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Fetal growth restriction and risk of chronic lung disease among infants born before the 28th week of gestation

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Abstract

Objective—Improvement in survival of extremely premature infants over the past several decades has resulted in an increase in the number infants with chronic lung disease (CLD). Historical neonatal exposures associated with CLD now less frequently precede the disease. There is now increasing interest in exposures and events before delivery that predict CLD. The objective of this study was to identify current antenatal predictors of CLD.

Patients and Methods—We collected data about antenatal, placental and neonatal characteristics of 1241 newborns delivered before completion of the 28th week of gestation who were enrolled in a 14-center, observational study conducted during the years 2002-2004. Associations between antenatal factors, microbiologic and histologic characteristics of the placenta, and selected neonatal characteristics and CLD risk were first evaluated in univariate analyses. Subsequent multivariate analyses investigated the contribution of antenatal factors, particularly fetal growth restriction (FGR), to CLD risk.

Results—Among the antenatal factors, birth weight Z-score, used as a marker of FGR, provided the most information about CLD risk. Indicators of placental inflammation and infection were not associated with increased risk of CLD. Within nearly all strata of antenatal, placental and neonatal variables, growth restricted infants were at increased CLD risk compared with infants who were not growth restricted. FGR was the only maternal or antenatal characteristic that was highly predictive of CLD after adjustment for other risk factors.

Conclusions—FGR is independently associated with the risk of CLD. Thus factors that control fetal somatic growth may have a significant impact on vulnerability to lung injury, and in this way

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increase CLD risk. Future investigations should focus on the impact of FGR on growth factors that modulate lung growth.

Keywords

chronic lung disease; bronchopulmonary dysplasia; prematurity; preterm infant

Introduction

Over the past several decades, mortality among extremely low gestational age newborns (ELGANs) has decreased dramatically.(1,2) However, the improvement in survival has been offset by an increase in the number of the most vulnerable preterm infants who survive with bronchopulmonary dysplasia (BPD)(3,4), also called chronic lung disease (CLD). The most common form of CLD is now less severe, with fewer infants requiring prolonged support with high levels of supplemental oxygen and mechanical ventilation.(5,6) When first reported, BPD was attributed primarily to neonatal exposures resulting from treatments for respiratory distress syndrome (i.e., high levels of supplemental oxygen and mechanical ventilation).(7) Currently, however, CLD often is preceded by little or no exposure to these therapies.(8,9) Although immaturity remains the primary determinant of an infant's risk of developing CLD, increasing attention is now being directed to the identification of exposures and events before delivery that predict CLD.

In a large, contemporary cohort of ELGANs, we investigated the relationship between antenatal factors and CLD. In addition to gestational age and birth weight, several antenatal factors predicted CLD, including fetal growth restriction (FGR). In this paper, we explore the associations among antenatal and neonatal risk factors to determine if FGR has an independent effect on CLD risk.

Patients and Methods

The ELGAN Study

The ELGAN Study was designed to identify characteristics and exposures that increase the risk of structural and functional neurologic disorders among infants born at extreme prematurity.(10) From 2002-2004, women who delivered before completion of the 28th week of gestation at 14 institutions were enrolled. The study was approved by the individual institutional review boards.

Demographic and pregnancy variables

Selected characteristics of the pregnancy and intrapartum period were recorded, including the clinical circumstances that led to each preterm delivery. These indications for delivery were operationally defined and mutually exclusive.(11) Two were particularly important in this study, preeclampsia (PE) and fetal indications (FI). Preeclampsia was defined as new onset hypertension and proteinuria of sufficient severity to warrant delivery. Fetal indications (FI) included non-reassuring fetal testing, oligohydramnios, Doppler abnormalities of umbilical cord blood flow, and severe intrauterine growth restriction based on clinical ultrasound testing.

Placenta microbiology and morphology

Placental samples were collected for both histologic examination and microbiologic studies. After removal of the amnion, a specimen of chorion was removed using sterile technique. This specimen was immediately frozen in liquid nitrogen and then stored in a -80°C freezer. Eighty-two percent of the samples were obtained within 1 hour of delivery. Frozen samples

were shipped on a regular basis using dry ice from the 14 study sites to the central microbiology laboratory. Cultures for selected placental pathogens were performed by methods described previously.(12,13) After removal of the specimen for microbiologic assessment, placentas were processed for morphologic assessment as part of the daily workflow of the clinical departments. Details describing the criteria for each histologic lesion are presented elsewhere.(14)

Newborn variables

Gestational age estimates were based on a hierarchy of the quality of available information including, in order of priority, estimates based on the dates of embryo retrieval or intrauterine insemination or fetal ultrasound before the 14th week (62%), 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 was recorded, and the birth weight Z-score (BW Z-score), 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(15), was calculated for each infant.

Physiologic, laboratory and therapy data from the neonatal medical record were collected daily for the first week of life and for postnatal days 7, 14, 21, 28. The final details of the infant's hospital course were collected at discharge, while selected respiratory outcomes were collected at 36 weeks post-menstrual age (PMA).

Infants were classified by their respiratory characteristics during the first two postnatal weeks into three mutually exclusive groups: those with *consistently low FiO_2* (FiO_2< 0.23 on all days between 3 and 7 postnatal days and receiving ≤ 0.25 on Day 14), those with *pulmonary deterioration* (FiO_2 < 0.23 on any days between 3 and 7 days and receiving > 0.25 on day 14), and those with *early and persistent pulmonary dysfunction* (FiO_2 consistently ≥ 0.23 on all days between 3 and 7 postnatal days and receiving > 0.25 on Day 14).(9) Other morbidities were reported if diagnoses were recorded in the hospital chart. The diagnosis of patent ductus arteriosus (PDA) was made on the basis of clinical signs and symptoms or by echocardiography. Necrotizing enterocolitis was classified according to the modified Bell staging system.(16) The diagnosis of CLD was based on whether or not the child was receiving supplemental oxygen at 36 weeks PMA. Decisions to administer supplemental oxygen were made by infants' clinical providers and were not based on a uniform threshold of blood oxygenation prescribed by the study.

Data analysis

The associations of antenatal factors and risk of CLD were first evaluated in univariate analyses. Subsequent analyses investigated whether FGR modified risk. The relationships between CLD and characteristics of the placenta, as well as neonatal characteristics, were examined in a similar manner. Neonatal characteristics were selected on the basis of their identified association with CLD in previously published studies.

Finally, we created conditional logistic regression models of CLD risk that enabled us to compare the contribution of PE and FI to the contribution of growth restriction in light of the potential confounding of gestational age.(17) To account for the possibility that infants born at a particular hospital are more like each other than like infants born at other hospitals, a hospital cluster term was included in all models.(18) We used step down procedures seeking parsimonious solutions without interaction terms. The contributions of relevant variables are presented as risk ratios with 95% confidence intervals.

Results

During the study period, mothers of 1506 infants consented to participate. Approximately 260 women were either missed or did not consent. Among the 1506 infants, 1251 survived to 36 weeks PMA. The CLD status at 36 weeks PMA was not known for 10 infants; the remaining 1241 infants constitute the population for this study.

In addition to gestational age, birth weight and gender, BW Z-score provided the most information about CLD risk. Table 1 summarizes risk of CLD in strata defined by antenatal and delivery characteristics among infants who had any degree of growth restriction (defined as a BW Z-score < -1) and those who did not (BW Z-score ≥ -1). The data are the percent of infants in each cell with CLD. For example, 74% of white infants with FGR had CLD, whereas 50% of white infants without FGR had CLD. Within nearly all strata defined by antenatal and infant characteristics identifiable at the time of birth, infants with FGR were at increased risk of CLD (Table 1). Two of six delivery indications (PE and FI) were associated with higher risk of CLD in the total sample. These indications also included a high percentage of infants with FGR (66% and 52%, respectively). Multi-fetal gestations constitute 32% of the sample, but this characteristic did not increase the risk of either FGR or CLD. In fact, severe growth restriction (BW Z-score < -2) was more common in singletons (6%) than in twins (4%) and triplets (1%). The incidence of CLD was similar among singletons (53%) compared to infants of multi-fetal gestations (50%).

The formats for Tables 2-4 are the same as that of Table 1. Although 51% of placental cultures were positive, culture results provided no additional information about the risk of CLD (Table 2). However, within each stratum defined by the presence or type of organism, growth restricted infants were at higher risk of CLD than were their normal weight peers. Except for the presence of increased syncytial knots, histologic characteristics of the placenta provided no additional information about CLD risk (Table 3). Neither chorioamnionitis nor funisitis (umbilical vasculitis) were associated with increased risk. Within each stratum of histologic characteristics, growth restricted infants were at higher risk of CLD than were their normal weight peers.

Previously reported associations between CLD risk and high SNAP, late infection, PDA, NEC and a variety of pulmonary variables were confirmed in our cohort (Table 4). Within nearly all strata defined by neonatal characteristics, infants with FGR were at higher CLD risk than were their peers without growth restriction. Even among infants without a postnatal variable associated with increased CLD risk, those with FGR were at increased risk. Indeed, this association was generally stronger among infants without postnatal risk factors for CLD. For example, we observed an association among infants without pulmonary interstitial emphysema, but not among those with this diagnosis.

Because FGR was associated with PE and FI, as well as with CLD, we evaluated the inter-relationships among gestational age, indication for delivery, growth restriction and CLD in greater detail, including after stratifying by degree of FGR (i.e., BW z-score < -2, ≥ -2 to < -1, and ≥ -1). Table 5a summarizes associations between delivery indication and CLD in strata defined by gestational age, whereas Tables 5b and 5c summarize associations between FGR and CLD in strata defined by gestational age (5b) or delivery indication (5c). Fetal growth restriction was associated with increased risk of CLD at all gestational ages, except among the least mature infants (23-24 weeks) with severe FGR (Table 5b). Our failure to detect an association in this stratum may reflect its small size (5 infants). The influence of FGR appears to be especially high at the oldest gestational ages. At 27 weeks, 25% of infants without FGR developed CLD compared to 60% of infants with moderate FGR and

90% of infants with severe FGR. Among infants of preeclamptic mothers, risk of CLD increased only in the presence of FGR (Table 5c).

We created logistic regression models to evaluate the contribution of FGR to CLD risk in light of potential confounders (Table 6). We evaluated the contribution of PE and FI (versus all other indications) while controlling for gestational age in the Z-score < -1 stratum. The analysis was repeated in the Z-score ≥ -1 stratum. Finally, the third model let the delivery indication variables compete with the growth restriction variables in the entire sample, again while controlling for gestational age. Delivery indication variables convey minimal information in either stratified or total sample models. In contrast, the two groups of growth restricted infants were at significantly greater risk of CLD than infants who were not growth restricted (i.e., birth weight Z-score ≥ -1) in the total sample model that included delivery indication and gestational age.

Discussion

The purpose of our study was to investigate relationships between antenatal factors and CLD risk. We found that among infants born before the completion of the 28th week of gestation, the presence of growth restriction during fetal life is prominently associated with an increased risk of CLD. Because FGR may result from a variety of maternal conditions, most notably preeclampsia, a critical aspect of our investigation was to explore the inter-relationships among these conditions and CLD risk. The association between FGR and CLD risk persists after adjustment for a variety of antenatal and neonatal characteristics also associated with CLD risk. In fact, FGR was the only maternal or antenatal characteristic that was highly predictive of CLD after these adjustments.

In contrast to some previous studies, we found no association between markers of placental or fetal infection and inflammation and CLD risk. Two of these studies report a relationship between elevated concentrations of the pro-inflammatory cytokine interleukin-6 (IL-6) in cord blood, and CLD risk.(19,20) One possible explanation for the difference between our observations and these reports is that we used funisitis, rather than cord blood IL-6, as a marker of fetal inflammation. However, this explanation is uncertain because funisitis has been associated with higher cord blood IL-6 levels.(21) An additional study reported an association between histologic chorioamnionitis, but not funisitis or elevated cord blood IL-6 levels, and CLD risk.(22) That study enrolled more mature infants compared to our cohort. It is possible that the antecedents of lung injury may vary with gestational age, with inflammation more likely to influence risk among infants born after the 27th week of gestation. Finally, two additional studies identified increased CLD risk following chorioaminionitis, but only among infants also exposed to prolonged mechanical ventilation during the early neonatal period.(23,24) These studies used varying techniques for accounting for the effect of confounders. After extensive adjustment of our data for critical antenatal confounders, particularly FGR, we conclude that, among infants at the earliest gestations, intrauterine infection and inflammation does not increase the risk of CLD.

Several large, contemporary studies have previously identified an association between FGR and CLD risk. In one study of a geographically-defined population in the United Kingdom, which did not adjust for potential confounders, the risk of CLD was increased among small for gestational age (SGA) infants and decreased among large for gestational age infants.(25) A study of infants from a regional population in Germany found that SGA infants were at increased risk of CLD defined as treatment with oxygen at 28 days of age (26), an endpoint with less relevance in extremely immature infants. A third study found that infants considered growth restricted at birth, based on an obstetrical diagnosis of intrauterine growth restriction or by identifying infants who were SGA, were more likely than their normal

weight peers to need respiratory support of any kind at 28 days of age.(27) Several other small studies report associations between restricted fetal growth and CLD risk.(28-30) Despite methodologic differences between these studies and ours, collectively they support the strong relationship between impaired fetal growth and CLD risk.

Our findings suggest that processes that limit fetal growth may also limit fetal lung growth and maturation, thereby making the lung more vulnerable to adversities after birth. Lung development is highly programmed and regulated by a variety of growth factors and hormones. For example, a critical phase in lung development is angiogenesis under the influence of vascular endothelial growth factors and their receptors. Abnormal angiogenesis appears to be a feature in the pathogenesis of CLD.(31) (32) An imbalance between angiogeneic and anti-angiogeneic factors also appears to be a critical feature in the pathogenesis of preeclampsia(33) and among preeclamptic mothers who deliver an infant with growth restriction.(34) In the presence of preeclampsia, this imbalance might result in a cascade of events, including disruption of normal placental angiogenesis, a cardinal feature of preeclampsia, and abnormal fetal angiogenesis, including the vasculature of the fetal lung. Our observed association between increased syncytial knots in the placenta, a histologic correlate of preeclampsia(35), and CLD supports this hypothesized scheme of events. Although we did not observe an increase in CLD risk among infants of preeclamptic mothers who were not growth restricted, it is possible that abnormal angiogenesis in the fetal lung occurs only when preeclampsia reaches a sufficient severity to cause FGR.

Fetal growth restriction has also been attributed to the failure of the placenta to meet the fetus's needs for oxygen and substrate(36), and hypoxia may have secondary effects on the fetal lung. In neonatal mice, chronic hypoxia during the first two weeks of life, a period of lung development that corresponds to human fetal lung development during the third trimester, interferes with alveolar and pulmonary artery development and up-regulates transforming growth factor beta (TGFβ).(37) Therefore, it is possible that chronic fetal hypoxia in humans causes both growth restriction and impairment of lung development, the latter perhaps mediated by TGFβ.

FGR may also cause ineffective or abnormal lung growth after birth as a result of abnormal programming of growth. This possibility is suggested by two observational studies. In one study, lung function was measured at approximately 10 months of age in SGA infants and compared to measurements in appropriately grown premature infants.(38) Increased airway resistance was associated with FGR after adjustment for confounders, including CLD. This observation suggests that FGR may impact subsequent growth and development of small airways. Another study confirmed a relationship between FGR and small airway pathology by identifying an association between FGR and the risk of childhood asthma.(39)

Rather than influencing lung growth and morphology, factors that result in FGR may alter the biochemical milieu of the immature lung. Growth restricted mice have reduced expression of mRNA for surfactant proteins.(40) Perhaps significant alterations in the surfactant system predispose growth restricted infants to pulmonary abnormalities, resulting either from a direct effect on the role of surfactant in lung mechanics or in its modulating role in lung inflammation.

One potential limitation of our study might follow from our defining FGR on the basis of the relationship between an infant's birth weight and a birth weight distribution for each gestational age in a similar population. This method may misclassify infants who have genetically determined growth percentiles that are peculiarly high or low. As an alternative, when accurate measurements of birth length are available, ponderal index can be used as an indicator of growth restriction, which for some outcomes may be a more discriminating

predictor compared to BW Z-score.(39) Finally, BW Z-scores can be calculated using weight distributions derived from sonographically determined estimates of fetal weights in a healthy obstetrical population.(41) Compared to this approach, the use of BW Z-scores calculated from birth weight distributions appears to underestimate fetal growth prior to term and therefore the frequency of impaired fetal growth.(42)

Because of the observational design of our study, we cannot be certain that FGR is critical in the causal pathway of CLD. It is possible that FGR is merely a surrogate for other characteristics of the uterine environment that cause the fetal or neonatal lung to grow or function poorly. However, it seems likely that factors that control fetal somatic growth in general have a significant impact on lung growth and development, and in this way increase CLD risk. Therefore, the ability to modify neonatal pulmonary outcomes among ELGANs may be dependent on a more precise understanding of the modulators of fetal growth in the context of problems that result in FGR. Future investigation should focus on these factors.

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Abbreviations

ELGAN	extremely low gestational age newborn
CLD	chronic lung disease
PE	preeclampsia
FI	fetal indication
FGR	fetal growth restriction

Table 1

The risks of CLD relative to birth weight Z-score in strata of antenatal and delivery and infant characteristics available at the time of delivery. These are cell specific (%) risks (for infants who have both the column and row characteristics, as well as for the total sample).

		Birth weight Z-score			
Characteristics		**< -1**	**≥ −1**	**All**	**N**
Maternal race	White	74	50	54	721
	Non-white	74	41	51	520
Maternal smoking	Yes	60	52	53	172
	No	77	45	51	1037
Antenatal corticosteroid course	Complete	71	45	50	787
	Partial	80	48	54	326
	None	81	50	54	124
Delivery indication*	PTL	65	48	49	548
	pPROM	71	44	47	271
	Preeclampsia	76	41	65	167
	Abruption	94	49	55	128
	Cerv Insuf	50	42	42	73
	Fetal Indication	75	58	67	54
Cesarean delivery	Yes	75	45	52	823
	No	70	49	51	417
Fever**	Yes	83	67	68	71
	No	74	45	51	1116
Gestational age (wks)	23-24	88	76	78	255
	25-26	74	48	54	575
	27	68	25	33	411
Birth weight (g)	≤ 750	76	73	75	471
	751-1000	50	43	43	527
	> 1000	---	26	26	243
Birth weight Z-score†	< -2	78	---	78	77
	≥ −2, < −1	72	---	72	166

		Birth weight Z-score			
Characteristics		**< -1**	**≥ −1**	**All**	**N**
	> 1	---	46	46	998
Sex	Male	79	50	54	655
	Female	71	41	49	586
Fetuses	Single	77	46	53	842
	Multiple	67	47	50	399
Magnesium	None	75	47	52	398
	Tocolysis	70	46	49	670
	Seizure prophylaxis	77	47	64	162
Percent CLD		74	49	52	
Maximum N		243	998	1241	

* PTL=preterm labor, pPROM = preterm premature rupture of membrane, Cerv Insuf = cervical insufficiency; delivery Indications are mutually exclusive. (See reference #11.)

** within the interval from before delivery to 48 hours post delivery

† based Yudkin et al., reference # 15

Table 2

The risks of CLD relative to birth weight Z-score in strata of infants whose placenta harbored the organisms listed on the left. These are cell specific (%) risks.

		Birth weight Z-score			
Microorgansim		**< -1**	**≥ −1**	**All**	**N**
Aerobe	Yes	75	51	54	357
	No	76	43	51	762
Anaerobe	Yes	68	51	53	316
	No	78	44	51	803
Mycoplasma	Yes	60	44	47	116
	No	77	46	52	1003
# organisms isolated	0	78	44	51	570
	1	74	43	50	270
	2+	69	52	54	279
Skin organisms†	Yes	77	48	52	223
	No	71	45	52	896
Vaginal organisms††	Yes	76	51	53	178
	No	75	45	51	941
Percent CLD		76	46	52	
Maximum N		218	901	1119	

†Corynebacterium sp, Propionebacterium sp, Staphylococcus sp

††Prevotella bivia, Lactobacillus sp, Peptostrep magnus, Gardnerella vaginalis

Table 3

The risks of CLD relative to birth weight Z-score in strata of infants whose placenta had the histologic characteristic listed on the left. These are cell specific risks (%).

		Birth weight Z-score			
Histologic characteristic		**< -1**	**≥ −1**	**All**	**N**
Inflammation chorionic plate*	Yes	60	52	53	220
	No	77	46	52	919
Inflammation chorion/decidua†	Yes	76	49	52	426
	No	75	45	53	716
Neutrophils in fetal stem vessels	Yes	74	54	56	281
	No	75	45	51	849
Umbilical cord vasculitis††	Yes	81	46	50	186
	No	74	47	52	927
Thrombosis of fetal stem vessels	Yes	88	49	59	61
	No	74	47	52	1068
Infarct	Yes	75	47	57	192
	No	75	47	51	956
Increased syncytial knots	Yes	81	49	61	228
	No	70	47	50	925
Decidual hemorrhage & fibrin deposition	Yes	66	50	53	186
	No	77	47	52	949
Percent CLD		75	47	52	
Maximum number		221	937	1158	

*stage 3 and severity 3

†grades 3 and 4

††grades 3, 4 and 5

Table 4

The risks of CLD relative to birth weight Z-score in strata of infants who had the early postnatal characteristic listed on the left. These are cell specific risks (%).

		Birth weight Z-score			
Postnatal characteristics		**< -1**	**≥ −1**	**All**	**N**
SNAP-II	< 20	70	35	41	643
	20-29	68	55	58	309
	30+	88	66	71	268
Late bacteremia (wk 2-4)	None/suspected	67	42	47	739
	Presumed	88	55	62	184
	Definite	79	53	59	313
Mechanical ventilation* day 7	Yes	83	65	69	749
	No	47	23	26	491
Patent ductus arteriosus	Yes	77	54	58	824
	No	69	32	39	417
Pneumothorax	Yes	86	69	73	93
	No	73	45	50	1148
Interstitial emphysema	Yes	86	80	82	195
	No	71	40	46	1046
Respiratory group classification	EPPD†	82	65	69	508
	PD††	70	47	52	456
	Low FiO_2	52	13	17	240
Necrotizing Enterocolitis	No/Stage I, II‡	72	45	50	1141
	Stage IIIa‡	86	50	69	13
	Stage IIIb‡	92	61	69	49
	Isolated perforation	100	67	74	38
Percent CLD		74	49	52	
Maximum N		243	998	1241	

* includes high frequency

† EPPD = early and persistent pulmonary dysfunction (See text for description.)

†† PD = pulmonary deterioration (See text for description.)

‡ Modified Bell's classification (See reference #16.)

Table 5

The interrelationships among gestational age, extent of fetal growth restriction, and indication for preterm birth in predicting CLD. Each of the three sets of tables has one table that provides the number of children in each cell at risk of CLD, and one that provides cell-specific risks of CLD.

a. Pregnancy complication by gestational age

Numbers of infants at risk

		Delivery Indication*			
		PE	**FI**	**Other**	**N**
Gestational age (wks)	23-24	16	6	233	255
	25-26	82	27	466	575
	27	69	21	321	411
Maximum N		167	54	1020	1241

Cell-specific percent with CLD

		Delivery indication*		
		PE	FI	Other
Gestational age (wks)	23-24	81	100	77
	25-26	71	72	50
	27	54	52	28

b. Birth weight Z-score by gestational age

Numbers of infants at risk

		Birth weight Z-score			
		< -2	≥ −2, < −1	≥ −1	N
Gestational age (wks)	23-24	5	29	221	255
	25-26	51	82	442	575
	27	21	55	335	411
Maximum N		77	166	998	1241

Cell-specific percent with CLD

		Birth weight Z-score		
		< -2	≥ −2, < −1	≥ −1
Gestational age (wks)	23-24	60	93	76
	25-26	75	73	48

a. Pregnancy complication by gestational age					
Numbers of infants at risk					
		Delivery Indication*			
		PE	**FI**	**Other**	**N**
	27	90	60	25	
c. Birth weight Z-score by delivery indication					
Numbers of infants at risk					
		Birth weight Z-score			
		< -2	≥ −2, < −1	≥ −1	N
Delivery indication*	PE	46	65	56	167
	FI	11	17	26	54
	Other	20	84	916	1020
Maximum N		77	166	998	1241
Cell-specific percent with CLD					
		Birth weight Z-score			
		< -2	≥ −2, < −1	≥ −1	
Delivery indication*	PE	78	75	47	
	FI	82	71	58	
	Other	75	70	47	

*PE=preeclampsia; FI=fetal indication; Other=preterm labor, preterm premature rupture of membranes, abruption, cervical insufficiency

Table 6

Logistic regression models with odds ratios (95% confidence limits) of the risk of CLD as a function of delivery indication, gestational age and fetal growth restriction. The first two models, which do not include birth weight Z-scores, are in sub-samples defined by their birth weight Z-scores. The last model, based on the entire sample, includes variables for birth weight Z-score. All models include a hospital "cluster" term to account for center effects.

		Models		
	Variable	**Z-score < -1**	**Z-score ≥ -1**	**Total**
Delivery indication*	Preeclampsia	1.6 (0.8, 3.1)	1.2 (0.6, 2.2)	1.4 (0.9, 2.1)
	Fetal indication	1.7 (0.6, 4.9)	2.4 (0.99, 5.9)	**2.1 (1.04, 4.1)**
Gestational age**	23-24 wks	**3.7 (1.1, 12)**	**11 (7.3, 17)**	**9.9 (6.7, 15)**
	25-26 wks	1.4 (0.7, 2.7)	**3.0 (2.2, 4.2)**	**2.5 (1.9, 3.4)**
Birth weight Z-score***	≥ −2, < −1			**3.2 (2.1, 5.0)**
	<-2			**4.4 (2.3, 8.2)**

* The referent group for each delivery indication category is the category of infants delivered for all other indications.

** The referent group for each gestational age category is the category of infants born at 27 weeks.

*** The referent group for each birth weight Z-score category is the category of infants with Z-scores ≥ -1.