white matter damage are similar to those associated with reduced head circumference two years later. Since recovery of organisms from the placenta was associated with increased risk of sonographic expressions of white matter damage [26], but not with an increased risk of congenital microcephaly [32], our findings are compatible with the view that some antenatal characteristics, such as the presence of low virulence organisms in the uterus/placenta, exert most of their effect on the brain shortly after delivery.

At 24 months, a small head circumference (i.e., Z-score ≥-2 , <-1), but not microcephaly was associated with maternal tobacco smoke exposure during pregnancy. Tobacco exposure during pregnancy has been associated with an increased risk of congenital microcephaly [33], but we

know of no studies documenting a relationship between maternal smoking and a reduced head circumference when the child is older.

Children whose placenta had neutrophilic infiltration of the fetal stem vessels were at reduced risk of a head circumference Z-score ≥ -2 , < -1 , while children whose placenta had increased syncytial knots were at increased risk of such a small head. Neither of these histologic characteristics predicted microcephaly. We are not sure why these histologic characteristics did not predict microcephaly but did predict a less severe head circumference reduction.

Inflammation of the fetal stem vessels is inversely related to increased syncytial knots. Thus, we expect them to have opposite associations with any outcome associated with either one.

Increased syncytial knots tend to be found most frequently in the placentas of preeclamptic pregnancies. Infants born to women with preeclampsia, whether at term or before, are more likely than other infants to have a smaller head circumference at birth [32,34]. Consequently, if preeclampsia still had an effect on head circumference two years later, we would expect increased syncytial knots in the placenta to predict a reduction in head circumference. Indeed, that is what we saw for a small head circumference (head circumference Z-score ≥ -2 , > -1 , but not microcephaly). Our finding that birth head circumference Z-score > -2 predicted a head circumference Z-score > -2 at age two years, was so strong that syncytial knots in the placenta did not provide supplemental information. On the other hand, our finding that birth head circumference Z-score > -2 did not predict a less severe reduction in two-year head circumference allows a correlate of microcephaly at birth, increased syncytial knots in the placenta to come to the fore.

Inflammation of the fetal stem vessels is inversely related to increased syncytial knots. Thus, we expect them to have opposite associations with any outcome associated with either one. That is what we saw in Table 6, and as expected one of these two variables that more strongly predicts a small head circumference (increased syncytial knots) is in the multivariable model in Table 7, while the weaker (neutrophilic infiltration of fetal stem vessels) is not in the model.

To our knowledge two of our findings have not been reported before. Tobacco exposure during pregnancy has been associated previously with reduction in head circumference at birth, but not with a small head circumference two years later. Recovery of organisms from the placenta predicted reduced head circumference at age two year, but apparently has not been associated with congenital microcephaly.

Our goal was to identify modifiable antecedents of limited head growth. We remain uncertain to what extent what we found will be modifiable. Certainly tobacco consumption abatement programs are in order. Efforts to identify early indicators of preeclampsia and related fetal brain growth might eventually might also contribute to reducing the occurrence of microcephaly at age two years and perhaps even less severe brain growth disorders.

Measuring head circumference at birth poses problems related to shape distortion and scalp edema, which can increase the probability of measurement error. Sensitive to this, our colleagues responsible for head measurements did all that they could to minimize this error. The quality of our data is documented by the correlates of microcephaly in this sample [6]. On the other hand, to the extent that misclassification of birth head circumference occurred, odds ratios for antecedents of reduced head circumference will be biased towards 1.0.

In summary, our findings lead to the inference that early antenatal phenomena influence the risk of reduced head circumference at 24-months post-term equivalent, perhaps via three mechanisms. First, limited head growth *in utero*, predicts a small head years later. Second, the presence of low virulence organisms in the uterus/placenta is associated with increased risk of

cerebral white matter damage, which in turn, limits postnatal head growth. Third, correlates of social class (including nurturing characteristics and environmental exposures) might also limit head growth. We hope that these inferences will provoke studies that will lead to strategies that promote brain growth and improved brain function.

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Table 1

Distribution of children's 24-month head circumference Z-scores in relation to social and demographic characteristics of the mother. These are row percents. They do not total to 100% because the groups with larger head circumferences are not shown.

Maternal characteristic		Head circumference Z-score ^a		Row N
		<-2	≥-2, <-1	
Racial identity	White	7	16	590
	Black	15	19	276
	Other	16	26	122
Hispanic	Yes	15	20	120
	No	10	18	879
Age (years)	<21	14	22	133
	21-35	11	19	675
	>35	7	15	196
Years of education	<12	15	23	157
	12 (HS)	15	15	260
	>12,<16	10	22	232
	16 (College)	3	16	174
Marital status	>16	6	16	147
	Single	15	21	423
Self supporting	Not single	7	17	581
	Yes	9	18	653
Public insurance	No	12	19	330
	Yes	15	23	386
Pre-pregnancy body mass index (BMI)	No	8	15	298
	<18.5	13	17	75
	18.5, <25	10	19	485
	25, < 30	9	19	201
Smoking Pre-pregnancy ^b	>30	13	16	204
	Yes	16	21	239
Smoking during pregnancy ^b	No	9	17	741
	Yes	18	22	131
Exposure to the smoke of others ^b	No	9	18	849
	Yes	16	22	244
Maximum number of infants %	No	9	17	732
		105	184	1004
		10	18	

^aThe external standard is the CDC data set [22].

^b Infants may be in more than one category.

Table 2

Distribution of children's 24-month head circumference Z-scores in relation to pregnancy characteristics and exposures of the mother. These are row percents.

Exposures and characteristics		Head circumference Z-score ^a		Row N
		<-2	≥-2, <-1	
First pregnancy	Yes	8	19	395
	No	12	18	584
Years since Last pregnancy	<1	7	14	114
	1-2	17	15	166
	2+	12	21	299
Conception assistance	Yes	8	15	210
	No	11	19	768
Vaginal bleeding ≤ 12 weeks ^b	Yes	10	16	387
	No	11	20	590
Vaginal bleeding > 12 weeks ^b	Yes	8	16	291
	No	12	19	686
Fever during pregnancy ^b	Yes	8	22	59
	No	11	18	917
Vaginal/cervical infection during pregnancy ^b	Yes	14	18	134
	No	10	18	842
UTI during pregnancy ^b	Yes	9	20	146
	No	11	18	830
Highest WBC ^c	>20	7	19	194
	≤20	11	18	793
Any medication during pregnancy ^b	Yes	11	18	864
	No	6	19	113
Aspirin during pregnancy ^b	Yes	10	19	58
	No	11	18	916
NSAID ^d during pregnancy ^b	Yes	17	21	71
	No	10	18	902
Acetaminophen during pregnancy ^b	Yes	11	20	504
	No	10	16	469
Antibiotic during pregnancy ^b	Yes	11	21	301
	No	10	17	673

^aThe external standard is the CDC data set [22].

^bInfants may be in more than one category.

^cThousands of WBCs within the interval from before delivery to 48 hours post delivery.

^dNon-steroidal anti-inflammatory drug.

Table 3

Distribution of children's 24-month head circumference Z-scores in strata defined by delivery characteristics. These are row percents.

Characteristics of the delivery		Head circumference Z-score ^a		Row N
		<-2	≥-2, <-1	
Antenatal steroid course	Complete	11	19	651
	Partial	9	16	244
	None	13	18	107
Magnesium	No	12	19	329
	Tocolysis	8	18	542
	Sz prophylaxis ^b	17	19	126
Cesarean delivery	Yes	10	20	662
	No	12	15	342
Initiator of preterm delivery	PTL ^c	8	17	447
	PPROM ^d	11	15	218
	Preeclampsia	14	27	132
	Abruption	12	19	112
	Cerv insuf ^e	11	13	53
	Fetal indication	19	29	45
Duration of labor	Oh	14	25	245
	>0 to ≤12h	7	15	223
	>12h	10	17	536
Duration of membrane rupture	<1 h	10	21	580
	1–24 hrs	12	14	164
	>24 h	12	14	260

^a A head circumference Z-score of <-2 or in the lowest quartile according to the CDC data set [22].

^b Seizure prophylaxis.

^c Preterm labor.

^d Pre-labor, premature rupture of membranes.

^e Cervical insufficiency.

Table 4

Distribution of children's 24-month head circumference Z-scores in strata defined by the newborn's characteristic listed on the left. These are row percents.

		Head circumference Z-score^a		N
		<-2	≥-2, <-1	
Number fetuses	1	11	20	372
	2+	9	16	332
Sex	Male	12	20	524
	Female	8	17	480
Gestational age (weeks)	23–24	18	25	200
	25–26	11	19	463
	27	6	14	341
Birth weight (g)	≤750	21	26	367
	751–1000	6	15	447
	>1000	2	11	190
Birth weight Z-score ^b	<-2	30	30	53
	≥-2, <-1	17	31	137
	≥-1	8	15	814
Birth head circumference Z-score ^b	<-2	28	31	81
	≥-2, <-1	15	26	234
	≥-1	7	14	689

^aExternal standard is the CDC data set [22].

^bExternal standard is the data set of Yudkin [21].

Table 5

Risk ratios (and 95% CI) of each 24-month head circumference Z-score entity associated with each placental organism or group of organisms listed on the left. Data are presented separately for the vaginal sample (first two data columns) and for the sample of placentas delivered by Cesarean section (last two data columns). The models are adjusted for gestational age (23–24, 25–26, and 27 weeks) and birth head circumference Z-score (<-2 ≥-2 but <-1 , ≥-1).

	Vaginal sample	Cesarean section sample		
	Head circumference Z-score			
	<-2	≥-2, <-1	<-2	≥-2, <-1
Microorganism				
# species				
1	1.3 (0.5, 3.6)	0.8 (0.3, 2.1)	1.4 (0.7, 2.7)	1.1 (0.6, 1.8)
2+	0.7 (0.3, 1.8)	0.7 (0.3, 1.6)	0.7 (0.3, 2.0)	0.9 (0.5, 1.7)
Any aerobe	0.5 (0.2, 1.2)	0.7 (0.3, 1.3)	1.5 (0.8, 3.0)	0.8 (0.5, 1.4)
Any anaerobe	0.8 (0.4, 1.8)	0.8 (0.4, 1.6)	0.6 (0.3, 1.4)	1.1 (0.7, 1.8)
Any mycoplasma	1.0 (0.4, 2.8)	1.1 (0.5, 2.7)	0.7 (0.2, 2.5)	1.6 (0.8, 3.3)
Propionibacterium sp	0.9 (0.1, 8.1)	2.8 (0.8, 10)	0.8 (0.2, 3.1)	2.4 (1.2, 5.0)
α hemolytic Strep	0.6 (0.1, 3.2)	1.7 (0.6, 4.7)	4.1 (1.5, 11)	0.3 (0.1, 1.5)
Skin organisms ^a	0.7 (0.3, 1.6)	1.2 (0.6, 2.5)	0.7 (0.3, 2.0)	2.0 (1.1, 3.5)
Vaginal organisms ^b	0.9 (0.4, 2.1)	0.6 (0.3, 1.4)	0.3 (0.1, 1.5)	0.7 (0.3, 1.5)

These bolded items are statistically significant at the $p < .05$ level.

^a Corynebacterium sp, Propionibacterium sp, Staphylococcus sp.

^b Prevotella bivia, Lactobacillus sp, Peptostrep magnus, Gardnerella vaginalis.

Table 6

Risk ratios (and 95% CI) of each 24 month head circumference Z-score entity associated with each histologic characteristic listed on the left. The models are adjusted for gestational age (23–24, 25–26, and 27 weeks) and birth head circumference Z-score (<-2 , ≥-2 and <-1 , ≥-1). This is for all placentas regardless of route of delivery.

Histologic characteristic	Head circumference Z-score	
	<-2	$\geq-2, <-1$
Inflammation chorionic plate ^a	0.9 (0.5, 1.6)	0.7 (0.4, 1.1)
Inflammation chorion/decidua ^b	1.1 (0.7, 1.7)	0.7 (0.5, 1.1)
Neutrophils in fetal stem vessels	1.1 (0.7, 1.9)	0.6 (0.4, 0.9)
Umbilical cord vasculitis ^c	0.9 (0.5, 1.7)	0.7 (0.4, 1.1)
Thrombosis of fetal stem vessels	1.2 (0.5, 3.2)	1.4 (0.7, 2.9)
Infarct	0.8 (0.5, 1.6)	0.9 (0.6, 1.4)
Increased syncytial knots	1.6 (0.9, 2.7)	1.8 (1.2, 2.8)
Decidual hem/fibrin deposition	1.1 (0.6, 2.0)	1.0 (0.6, 1.6)

^a Stage 3 and severity 3.

^b Grades 3 and 4.

^c Grades 3, 4 and 5.

Table 7

Risk ratios (point estimates and 95% confidence intervals) for each 24 month head circumference Z-score entity associated with each of the variables listed on the left in models of that contain all the other variables in this table.

Variables	<u>Head circumference Z-score</u>	
	<-2	≥-2, <-1
Birth head circ. Z-score <-2	8.8 (3.7, 21)	3.7 (1.7, 7.9)
Gestational age 23–24 wks	6.1 (2.9, 13)	3.4 (2.0, 5.8)
Gestational age 25–26 wks	2.1 (1.1, 4.0)	1.9 (1.2, 3.0)
<i>α hemolytic Streptococci</i>	2.9 (1.2, 6.9)	1.1 (0.6, 2.6)
Male	2.8 (1.6, 4.9)	1.7 (1.2, 2.5)
Single mother	2.5 (1.5, 4.3)	1.2 (0.8, 1.7)
Birth weight Z-score<-2	2.2 (0.8, 6.0)	1.0 (0.4, 2.7)
Tobacco smoke ^a	1.5 (0.9, 2.6)	2.0 (1.4, 3.0)
NSAIDs during pregnancy	1.7 (0.7, 3.9)	1.2 (0.6, 2.4)
Increased syncytial knots	1.7 (0.9, 3.1)	2.0 (1.2, 3.2)
Maternal or fetal indication	1.6 (0.8, 3.3)	1.5 (0.9, 2.6)
<i>Propionibacterium</i> sp	0.8 (0.2, 2.7)	2.9 (1.5, 5.5)

^a Smoking and/or exposure to the smoke of others during pregnancy.