ARTICLE IN PRESS

Advances in Ophthalmology and Optometry ■ (2018) ■–■

ADVANCES IN OPHTHALMOLOGY AND OPTOMETRY

Prediction Models for Retinopathy of Prematurity

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Keywords

• Infant • Prediction model • Retinopathy of prematurity • Risk model

Key points

- Slow postnatal growth is a surrogate measure for low serum insulin-like growth factor 1, which is an important risk factor for severe retinopathy of prematurity.
- Risk models that consider postnatal weight gain, along with birth weight and gestational age, predict severe retinopathy of prematurity with greater specificity than current screening guidelines.
- Two important limitations are model development study sample size and poor generalizability in countries with developing neonatal care systems.
- Postnatal growth-based models have great potential to reduce the number of diagnostic examinations for retinopathy of prematurity being performed.

INTRODUCTION

Retinopathy of prematurity (ROP) is a disease of the developing retinal vasculature that affects premature infants. It is one of the leading causes of preventable childhood blindness [1]. Infants at risk for developing ROP undergo serial retinal examinations to identify treatment-requiring disease and undergo laser retinal photocoagulation or intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agent to decrease the risk of retinal detachment [2,3]. In the United States, the current screening guidelines recommend that infants receive ophthalmologic examinations if they either have a birth weight (BW) of less than 1501 g or a gestational age (GA) at birth of 30 weeks or less [4]. Approximately 70,000 infants per year meet these criteria in the United

Disclosure: The authors have nothing to disclose.

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https://doi.org/10.1016/j.yaoo.2018.04.003
2452-1760/18/

States. This simple screening model has high sensitivity, catching nearly all cases of severe ROP, but low specificity, because only about 5% of infants examined require treatment [3,5–11]. In addition, the availability of ophthalmologists with expertise in ROP management serves as a barrier to screening in many areas [12]. As a result, there have been efforts to develop a predictive model incorporating risk factors in addition to BW and GA, to improve the specificity of the screening process [13].

Prognostic models allow clinicians to predict a patient's risk of developing a specific medical outcome, such as severe ROP [14]. The current ROP screening guidelines are a simple risk model, consisting of 2 dichotomized factors: BW and GA. This "model" has less than 100% sensitivity for predicting severe ROP, because infants with BW and GA above the screening thresholds uncommonly develop severe ROP, so a subjective third criterion exists for larger BW and GA infants who have a poor postnatal course in the judgment of the neonatologist. This third criterion is a practical but unsystematic approach to incorporating predictive information from other risk factors for ROP.

Through landmark work, Smith, Hellstrom, Lofqvist, and colleagues have demonstrated that although there are many risk factors associated with severe ROP, low insulin-like growth factor 1 (IGF-1) plays a role in the pathogenesis of ROP and represents a potential common pathway through which many other risk factors act to increase risk for ROP. Postnatal weight gain is a surrogate measure for IGF-1 and similarly is predictive of ROP. In countries with highly developed neonatal care systems, predictive models that include postnatal weight gain have been able to accurately predict ROP risk while reducing the number of infants who need examinations, compared with the current screening guidelines. These weight gain–based models include WINROP, which calculates and accumulates deviations from expected weight gain over time; ROPScore and CHOP ROP, which consist of logistic-regression based equations; and CO ROP, which includes weight gain, BW, and GA criteria. Each of these models, however, were developed using cohorts with small numbers of infants developing severe ROP and did not perform adequately in subsequent validation studies, as discussed elsewhere in this article. The Postnatal Growth and ROP (G-ROP) Study addresses this limitation by using very large cohorts for model development and validation. Nevertheless, such models are not generalizable to regions with developing neonatal care systems, owing to differing pathogenesis of disease.

INSULIN-LIKE GROWTH FACTOR-1, GROWTH, AND RETINOPATHY OF PREMATURITY

The weight-based ROP predictive models are rooted in a current understanding of ROP pathogenesis, based largely on the work of Smith and colleagues. VEGF is a vasoactive factor that induces retinal vessel growth during development in response to hypoxia in the developing retina. IGF-1 is a somatic growth factor that plays a permissive role for VEGF activity [15,16]. During