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Antecedents and correlates of visual field deficits in children born extremely preterm

Mari Holm[1,2], **Michael E. Msall**[3], **Jon Skranes**[1], **Olaf Dammann**[2,4], **Elizabeth Allred**[5], and **Alan Leviton**[5]

[1]Department of Laboratory Medicine, Children's and Women's Health, Norwegian University of Science and Technology, Trondheim, Norway

[2]Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA, USA

[3]Department of Pediatrics, Section of Developmental and Behavioral Pediatrics and JP Kennedy Research Center on Intellectual and Developmental Disabilities, University of Chicago Comer Children's Hospital, Chicago, IL, USA

[4]Neuroepidemiology Unit, Hannover School of Medicine, Hannover, Germany

[5]Neurology Departments, Boston Children's Hospital, and Harvard Medical School, Boston, MA, USA

Abstract

Aim—We sought to identify the antecedents and correlates of visual field deficits (VFDs) at age 2 years among infants born before the 28th week of gestation.

Methods—The visual fields of 1023 infants were assessed by confrontation at age 2 years. We compared the ante-and postnatal characteristics and exposures of the 65 infants with a VFD to their peers who did not have a VFD. We used time-oriented logistic regression risk models to assess the associations of potential antecedents and correlates with a VFD.

Results—In the final regression model, VFD was associated with maternal consumption of aspirin during the current pregnancy, recurring/persistent acidemia during the first 3 postnatal days, cerebral ventriculomegaly seen on neonatal ultrasound, prethreshold retinopathy of

Correspondence to: Mari Holm.

Postal and e-mail address
Mari Holm: mari.holm@ntnu.no, Phone: +1617 938 7146
Olaf Dammann: olaf.dammann@tufts.edu, Tufts University School of Medicine, 136 Harrison Ave. Boston, MA 02111, USA
Michael Msall: mmsall@peds.bsd.uchicago.edu, Comer Children's Hospital at the University of Chicago, 5721 S. Maryland Avenue. Chicago, IL 60637, USA
Jon Skranes: jon.skranes@ntnu.no, Medical Faculty, Norwegian University of Science and Technology, N-7489 Trondheim, Norway
Allan Leviton: alan.leviton@childrens.harvard.edu
Elizabeth Allred: lizard@hsph.harvard.edu, Boston Children's Hospital, Au-414, 300 Longwood Avenue, Boston MA 02115-5724, USA

prematurity (ROP), and supplemental oxygen and ventilator dependence at 36 weeks post-menstrual age. Birth before the 27th week was also associated with increased risk, but its significance was diminished by the addition of postnatal variables.

Conclusion—In this sample of extremely preterm born infants, antenatal as well as early and late postnatal characteristics and exposures are associated with an increased risk of having a VFD. Our study adds to our knowledge about the complex etiology of visual deficits of prematurity, and supports a multifactorial cause of these deficits.

Keywords

Visual field deficits; ventriculomegaly; ROP; prematurity; preterm birth; brain development

1. Introduction

Preterm infants are at increased risk of visual impairments, including acuity deficits [1], strabismus [2], reduced contrast and color sensitivity [1], refractive errors [3], and visual field deficits (VFDs) [4]. Visual problems among infants born preterm are associated with cognitive disability at 2 years of age [2], lower IQ scores at 5 years of age [5], and motor problems among teenagers [6].

Cerebral visual impairment and retinopathy of prematurity (ROP) represent the two main causes of visual impairment in preterm born children, and appear to contribute to VFDs independently [7, 8]. In the brain, the primary visual pathway is anatomically close to where white matter damage tends to occur, and VFDs may be a result of such injury [9]. In addition, visual field deficits are specifically associated with cerebral damage such as unilateral spastic CP [10, 11].

The increased risk of VFD in infants with ROP is probably mediated both via the pathological process of ROP itself, and an iatrogenic effect of cryotherapy or laser coagulation [4, 8, 12]. On the other hand, children with ROP in the ELGAN Study were at increased risk of dysfunctions associated with brain damage [13]. Further, severe ROP is associated with nonvisual disabilities such as physical and cognitive impairment at age 5 [14, 15], below-grade-level academic performance at 8 years [16], and lower health-related quality of life at 10 years [17]. These studies suggest a shared etiology for visual and non-visual developmental disabilities in preterm born children.

In this study we examined the association between maternal, perinatal, and postnatal factors and VFDs in a cohort of more than 1,000 extremely low gestational age newborns (ELGANs) [18]. We are not aware of any previous study that has explored this topic in such a large cohort of extremely preterm children. The identification of VFD and their preventable risk factors is crucially important so that caretakers and professionals can improve long-term visual outcomes

2. Material and methods

2.1. Participants

The ELGAN study was designed to identify characteristics and exposures that increase the risk of structural and functional neurological disorders in infants born extremely preterm [18]. During the years 2002–2004, women who gave birth before 28 weeks gestation at one of 14 participating hospitals in 5 states in the U.S. were asked to enroll. The individual institutional review boards approved the study.

Mothers were approached for consent either upon antenatal admission or shortly after delivery, depending on clinical circumstances and institutional preference. A total of 1506 infants born to 1249 mothers were enrolled. The sample presented in this study consists of the 1023 infants who had a developmental and visual field assesment at 2 years corrected age.

2.2. Demographic and pregnancy variables

After birth, a trained research nurse interviewed each mother in her native language using a structured form. Shortly after the mother's discharge, the nurse reviewed the maternal chart using a second structured form. Circumstances that led to preterm delivery were identified using data from the maternal interview, and data abstracted from the medical record [19].

2.3. Placenta

Placentas were biopsied under sterile conditions. Eighty-two percent of the samples were obtained within 1 hour of delivery. The microbiologic and histological procedures of the placenta are described in detail elsewhere [20, 21]. In keeping with guidelines [22], 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 [23, 24].

2.4. Newborn variables

Gestational age (GA) was estimated based on date of embryo retrieval, intrauterine insemination, or fetal ultrasound before the 14th week (62%). When these were not available, the estimate was based on fetal ultrasound at week 14 or later (29%), last menstrual period (7%), or GA recorded in the log of the Neonatal Intensive Care Unit (NICU) (1%).

Birth weight Z-score was defined as number of standard deviations above or below the median weight of infants of same GA in referent samples not delivered for preeclampsia or fetal indications [25]. Infants with birth weight Z-score between ≥ -2 and < -1 were identified as moderately growth restricted, and infants with a Z-score ≤ -2 were identified as severely growth restricted. Physiology, laboratory, and therapy data were collected during the first 12 postnatal hours so we could calculate a Score for Neonatal Acute Physiology (SNAP-II™) [26].

The infants were classified by their most extreme blood gas measurements on postnatal days 1, 2, and 3. For each day, the lowest and highest PaO_2, PCO_2, and pH were recorded. The infants were classified by whether or not their value was in the extreme quartile for their GA (23–24, 25–26, and 27 weeks) in the cohort on each postnatal day, and whether the specimen was arterial or venous. Values in the extreme quartile on at least 2 of the 3 days were considered as "exposed." Since infants who did not have blood gas measurements on postnatal day 3 were less likely than others to have extreme measurements on postnatal day 2, we assigned these newborns to the group with non-extreme measurements on postnatal day 3. This allowed us to include children with no measurement on the 3rd postnatal day.

Blood culture results were recorded for each of the first 4 postnatal weeks. We define bacteremia in the 1st week as "early," and in weeks 2, 3 or 4 as "late."

2.5. Retinal examinations in the NICU

A manual and a data collection form were created to minimize observer variability of the retinal assessments. In keeping with guidelines the first ophthalmologic examination was within the 31st to 33rd week post-menstrual age [27]. Follow-up exams were as clinically indicated until normal vascularization began in retinal anatomical zone lll. Definitions of terms were those accepted by the International Committee for Classification of retinopathy of prematurity (ROP) [28]. The severe forms of ROP were classified in four ways: stage 3 or higher, zone I disease, any prethreshold or worse, and plus disease. Infants with each of these severe forms of ROP were compared to infants who had lower grade ROP or no ROP.

2.6. Protocol ultrasound scans

Routine scans were performed by technicians, and included the six standard quasicoronal views and five sagittal views using the anterior fontanel as the sonographic window [29]. All the 1023 infants who had a visual field assessment at 2 years had at least 1 set of protocol ultrasound scans. The 3 sets of protocol scans were defined by the postnatal day on which they were obtained. Protocol 1 scans were obtained between the 1st and 4th day (N=767), protocol 2 scans were obtained between the 5th and 14th day (N=956), and protocol 3 scans were obtained between the 15th day and the 40th week (N=994).

All ultrasound scans were examined by 2 independent readers who were unaware of all clinical information. If the readers differed in their recognition of intraventricular hemorrhage (IVH), moderate/severe ventriculomegaly, echodense/hyperechoic lesion, and echolucent/hypoechoic lesion, the films were sent to a third tie breaking reader.

2.7. 24-month developmental assessment

Eighty-five percent of surviving children were assessed close to 24-months corrected age. Seventy-seven percent had their exam within the range of 23.5–27.9 months. Most others were examined before 23.5 months. Procedures to standardize the neurological examination and minimize examiner variability are presented elsewhere [30].

Visual fields were assessed by confrontation. Testing required that the infant initially maintained a fixated gaze straight ahead on a target item. The examiner then brought a

brightly colored item into one of the child's four visual fields (left and right upper and left and right lower). Visual field was considered to be intact if the infant moved the gaze from the target straight-ahead to the object coming into the quadrant field assessed. If the infant did not attend to the moving stimulus, the evaluation was repeated to confirm the result. The child's failure to see an object in each of the four quadrants of the visual field was recorded.

Every child was assessed for strabismus causing dysconjugate gaze. Esotropia or exotropia in each eye was recorded. Esotropia and exotropia were defined as an eye that exhibited either convergent or divergent strabismus, respectively. Some children were classified as having both esotropia and exotropia.

The child was considered to have impaired fixation if s/he could not fixate even briefly (N=18), or could not sustain eye contact long enough to follow the examiner across the midline (N=55).

Head circumference was measured as the largest possible occipital-frontal circumference. Measurements were rounded to the closest 0.1 centimeter. Microcephaly was defined as a head circumference more than 2 standard deviations below the mean for age in Centers for Disease Control and Prevention (CDC) data sets [31]

The children's motor function were evaluated according to a worksheet based on the Gross Motor Function Classification System (GMFCS) [32], with scores ranging from 0 to V. Level <I indicates that the child can walk independently, and level =I indicates that the child creeps or crawls on hands and knees, pulls to stand and cruises or walks with hands held. Level ≥II indicates that the child cannot walk even when her hand is held. The topographic diagnosis of cerebral palsy (CP) (quadriparesis/quadriplegia, diparesis/diplegia, or hemiparesis) was based on an established algorithm for CP [33].

Certified examiners administered and scored the Bayley Scales of Infant Development - Second Edition [34]. A score of less than 55 (3 or more standard deviations below the expected mean) defined severe impairment on the Mental and Psychomotor Development Indices (MDI and PDI). Because some MDI test items require intact motor function, all infants with significantly impaired gross motor function (Gross Motor Function Classification System level ≥I) were excluded.

2.8. Data analysis

We evaluated the null hypothesis that infants with a VFD at 2 years were no more likely than their peers whose visual fields were intact to have an antenatal or early postnatal characteristic or exposure, or have an indicator of concurrent brain damage. Because postnatal phenomena can be influenced by antepartum events and characteristics, we created logistic regression models in which risk factors are ordered in a temporal pattern. This implies that the earliest occurring predictors/covariates of impaired fixation are entered first, and not displaced by later occurring covariates. For the time-oriented logistic regression risk models, we categorized sets of antecedents/covariates by the time they occur or are identified, e.g. antenatal and postnatal. We used a step down procedure seeking a

parsimonious solution without interaction terms. These models allowed us to calculate odds ratios and 95% confidence intervals.

3. Results

3.1. Sample description (Table 1)

A total of 65 children had a VFD at 2 years. This constitutes 6.4% of the sample. In the NICU, infants who later developed a VFD were more likely than others to have had ventriculomegaly and/or a hypoechoic (echolucent) white matter lesion on the cerebral ultrasound scan, and prethreshold ROP. The infants with a VFD were also more likely to have esotropia, quadriparetic or hemiparetic cerebral palsy, mental and motor development indices < 55, and a head circumference more than 2 standard deviations below the mean of the CDC standard.

3.2. Maternal and pregnancy characteristics (Appendix Table A)

Children, whose mothers identified themselves as Black, were overweight (BMI 25–30) but not obese (BMI >30), had some post-college education, experienced vaginal bleeding, or were exposed to tobacco smoke, either actively or passively during the pregnancy, were less likely to have a VFD than their peers whose mothers did not have these characteristics.

3.3. Maternal illnesses and medications (Table 2)

Children were at increased risk of a VFD if their mother experienced fever or took aspirin during the pregnancy. No other medication or recorded illness was associated with a VFD in the child.

3.4. Delivery exposures and characteristics (Appendix Table B)

There was a higher frequency of VFDs among the infants with low GA and birth weight. No association was found between VFDs and Cesarean delivery, male sex, or exposure to a course of antenatal corticosteroids or magnesium.

3.5. Placenta bacteriologic and histologic characteristics (Appendix Table C)

Children whose placenta harbored an anaerobe or a skin organism (*Corynebacterium sp, Propionebacterium sp, Staphylococcus sp*) were more likely than others to have a VFD, as were those whose placenta had inflammation of the chorionic plate.

3.6. Early postnatal characteristics (Appendix Table D)

The higher the Score for Neonatal Acute Physiology (SNAP-II) during the first 12 postnatal hours, the higher was the prevalence of a VFD. Having a VFD was also associated with a PaO_2 or pH in the lowest quartile and a PCO_2 in the highest quartile on two of the first three postnatal days. Assisted ventilation on postnatal days 14, 21, 28, and at 36 weeks post-menstrual age was also associated with having a VFD.

3.7. Postnatal medication (Appendix Table E)

Children who received any of the following had a higher prevalence of a VFD than their peers: postnatal steroids, any sedative or antibiotic drug during the first postnatal month, and a transfusion of packed cells or whole blood during three of the first four postnatal weeks.

3.8. Diagnostic and classification entities (Table 3)

Infants who had a pneumothorax, pulmonary interstitial emphysema, pulmonary hemorrhage, early and persistent pulmonary dysfunction, necrotizing enterocolitis requiring surgery or an isolated intestinal perforation had a higher prevalence of VFDs than their peers. ROP stage 3–5, plus disease, threshold, and prethreshold ROP, as well as ventilator dependence at 36 weeks post-menstrual age were also associated with increased risk of VFD.

3.9. Time-oriented logistic regression risk models (Table 4)

Children whose mother took aspirin during the pregnancy were at increased risk of a VFD, as were children born before the 27th week of gestation. Of all the postnatal variables, only recurrent/persistent acidemia, ultrasound-defined ventriculomegaly, prethreshold ROP, and supplemental oxygen and ventilator dependence at 36 weeks post-menstrual age added discriminating information about the risk of a VFD. Gestational age lost its statistical significance when the postnatal variables were added.

Ventriculomegaly and ROP were the two factors with the largest odds ratios for VFDs in our model. To evaluate their influence on VFDs independently of each other, we created separate models, one without ROP and one without ventriculomegaly (Appendix Table F). The odds ratio of each variable remained essentially unchanged when the other variable was excluded.

4. Discussion

We identified six risk factors for having a VFD at age 2 years in children who were born extremely prematurely: mother’s consumption of aspirin during the pregnancy, gestational age < 27 weeks, acidemia during the first postnatal days, ventriculomegaly, prethreshold ROP, and supplemental oxygen and ventilator dependence at 36 week post-menstrual age.

The diminished statistical significance of the low gestational age variables following the addition of postnatal variables is best interpreted in light of our time-oriented risk model (TORM). In this model, once a variable is significant, it remains an important risk factor, even if its significance is reduced by the addition of later-occurring or later-identified variables. The variables added subsequently convey information about the variable(s) whose statistical significance is diminished by their inclusion in the model, as well as conveying additional risk information.

Of the antenatal factors only maternal consumption of aspirin during pregnancy remained significant as later-occurring antecedents, including preeclampsia, were added to the model. Aspirin has the ability to cross the placenta [35], and when taken in low doses, it appears to reduce the risk of preeclampsia [36] without adversely affecting the fetus [37]. In the ELGAN

Study cohort, mother's consumption of aspirin was also associated with an increased risk of quadriparetic cerebral palsy [38]. Preterm-born children whose mother experienced infections during pregnancy appear to be at increased risk of visual complications [39]. We do not have information on the indication, dosage or timing of maternal aspirin intake. Further on, we are not able to distinguish between the possibility that aspirin consumption is an indicator of the mother's inflammatory illness for which she might have taken the aspirin, and the possibility that the aspirin itself contributed to VFD risk. Still no other non-prescription medication such as acetaminophen or NSAIDs was associated with VFD.

Recurrent postnatal acidemia conveyed more discriminating information than any other blood gas derangement. Low pH in the ELGAN cohort has been associated with severe ROP [40]. In animal models, metabolic acidosis increases retinal neovascularization and development of ROP [41]. To what extent acidemia contributes to organ damage remains to be clarified.

Ventriculomegaly added explanatory value to our model of VFD. Infants in the ELGAN Study most often had the form of ventriculomegaly identified as hydrocephalus *ex vacuo*, which is often an indicator of cerebral white matter damage with enlarged ventricles as a cause of diminished white matter bulk [42]. Such loss of white matter might reflect damage to the primary visual pathways, which further may be an indicator of damage of cortical and deep grey matter [43]. Both grey and white matter damage may contribute to the VFDs detected here. Thus, our finding is in keeping with a report that preterm born teenagers with white matter injury are at increased risk of a VFD [44].

Prethreshold ROP was a significant risk factor of VFD in our final model. This is in keeping with previous studies that identified ROP as a risk factor of VFD [4, 8, 12]. The VFDs following ROP are reported as less extensive than a whole visual field quadrant [4, 45], and the association presented here may be a proxy of cerebral injury or low visual acuity. We have no measurements of visual acuity in this cohort, and it is likely that some of what was here interpreted as a VFD is a consequence of low acuity. The high rate (39%) of fixation problems in the VFD group raises this possibility. More accurate testing at an older age can provide better estimates of the extent of visual deficits and the influence these may have on the children's everyday life.

The need for supplemental oxygen and mechanical ventilation at 36 weeks post-menstrual age added discriminating information to the TORM. Respiratory complications like BPD requiring prolonged oxygen support can affect brain and retina development, and have previously been associated with cerebral palsy [46] and severe ROP [47] in the ELGAN cohort.

Several of the variables in the TORM support the view that systemic inflammation plays a role in the pathogenesis of VFD [39]. Maternal use of aspirin as identified here may be seen as a surrogate for prenatal inflammatory disorders [38]. Further, prolonged mechanical ventilation [48] and acidemia [49] were associated with a systemic inflammation response in the ELGAN cohort. Inflammation has also been associated with ROP both in the ELGAN cohort [50] and in other studies [51–53]. An inflammatory contribution to the occurrence of VFD

is in keeping with animal models that document that systemic inflammation can affect white matter development [54], and retinal development [55].

Our study has several strengths. First, we included a large number of infants, 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. Second, we selected infants based on gestational age, not birth weight, in order to minimize confounding due to factors related to fetal growth restriction [56]. Third, we collected all of our data prospectively. We have minimized observer variability as best we can in the interpretation of ultrasound scans [57] and assessments of visual fields [33].

The prevalence of VFD in this study was 6.4%, which is higher than reported elsewhere [58, 59], but differences in age and mode of assessment make direct comparisons difficult. A visual field evaluation done at this age has limitations [60], and it is possible that minor deficits were underreported.

In conclusion, our results suggest that VFD in children aged two years who were born extremely prematurely has multiple antecedents and correlates, including maternal consumption of aspirin during pregnancy, low gestational age, early postnatal acidemia, ventriculomegaly, prethreshold ROP, and bronchopulmonary dysplasia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Visual field deficits in extremely preterm born infants have multiple antecedents.
- Most antecedents of visual field deficits are shared with expressions of brain injury.
- Visual field deficits tend to accompany developmental disabilities.

Table 1

Visual, retinal, and brain disorders and percent of infants with a reduction in any visual field. Column percents.

		Visual field deficit [a]	
		Yes	**No**
Strabismus	Esotropia	46	9
	Exotropia	8	3
Fixation	No	39	4
Retinopathy	Prethreshold [b]	42	11
Ventriculomegaly [c]	Yes	25	9
Echolucent lesion [c]	Yes	14	9
Cerebral palsy	Quadriparesis	23	4
	Diparesis	3	3
	Hemiparesis	5	1
GMFCS [d]	≥ II	20	4
MDI [e]	< 55	37	13
PDI [f]	< 55	37	14
M-CHAT screen [g]	Positive	27	16
2 year head circumference Z [h]	< −2	23	9
2 year body weight Z [h]	< −2	7	3
Maximum column N		65	958

[a] Alone or with other lesions

[b] Meets Early Treatment for Retinopathy of Prematurity (ET-ROP) criteria

[c] Seen on neonatal ultrasound

[d] Gross Motor Function Classification System

[e] Mental Development Index of the Bayley Scales for Infant Development II at 24 months of age

[f] Motor Development Index of the Bayley Scales for Infant Development II 24 months of age

[g] Modified Checklist for Autism in Toddlers. GMFCS score <I and no visual or hearing impairment

[h] Centers for Disease Control and Prevention (CDC) standard data set

Table 2

Mother's illnesses and use of medication during pregnancy and percent of infants with a reduction in any visual field. Row percents.

Exposures during pregnancy		Visual field deficit [a]	Row N
Fever	Yes	10	62
	No	6	933
Vaginitis	Yes	8	138
	No	6	857
Urinary tract infection	Yes	8	150
	No	6	845
Any medication	Yes	6	874
	No	4	121
Aspirin	Yes	18	56
	No	5	936
NSAID[b]	Yes	8	71
	No	6	921
Acetaminophen	Yes	5	503
	No	7	489
Antibiotics	Yes	5	303
	No	7	690

[a] Alone or with other lesions.

[b] Non-steroidal anti-inflammatory drug

Table 3

Infant's diagnoses and classification entities and percent of infants with a reduction in any visual field. Row percents.

Diagnostic & classification entities		Visual field deficit [a]	Row N
Quartile of growth velocity (g/kg/day)	Low	9	241
	Low mid	5	250
	Mid high	5	259
	High	7	246
Patent ductus Arteriosus	Yes	7	690
	No	5	333
Pneumothorax	Yes	12	77
	No	6	946
PIE[b]	Yes	12	155
	No	5	868
Pulmonary hemorrhage	Yes	23	31
	No	6	992
Respiratory group classification	EPPD [c]	8	415
	PD [d]	6	377
	Low FiO_2	4	169
Necrotizing Enterocolitis (Bell stage)	III b	12	33
	Isolated perforation [e]	10	31
	None [f]	6	959
ROP: stage	3–5	14	280
	< 3 [f]	3	728
ROP: plus disease	Yes	22	103
	No	5	905
ROP: threshold [g]	Yes	38	21
	No	6	987
ROP: prethreshold [h]	Yes	21	129
	No	4	879
Bronchopulmonary dysplasia	Severe [j]	16	89
	Moderate[k]	6	425
	No	5	502

[a] Alone or with other lesions

[b] Pulmonary interstitial emphysema

[c] Early and persistent pulmonary dysfunction

[d] Pulmonary deterioration

[e] Isolated intestinal perforation

[f] Includes less severe disease

[g] Satisfied CRYO-ROP criteria for ablative surgery (threshold disease)

[h] Satisfied ET-ROP criteria for ablative surgery (prethreshold disease)

[j] On ventilator as well as oxygen at 36 weeks post-menstrual age

[k] On oxygen but not on ventilator at 36 weeks post-menstrual age

Table 4

Odds ratios (95% confidence intervals) of visual field deficit at age 2 years associated with antecedents and correlates calculated from time-oriented logistic regression risk models. Variables were retained in the model if the initial p-value was < 0.05. Bold indicates statistical significance.

		Odds Ratio (95% Confidence Interval)	
		Ante/neonatal	**Postnatal**
Mother	Fever		
	Took aspirin	**3.6 (1.7, 7.5)**	**2.8 (1.1, 6.8)**
Placenta	Anaerobe		
	Skin organism		
	Chorion plate inflammation		
Baby	Gest age: 23–24	**3.0 (1.4, 6.5)**	2.0 (0.8, 5.3)
	Gest age: 25–26	**2.1 (1.04, 4.3)**	2.0 (0.8, 4.7)
Postnatal	SNAP-II ≥ 30 [a]		
	Lowest Q P_aO_2 [b]		
	Highest Q PCO_2 [b]		
	Lowest Q pH [b]		**2.3 (1.3, 4.3)**
	Ventilation on day 14		
	Any corticosteroid		
	Any sedative, week 1–4		
	Transfusion [c]		
	Antibiotic, week 2–4		
	PTX/ PIE/ Pulm hemor [d]		
	NEC–surg / isol perf [e]		
	Ventriculomegaly		**3.4 (1.7, 6.8)**
	Echolucent lesion		
	ROP – prethreshold [f]		**4.2 (2.2, 8.0)**
	Severe BPD [g]		**3.1 (1.5, 6.4)**

[a] Score for Neonatal Acute Physiology

[b] Lowest or highest quartile for gestational on two of the first three postnatal days

[c] Packed cells or whole blood during 3 of the first 4 weeks

[d] Pneumothorax, pulmonary interstitial emphysema, pulmonary hemorrhage

[e] Necrotizing enterocolitis requiring surgery or isolated intestinal perforation

[f] Satisfied ET-ROP criteria for ablative surgery (pre-threshold disease)

[g] Severe Bronchopulmonary dysplasia. On ventilator and receiving oxygen at 36 weeks post-menstrual Age