Relationships between Maternal Ethnicity, Gestational Age, Birth Weight, Weight Gain, and Severe Retinopathy of Prematurity

Shahid M. Husain, MD[1,2], Ajay K. Sinha, MD[1,3], Catey Bunce, DSc[4], Puneet Arora, MRCPCH[2], Wilson Lopez, FRCPCH[2], Kwok S. Mun, MBChB[2], M. Ashwin Reddy, FRCOphth[3,5], and Gillian G. W. Adams, FRCOphth[2,5]

Objective To develop an algorithm that allows advanced identification of infants requiring treatment for retinopathy of prematurity (ROP).

Study design A retrospective observational study was performed at 2 tertiary neonatal units serving a multiethnic population in the UK, using data on 929 infants eligible for ROP screening. The relationships between study variables and the risk of developing ROP requiring treatment were analyzed using multiple logistic regression.

Results After applying exclusion criteria, data from 589 infants were analyzed; of these, 57 required laser treatment. The proportion of treated infants was 5.9% of those born to black mothers, 9.39% of those born to white mothers, and 12.8% of those born to Asian mothers ($P = .047$). Multiple logistic regression showed that gestational age, birth weight, maternal ethnicity, and early weight gain were predictors for the development of ROP requiring treatment, with maternal ethnicity having greater predictive power compared with early weight gain. We developed an algorithm for predicting the development of ROP requiring treatment with sensitivity, specificity, and positive and negative predictive values of 100%, 65.7%, 23.8%, and 100%, respectively.

Conclusion Gestational age, birth weight, early weight gain, and maternal ethnicity are important predictors for the development of ROP requiring treatment. In a multiethnic population, an algorithm to predict development of ROP requiring treatment should include maternal ethnicity. If confirmed through prospective studies, this algorithm could reduce the number of opthalmologic examinations performed for ROP screening. *(J Pediatr 2013;163:67-72)*.

Retinopathy of prematurity (ROP) is a retinal neovascular disease that occurs in preterm and/or very low birth weight (VLBW) infants (defined as birth weight [BW] <1500 g). Most ROP is mild or moderate and will regress, but severe ROP causes blindness. Estimates suggest that ROP is the cause of blindness in at least 50 000 children in countries with levels of development ranging from low to high.[1] Some have expressed concern that improvements in perinatal services and neonatal outcomes in developing countries might lead to another epidemic of ROP similar to the one that arose in developed countries in the 1970s.[2]

The etiology and pathogenesis of ROP are complex and not fully understood. Low gestational age (GA), VLBW, and hyperoxia are known risk factors. ROP appears to develop in 2 phases. Initially, the relative hyperoxic environment after preterm birth interrupts normal vascular growth; this is followed by delayed retinal vascularization and then neovascularization, depending on the balance of angiogenic and angiostatic factors. Vascular endothelial growth factor and insulin-like growth factor 1 (IGF-1) are thought to play roles in the development of the neovascular process.[3]

The development of ROP cannot be prevented, and thus infants believed to be at risk are entered into screening programs embedded in the neonatal services of developed countries. Screening guidelines vary among countries, but infants born at <32 weeks GA or at VLBW are generally screened. The aim of these programs is to detect infants who have developed severe ROP and to halt the progression of ROP, usually with laser therapy and in some cases with anti–vascular endothelial growth factor therapy.

Although many infants born at <32 weeks GA develop early-stage ROP, in most cases ROP does not progress and resolves spontaneously.[4] Less than 10% of infants who develop ROP require treatment to reduce the risk of an unfavorable outcome.[5-11] Screening and treatment for ROP require significant infrastructure investment, coordination, and skilled ophthalmology resources.[12] Infants in screening programs undergo repeated ophthalmologic examinations that are not without side effects.[13,14]

BW	Birth weight
GA	Gestational age
IGF-1	Insulin-like growth factor 1
NHS	National Health Service
ROP	Retinopathy of prematurity
VLBW	Very low birth weight

From the [1]Center for Pediatrics, Barts and the London School of Medicine and Dentistry, Queen Mary College; [2]Department of Neonatology, Homerton University Hospital NHS Foundation Trust; [3]Department of Neonatology, Barts Health NHS Trust; [4]Department of Research and Development, National Institute for Health Research Biomedical Research Center for Ophthalmology, and [5]Department of Pediatric Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust, London, United Kingdom

Supported by Homerton University Hospital NHS Foundation Trust. The authors declare no conflicts of interest.

Portions of this study were presented at the European Society of Paediatric Research Meeting, October 14-17, 2011, Newcastle, UK.

 http://dx.doi.org/10.1016/j.jpeds.2012.12.038

The majority of infants deemed to be at risk for ROP could avoid screening if tools other than ophthalmologic examinations were available to accurately identify those infants who will later develop ROP requiring treatment. An algorithm incorporating GA, BW, and cumulative early postnatal weight gain was developed and initially validated in Swedish populations of preterm infants, who were likely largely white.[8] Ethnicity is another risk factor associated with the development of ROP requiring treatment,[9,15,16] but its significance in a predictive model of ROP is unknown.

The aim of the present study was to develop an algorithm using the relationships among GA, BW, early weight gain (defined as cumulative weight gain from birth to age 6 weeks), maternal ethnicity, and the development of ROP requiring treatment.

Methods

A retrospective observational study was performed at Homerton University Hospital National Health Service (NHS) Foundation Trust and Barts and the London NHS Trust. Both hospitals have tertiary neonatal units serving a high-risk, multiethnic population in northeast London. This population's country of origin is mainly the UK (60%), but significant numbers of residents have migrated from Bangladesh, India, Pakistan, and Sri Lanka (21%) and from Africa and the Caribbean (12%). The study received ethical approval from the UK National Research Ethics Service.

Infants born between January 1, 2006, and July 31, 2010 (for Barts and the London NHS Trust) and January 1, 2006, and December 31, 2009 (for Homerton University Hospital NHS Foundation Trust) who fulfilled the UK ROP guideline criteria[17] and who were admitted to the neonatal units at these hospitals within the first 48 hours of life were eligible for this study. Exclusion criteria were major congenital anomaly, congenital infection, chromosomal abnormality, death before the start or end of ROP screening, and ROP screening performed at another center or outcome unknown.

Infants eligible for ROP screening were identified from local databases. Infants in both hospitals were screened by pediatric ophthalmologists in accordance with current UK guidelines. In the UK, ROP screening criteria are GA <32 weeks and BW <1501 g. The first screening examination is performed at 30-31 weeks postmenstrual age in infants born at <27 weeks GA and at 4-5 weeks postnatal age in infants born at 27-32 weeks GA or >32 weeks GA but with BW <1501 g. ROP screening was performed using RetCam (Clarity Medical Systems, Pleasanton, California) imaging and/or indirect ophthalmoscopy. All infants were screened weekly or biweekly depending on retinal examination findings. The examinations were continued until vascularization had extended into zone 3 or regression of ROP was detected on at least 2 successive examinations. Staging of ROP was recorded using the grading system of the International Committee for the Classification of Retinopathy of Prematurity,[18] and treatment was undertaken in accordance with Early Treatment for Retinopathy of Prematurity Study criteria.[6]

Data on BW, GA, routinely measured weekly weight, and maternal ethnicity were obtained from case records and local databases. GA was determined from dating ultrasound scans, date of mother's last menstrual period, or clinical estimation, in that order of preference. Weight measurements for infants transferred back from the 2 tertiary units to local referring hospitals were obtained from a national neonatal database housed by the BadgerNet platform (http://www.clevermed.com). This database, used by the majority of neonatal units in the UK, captures a number of variables, including infant weight measurements and ROP screening outcome. Weight measurements were used to calculate early weight gain by subtracting BW from weight at age 6 weeks. Maternal ethnicity was self-reported and combined into categories commonly used in the UK: black (eg, African, Afro-Caribbean), white (eg, European, North American, Australian), Asian (eg, Bangladeshi, Indian, Pakistani, Sri Lankan), and other (eg, central and southeast Asian [eg, Chinese, Japanese], South American, Middle Eastern).

Summary statistics were computed for all study variables and are presented as median (IQR) because of nonnormality of the data. Data analysis was performed on the entire cohort of infants and on a subgroup in whom complete weight data were available. Rank-sum tests were used to assess for any associations between developing ROP requiring treatment and BW, GA, and early weight gain. The Kruskal-Wallis test was used to assess for any associations between maternal ethnicity and BW, GA, and early weight gain. The Fisher exact test was used to test for any association between ROP requiring treatment and maternal ethnicity. Given the marked difference between rates of treatment for ROP in black and nonblack infants, further analyses were performed to examine ethnicity as a 2-factor variable (black vs nonblack). Logistic regression was then used to assess the evidence for the odds of developing ROP requiring treatment related to each of the study variables. Variables that were significant at the 0.1 level were entered into a multivariate model.

In infants with incomplete weekly weight data, regression analysis was used to impute missing data on weight, and the multivariate model was refitted using the imputed weight data. A receiver operating characteristic curve was constructed for the multivariate logistic regression model, and summary statistics were computed for a model with a cutoff probability of 0.015.

Results

The number of infants eligible for ROP screening and included in the study is shown in the **Figure**. A common reason for incomplete weight data in 211 infants was that these infants were of higher GA and BW and were