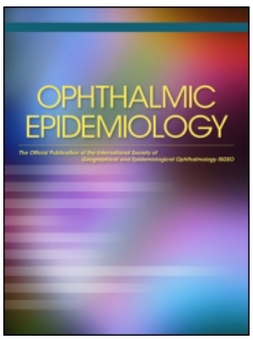

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ORIGINAL ARTICLE

Perinatal Risk Factors for the Retinopathy of Prematurity in Postnatal Growth and Rop Study

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ABSTRACT

Objective: To evaluate perinatal risk factors for retinopathy of prematurity (ROP), in a large, broad-risk cohort of premature infants.

Study design: Secondary analysis of data from the Postnatal Growth and ROP (G-ROP) Study, a retrospective cohort study of infants undergoing ROP examinations at 29 North American hospitals in 2006–2012.

Results: Among 7483 infants, 3224 (43.1%) had any ROP and 931 (12.4%) had severe ROP (Type 1 or 2 ROP). In multivariable logistic regression analysis, significant risk factors for any ROP were lower birth weight (BW, odds ratio (OR) = 5.2, <501 g vs. >1250 g), younger gestational age (GA, OR = 32, <25 vs. >29 weeks), 1-min Apgar score <4 (OR = 1.2), race (OR = 1.6, White vs. Black), outborn (OR = 1.5), and delivery room intubation (OR = 1.3); and for severe ROP were lower BW (OR = 20, <501 g vs. >1250 g), younger GA (OR = 30, <25 vs. >29 weeks), male (OR = 1.5), Hispanic ethnicity (OR = 1.8), race (OR = 1.6, White vs. Black), outborn (OR = 1.6), and delivery room intubation (OR = 1.6). Together, these factors predicted well for any ROP (area under ROC curve (AUC) = 0.87) and severe ROP (AUC = 0.89), but BW and GA were the dominant factors for ROP (AUC = 0.86) and severe ROP (AUC = 0.88).

Conclusions: Based on the largest report to date with detailed ROP data from infants meeting current screening guidelines, ROP risk is predominantly determined by the degree of prematurity at birth, with other perinatal factors contributing minimally.

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Risk factors; retinopathy of prematurity; perinatal; birth weight; gestational age

Introduction

Retinopathy of prematurity (ROP) is a significant cause of visual impairment and blindness in children.[1] As significant improvements in neonatal care have increased the survival of premature infants, epidemic rates of ROP are being observed in developing countries.[1,2] Early detection of ROP for timely treatment can reduce the risk of retinal detachment and blindness.[3,4] As ROP pathogenesis is multifactorial,[5] understanding ROP risk factors and particularly perinatal risk factors for ROP may facilitate earlier identification of high-risk infants at birth in order to direct resources for ROP screening and timely ROP treatment, thus reducing blindness from ROP.[6] Although various studies[7–12] have evaluated perinatal or postnatal risk factors for ROP, most of these studies are limited by small sample sizes, selective study populations or limited geographic settings, limiting their generalizability. Only a small percentage of examined infants require treatment, and examinations are stressful for the infants and resource intensive with regards to ophthalmologist, nursing, and ROP coordinator time, so having better data to guide screening decisions and examination frequency can directly impact care efficiency and resource allocation.

We completed a multicenter study that examined a large racially and geographically diverse cohort of infants undergoing ROP screening in the US and Canada.[13,14] The detailed data for perinatal risk factors and ROP examinations from this large, broad-risk cohort study provide a unique opportunity to evaluate perinatal risk factors for ROP. We sought to identify important perinatal risk factors for the development of ROP and of severe ROP.

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Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/iope.

Supplemental data for this article can be accessed here.

Methods

This is a secondary analysis of data from the Postnatal Growth and ROP (G-ROP) Study. Major features of the G-ROP Study related to data collection for risk factors and the ROP examinations are described below. Additional details about the design of the G-ROP Study are available in publication.[14]

The G-ROP Study was a multicenter, retrospective cohort study of infants who underwent ROP screening at 27 hospitals in the United States and 2 hospitals in Canada. Institutional Review Board approval for the study was obtained at all study sites, and waiver of informed consent was granted at each center.

The study enrolled infants born between 1 January 2006 and 31 December 2011 who underwent ROP examinations and had a known ROP outcome. All infants receiving ROP examinations were eligible for inclusion, without restriction by birth weight (BW) or gestational age (GA), so that there would not be a selection bias. However, the ROP screening criteria used during that time at the study hospitals were typically BW less than 1501 g, or GA less than 30 weeks, or an unstable clinical course, as determined by the neonatologist, in an infant with larger BW and/or older GA.[14] A known ROP outcome included Early Treatment of ROP Study Type 1 ROP, Type 2 ROP, or ROP treatment in *either* eye; or retinal vasculature maturity, immature vasculature extending into zone III without prior disease in zone I or II, or regression of ROP not reaching criteria for Type 1 or 2 ROP in *both* eyes.[14]

We specifically studied perinatal factors, defined as prenatal/maternal factors and immediate postnatal factors, but not later postnatal factors. Detailed infant characteristics, such as BW, GA, sex, and Apgar score at 1 min; birth characteristics, including mode of delivery (vaginal or cesarean), plurality (singleton, twin, etc.), birth location (inborn or outborn), delivery room resuscitation measures (epinephrine, intubation, supplemental oxygen, positive airway pressure, and chest compressions); and maternal characteristics, such as age, race, ethnicity, gravidity, prenatal care for this pregnancy, gestational diabetes, chorioamnionitis, treatment with prenatal steroids, and complete or partial course of steroids; were collected from the medical record by certified data abstractors. Detailed ROP data were collected from all ophthalmologic examinations until retinal vascular maturity or disease regression. All data were entered into a web-based database, and data quality was ensured through data entry validation rules, data audits, and discrepancy check algorithms, with investigation and resolution of all flagged values.

Statistical analysis

We described perinatal risk factors using percentages for categorical features, and mean with standard deviation for continuous measures. Small for gestational age (SGA) was determined as birth weight less than the 10 percentile for infants with the same gestational age and sex, using cutpoints derived from a large dataset of 3,986,456 preterm infants in the United States, Germany, Italy, Australia, Scotland and Canada.[15] We first analyzed risk factors for any stage ROP and for severe ROP using univariable logistic regression models followed by a multivariable logistic regression model that included risk factors with $p < .10$ in the univariable analyses. The multivariable model went through backward selection of risk factors, and the final multivariable model only retained risk factors with $p < .05$. The odds ratio (OR) and its 95% confidence intervals (95% CI) of each risk factor were calculated from the logistic regression models. These analyses were performed for any ROP and severe ROP, where severe ROP was defined as Type 1 ROP, Type 2 ROP, or ever having ROP treatment, in either eye.

The predictions for ROP and severe ROP using the statistically significant risk factors in the final multivariable logistic regression model were evaluated using area under receiver operating characteristic (ROC) curve (AUC). All statistical analyses were performed using SAS v9.4 (SAS Institute Inc., Cary, NC).

Results

Infant, maternal, and birth characteristics

Among 7483 infants enrolled in the G-ROP study and included in this analysis, the mean (SD) BW was 1099 (359) grams, the mean GA was 28 (3) weeks; 48% of infants were female, 74% of infants were inborn at a G-ROP hospital, and 30% of infants had a 1-min Apgar score <4. Initial resuscitation included supplemental oxygen in 54%, positive airway pressure in 77%, intubation in 55%, chest compression in 6%, and epinephrine in 3% of patients.

With regard to self-described maternal characteristics, 7.5% of mothers were Hispanic or Latino, 48% White, and 31% Black; 33% of births were via vaginal delivery, 28% of pregnancies were multiple gestations, 78% of mothers had received prenatal care, and 7.5% of mothers had gestational diabetes. Prenatal steroid treatment had been administered to 66% of mothers; 17% received a partial course, and 49% received a complete course of steroids.

ROP of any stage developed in 3224 (43%) infants. Severe ROP developed in 931 (12%) infants, including Type 1 ROP in 459 (6%) infants, Type 2 ROP in 472 (6%) infants and treated ROP in 524 (7%) infants.

Perinatal risk factors for any stage ROP

In univariable analysis for risk factors of any stage ROP, sex, maternal age, gravidity and prenatal care were not associated with ROP; birth weight, gestational age, Apgar score at 1 min, maternal ethnicity, maternal race, maternal diabetes, prenatal steroid treatment, mode of delivery, number of births, birth location, initial resuscitation (supplemental oxygen, positive airway pressure, intubation, chest compression, and epinephrine) were significantly associated with ROP. "Small for GA" was marginally associated with a lower risk of any stage ROP (OR = 0.87, p = .049). Univariable analysis results are shown in the left panels of Online Supplement Table 1 for infant characteristics, Online Supplement Table 2 for maternal characteristics and Online Supplement Table 3 for birth characteristics.

In multivariable analysis (Table 1), statistically significant perinatal risk factors for ROP were lower BW, younger GA, 1-min Apgar score <4 (OR = 1.2), race (OR = 1.6, White vs. Black), outborn delivery (OR = 1.5), and delivery room intubation (OR = 1.3). Maternal ethnicity, maternal diabetes, prenatal steroid treatment, mode of delivery, plurality, and other initial resuscitation measures (supplemental oxygen, positive airway pressure, chest compression, epinephrine), which were all significant in univariable analysis, became non-significant in multivariable analysis.

These six statistically significant risk factors in combination predicted ROP well, with an AUC of 0.87 (95% CI: 0.86–0.88) (Figure 1). However, the marginal improvement in prediction comparing this combination of risk factors to prediction of ROP using BW alone (AUC = 0.83 95% CI: 0.82–0.84), GA alone (AUC = 0.85, 95% CI: 0.84–0.85), or a combination of BW and GA (AUC = 0.86, 95% CI: 0.85–0.87), was minimal, despite statistical significance (Table 2).

Perinatal risk factors for severe ROP

In univariable analysis for risk factors of severe ROP, SGA, maternal age, gravidity, prenatal care, plurality, and supplemental oxygen use for initial resuscitation were not associated with severe ROP, while all other risk factors including birth weight, gestational age, sex, Apgar score, maternal ethnicity, maternal race, maternal diabetes, prenatal steroid treatment, mode of

Table 1. Multivariable analysis for perinatal risk factors of **any ROP (N = 7373*).**

Risk factors	# of infants	ROP cases (%)	OR (95% CI)	P-value
Birth weight (grams)				<0.0001
≤500	110	98 (87.3%)	5.20 (2.76–9.80)	
501–750	1310	1134 (86.6%)	6.04 (4.63–7.87)	
751–900	1084	737 (68.0%)	3.66 (2.91–4.59)	
901–1000	700	359 (51.3%)	2.47 (1.96–3.13)	
1001–1100	721	281 (39.0%)	2.10 (1.68–2.63)	
1101–1250	1001	263 (26.3%)	1.61 (1.31–1.97)	
≥1251	2447	293 (12.0%)	1.00	
Gestational age (weeks)				<0.0001
≤24	778	738 (94.9%)	32.3 (21.7–48.2)	
25	675	560 (83.0%)	11.3 (8.44–15.2)	
26	793	573 (72.3%)	7.55 (5.86–9.72)	
27	873	451 (51.7%)	4.21 (3.37–5.27)	
28	953	356 (37.4%)	3.06 (2.49–3.78)	
29	869	231 (26.6%)	2.33 (1.89–2.87)	
≥30	2432	254 (10.4%)	1.00	
Apagar score at 1 minute*				0.004
≥4	5104	1833 (35.9%)	1.00	
<4	2269	1330 (58.6%)	1.23 (1.07–1.41)	
Maternal race				<0.0001
Black	2285	985 (43.1%)	1.00	
White	3555	1587 (44.6%)	1.64 (1.42–1.89)	
Asian	232	68 (29.3%)	0.75 (0.51–1.11)	
American Indian/Alaskan Native	40	13 (32.5%)	1.19 (0.53–2.70)	
Native Hawaiian/Other Pacific Islander	92	19 (20.7%)	0.29 (0.16–0.55)	
Other	513	216 (42.1%)	1.25 (0.96–1.62)	
Unknown	656	275 (41.9%)	1.07 (0.85–1.35)	
Birth location				<0.0001
Inborn	5480	2123 (38.7%)	1.00	
Outborn	1893	1040 (54.9%)	1.48 (1.29–1.71)	
Intubation				0.0009
No	3355	777 (23.2%)	1.00	
Yes	4018	2386 (59.4%)	1.27 (1.10–1.46)	

OR = odds ratio; CI = confidence interval; ROP = retinopathy of prematurity.
*Missing data occurred in 110 infants for Apgar score at 1 min and were excluded from analysis.

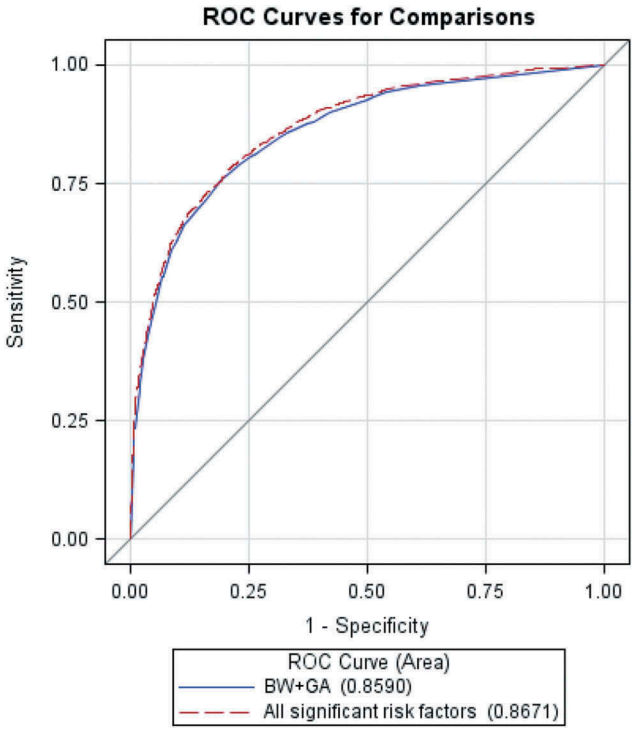

Figure 1. ROC curves for prediction of **any ROP** using birth weight and gestational age with and without including other risk factors (Apgar score at 1 min, maternal race, birth location and intubation).

delivery, birth location, and initial resuscitation (positive airway pressure, intubation, chest compression, and epinephrine) were significantly associated with severe ROP in univariable analysis. The univariable analysis is shown in the right panels of Online Supplement Table 1 for infant characteristics, Online Supplement Table 2 (online) for maternal characteristics and Online Supplement Table 3 for birth characteristics.

In multivariable analysis (Table 3), statistically significant perinatal risk factors for severe ROP were lower BW, younger GA, male sex (OR = 1.5), Hispanic ethnicity (OR = 1.8), race (OR = 1.7, White vs. Black), outborn delivery (OR = 1.6), absence of positive airway pressure (OR = 1.4), and delivery room intubation (OR = 1.6). One-minute Apgar score, maternal diabetes, prenatal steroid treatment, mode of delivery, plurality and other initial resuscitation measures (chest compression, epinephrine) that were significant in univariable analysis became non-significant in multivariable analysis.

These statistically significant perinatal risk factors in combination predicted well for severe ROP with an AUC of 0.89 (95% CI: 0.88–0.90) (Figure 2). However, the marginal improvement in prediction in comparison to using BW alone (AUC = 0.85, 95% CI: 0.83–0.86), GA alone (AUC = 0.87, 95% CI: 0.86–0.88), or a combination of BW and GA (AUC = 0.88, 95% CI: 0.87–0.89), was minimal despite statistical significance (Table 2).

Discussion

In the largest ROP perinatal (prenatal and immediate postnatal) risk factors analysis to date among infants meeting current ROP screening guidelines,[16,17] we found that ROP risk is predominantly determined by the birth weight and gestational age, with other perinatal risk factors contributing minimal additional predictive information. Our study confirmed smaller BW or lower GA are the most important perinatal risk factors for both ROP and severe ROP. In multivariable analysis, both BW and GA were associated with ROP and severe ROP in a "dose-response" manner. In particular, the OR of severe ROP was 30 for infants with GA 24 weeks or less compared to infants with GA 30 weeks or greater, and the OR of severe ROP was 20 for infants with BW 500 g or less compared to infants with BW greater than 1250 g. These results are consistent with previous studies in various populations that showed increasingly greater prematurity is a strong risk factor for ROP.[5,8,9,18–29] Low BW and early GA are surrogate measures for retinal neural and vascular immaturity at birth, both of which are important factors in the development of ROP. Retinal development results in increasing metabolic demand, localized-hypoxia-

Table 2. The prediction of any ROP and severe ROP from statistically significant risk factors.

	Any ROP (N = 7373[§])		Severe ROP (n = 7483)	
Risk factors	AUC (95% CI)	P-value*	AUC (95% CI)	P-value*
All significant risk factors[□]	0.87 (0.86–0.88)		0.89 (0.88–0.90)	
Birth weight	0.83 (0.82–0.84)	<0.0001	0.85 (0.83–0.86)	<0.0001
Gestational age	0.85 (0.84–0.85)	<0.0001	0.87 (0.86–0.88)	<0.0001
Birth weight + Gestational age	0.86 (0.85–0.87)	<0.0001	0.88 (0.87–0.89)	<0.0001

AUC = Area under ROC curve; CI = confidence interval; ROP = retinopathy of prematurity.
[□]Statistically significant risk factors for any ROP include birth weight, gestational age, Apgar score at 1 min, maternal race, birth location and intubation; the statistically significant risk factors for severe ROP include birth weight, gestational age, gender, maternal ethnicity, maternal race, birth location, positive airway pressure and intubation.
[§]Missing data occurred in 110 infants for Apgar score at 1 min and were excluded from analysis.
*For comparison between predictions using all significant risk factors versus predictions using birth weight alone, using gestational age alone, using the combination of birth weight and gestational age.

Table 3. Multivariable analysis for perinatal risk factors of **severe ROP** (N = 7483).

Risk factors	# of infants	Severe ROP cases (%)	OR (95% CI)	P-value
Birth weight (grams)				<0.0001
≤500	112	69 (61.6%)	20.4 (9.91–42.1)	
501–750	1341	512 (38.2%)	7.08 (3.86–13.0)	
751–900	1098	197 (17.9%)	3.77 (2.06–6.89)	
901–1000	707	73 (10.3%)	3.09 (1.66–5.76)	
1001–1100	725	33 (4.6%)	1.92 (1.00–3.70)	
1101–1250	1011	29 (2.9%)	1.95 (1.03–3.70)	
≥1251	2489	18 (0.7%)	1.00	
Gestational age (weeks)				<0.0001
≤24	797	393 (49.3%)	30.3 (15.3–60.3)	
25	691	236 (34.2%)	20.3 (10.3–40.3)	
26	801	150 (18.7%)	11.4 (5.79–22.6)	
27	884	82 (9.3%)	7.37 (3.74–14.5)	
28	962	39 (4.1%)	3.99 (2.00–7.97)	
29	879	18 (2.1%)	2.62 (1.25–5.50)	
≥30	2469	13 (0.5%)	1.00	
Sex				<0.0001
Female	3575	406 (11.4%)	1.00	
Male	3908	525 (13.4%)	1.47 (1.24–1.74)	
Maternal ethnicity				0.0002
Hispanic or Latino	564	83 (14.7%)	1.75 (1.25–2.46)	
Not Hispanic or Latino	5251	560 (10.7%)	1.00	
Unable to answer	1668	288 (17.3%)	1.43 (1.16–1.75)	
Maternal race				<0.0001
Black	2310	265 (11.5%)	1.00	
White	3615	454 (12.6%)	1.67 (1.37–2.02)	
Asian	233	27 (11.6%)	2.03 (1.21–3.40)	
American Indian/Alaskan Native	40	4 (10.0%)	2.11 (0.61–7.37)	
Native Hawaiian/Other Pacific Islander	93	5 (5.4%)	0.68 (0.25–1.85)	
Other	526	76 (14.5%)	1.26 (0.87–1.82)	
Unknown	666	100 (15.0%)	1.34 (0.97–1.85)	
Birth location				<0.0001
Inborn	5512	536 (9.7%)	1.00	
Outborn	1971	395 (20.0%)	1.55 (1.30–1.85)	
Positive airway pressure				0.0003
Yes	5729	676 (11.8%)	1.00	
No	1754	255 (14.5%)	1.43 (1.18–1.72)	
Intubation				0.0003
No	3404	117 (3.4%)	1.00	
Yes	4079	814 (20.0%)	1.55 (1.22–1.96)	

OR = odds ratio; CI = confidence interval; ROP = retinopathy of prematurity.

induced retinal vascular endothelial growth factor (VEGF) secretion, and VEGF-mediated retinal vessel development. In addition, the earlier the GA at birth, the greater the loss of factors normally provided by the intrauterine environment for which the immature fetus is unable to take over production, specifically insulin-like growth factor 1 (IGF-1). IGF-1 plays a permissive role in VEGF-mediated retinal vessel development, so low postnatal serum IGF-1 results in poor retinal vessel development and worsening localized hypoxia in the retina. Finally, earlier GA at birth increases the duration of an infant's potential exposure to adverse postnatal insults, such as sepsis and necrotizing enterocolitis, which also contribute to the risk of ROP, at least in part through lower serum IGF-1 levels.[5] Consistent with other studies,[5,18,28] our study found GA was marginally more predictive than BW for both ROP (AUC = 0.85 vs. 0.83) and severe ROP (AUC = 0.87 vs. 0.85).

We found some perinatal risk factors in addition to BW and GA were significantly associated with ROP or severe ROP. Specifically, we found that white race, outborn delivery, and delivery room intubation were significantly associated with higher risks of both ROP and severe ROP; while a 1-min Apgar score less than 4 was associated with a higher risk of ROP; and male sex, Hispanic ethnicity and absence of positive airway pressure use were associated with a higher risk of severe ROP. Male sex and White race have been shown to be associated with a higher risk of ROP in several large studies.[8,28,30,31] However, in spite of statistically significant associations with ROP or severe ROP, combinations of these perinatal risk factors did not add much predictive information over just BW and GA, with AUC only increased by 0.01 for predicting ROP and severe ROP. Therefore, there may be little value to considering these other perinatal factors in ROP risk stratification, as they do not add much additional predictive information over just BW and GA, and logistical resources that would be devoted to collecting such data can be saved.

We found maternal age, SGA, gravidity, prenatal care, maternal diabetes, prenatal steroids use, mode of delivery, multiparity and other resuscitation measures were not independently associated with ROP or severe ROP.

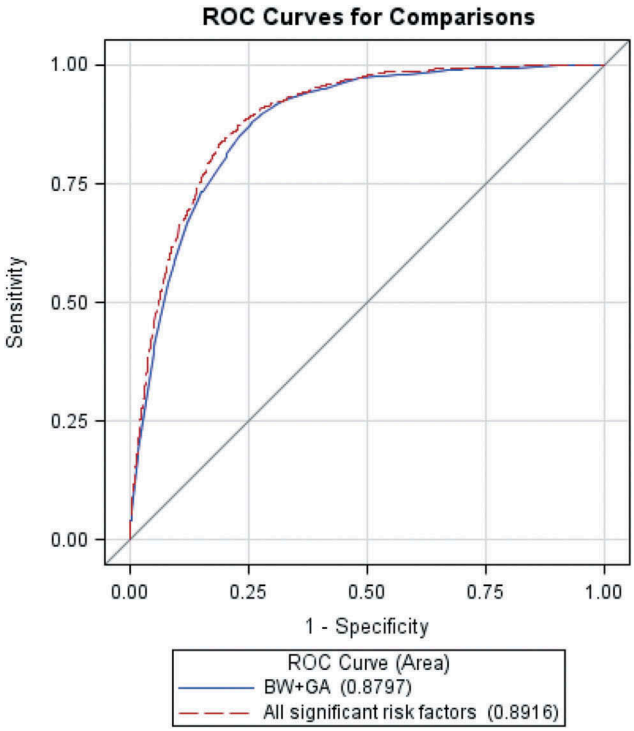

Figure 2. ROC curve for prediction of **severe ROP** using birth weight and gestational age with and without the inclusion of other risk factors (gender, maternal ethnicity, maternal race, birth location, positive airway pressure and intubation).

The largest previous study by Darlow et al. evaluated the prenatal and perinatal risk factors for clinically severe (stage 3 or 4) ROP among 4382 infants born in 1998–2001 with GA of <29 weeks in the Australian and New Zealand Neonatal Network. They found that only male sex, lower GA, and lower weight for GA were independently associated with clinically severe ROP, and these three risk factors predicted well for severe ROP with an AUC of 0.80–0.82,[8] similar to our study findings. Similarly, they found that maternal age, plurality, and prenatal steroid use were not associated with severe ROP. Aside from a sample size nearly double that of the Darlow et al. study, our study differs from this study in several ways. First, our study evaluated perinatal risk factors for both any stage ROP and severe ROP where the determination of severe ROP considered ROP stage, ROP zone, and the presence of plus disease, while Darlow et al. defined clinically severe ROP as stage 3 or 4 without consideration of ROP zone or presence of plus disease. Second, we studied all infants meeting ROP screening criteria, including those large BW and older GA infants with an unstable clinical course, while Darlow et al. only evaluated the risk factors among infants with GA less than 29 weeks. Finally, our study is racially and ethnically diverse, potentially making our results more generalizable.

In our study, we defined SGA as birth weight less than the 10 percentile of infants with the same gestational age and sex, using robust cutpoints derived from a large dataset of approximately 4 million preterm infants from the United States, Germany, Italy, Australia, Scotland and Canada.[15] We found that SGA was not associated with increased risk of any stage ROP or severe ROP, in contrast to the findings of many investigators using smaller study cohorts to examine the association between SGA and ROP. Our finding was consistent with a study of 345 very low BW infants in Brazil,[32] but in a case-control study of European infants, Allegaert et al. found that BW less than the 10th percentile for GA was associated with increased risk (relative risk 3.7) of threshold ROP.[33] Similarly, Darlow et al. found preterm infants in Australia and New Zealand with BW more than two standard deviations below the mean had twice the risk of stage 3 or 4 ROP. These inconsistencies in the association of SGA with ROP across studies could be due to the use of different reference growth charts for defining SGA. Lundgren et al. found that the choice of reference growth chart for defining SGA provided different associations with ROP.[34] In their study of 2941 preterm infants from Sweden and North America, SGA defined using a Swedish growth chart was not associated with treatment-requiring ROP, while SGA defined using a Canadian growth chart was associated with increased risk of treatment-requiring ROP.[34]

This study specifically focused on the evaluation of prenatal and immediate postnatal risk factors, as such risk factors can be used to make predictions of the risk of ROP at the time of birth. We did not evaluate later postnatal risk factors that may have significant predictive information with regards to ROP risk stratification. Two important postnatal factors include excessive oxygen administration and slow postnatal weight gain. High arterial oxygen saturations cause inhibition of retinal vascular development and damage to nascent retinal vessels. Slow postnatal weight gain is a surrogate measure for low serum IGF-1, which also results in poor retinal vessel growth. Multiple other reported risk factors for ROP may also be predictive, including sepsis, necrotizing enterocolitis, thrombocytopenia, and red blood cell transfusion, although many of the factors may cause lowering of serum IGF-1 and therefore by captured through measurements of slow postnatal weight gain.

With regards to the study limitations, the study data were collected retrospectively. However, the types of medical information evaluated were chosen to be reliably collectable from the medical record. The ROP examinations were not subject to a study schedule or

confirmed using photographic documentation, but the examiners were pediatric ophthalmologists and retinal specialists with clinical expertise in ROP management, using standard International Classification of ROP terminology and national scheduling recommendations with regards to the diagnosis of ROP. Another important consideration is generalizability. The very large sample size and geographically and racially diverse study sample increases the likely generalizability of the findings to other preterm infants in North America and more generally to infants in countries with highly developed neonatal care systems. However, the findings are of less generalizability to settings where excessive oxygen use or other postnatal risk factors more directly drives the development of ROP. In such areas with developing neonatal care, which are of the most resource-starved areas, excessive oxygen use leads to a true "oxygen-induced retinopathy" with larger BW and older GA infants developing treatment-requiring disease. Finally, unidentified genetic factors may further limit the generalizability of our results to other populations of preterm infants.

We used data from a multicenter study that enrolled a large, racially and geographically diverse cohort of infants undergoing ROP screening examinations in North America. We found ROP risk is predominantly determined by birth weight and gestational age, together they provided AUC of 0.86 for any ROP and 0.88 for severe ROP. Although we also found that other factors, such as male sex, hispanic ethnicity, White race, low Apgar score at 1 min, and delivery-room intubation were associated with ROP or severe ROP, these perinatal risk factors contributed minimal additional information to the prediction of ROP risk (AUC increase less than 0.02). Future study of later postnatal risk factors, such as oxygen administration and slow postnatal weight gain, may provide additional predictive value for ROP screening decisions and schedules.

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