

Predicting Proliferative Retinopathy in a Brazilian Population of Preterm Infants With the Screening Algorithm WINROP

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Objective: To retrospectively validate the WINROP (weight, insulinlike growth factor I, neonatal, retinopathy of prematurity [ROP]) algorithm in a Brazilian population. WINROP aims to predict ROP and is based on longitudinal weight measurements from birth until postmenstrual age 36 weeks. WINROP has predicted 100% of severe ROP in 3 neonatal intensive care unit settings in the United States and Sweden.

Methods: In children admitted to the neonatal intensive care unit at Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, from April 2002 to October 2008, weight measurements had been recorded once a week for children screened for ROP, 366 of whom had a gestational age of 32 weeks or less. The participating children had a median gestational age of 30 weeks (range, 24-32 weeks) at birth and their median birth weight was 1215 g (range, 505-2000 g).

Results: For 192 of 366 children (53%), no alarm or low-risk alarm after postmenstrual age 32 weeks occurred. Of these, 190 of 192 did not develop proliferative disease. Two boys with severe sepsis who were treated for ROP received low-risk alarms at postmenstrual age 33 and 34 weeks, respectively. The remaining 174 children (47%) received high- or low-risk alarms before or at 32 weeks. Of these infants, 21 (12%) developed proliferative ROP.

Conclusions: In this Brazilian population, WINROP, with limited information on specific gestational age and date of weight measurement, detected early 90.5% of infants who developed stage 3 ROP and correctly predicted the majority who did not. Adjustments to the algorithm for specific neonatal intensive care unit populations may improve the results for specific preterm populations.

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PRETERM INFANTS ARE ROUTINELY and repeatedly screened with eye examinations starting at approximately 30 to 32 weeks' postmenstrual age (PMA) until the retina is fully vascularized (approximately 40 weeks' PMA). These examinations are performed to identify those infants who will need laser or cryotherapy to help prevent retinal detachment, although fewer than 10% of those screened require treatment.^{1,2} Recently, we have published 2 reports that indicate that monitoring postnatal weight development and insulinlike growth factor I with the algorithm WINROP (weight, insulinlike growth factor I, neonatal, retinopathy of prematurity [ROP]) might be a robust and safe screening tool to predict early a select group of infants who need eye examinations for ROP.^{3,4} WINROP calculates the difference between expected weight gain, obtained from infants with no or stage 1 ROP, and observed values of postnatal weight development at each point. Based on this difference, a risk for developing severe ROP is

calculated each week and thereafter accumulated. The sensitivity of WINROP in Swedish and US neonatal intensive care unit populations has been shown to be 100% and data indicate that the number of infants needing ophthalmologic screening could be reduced by about 75%. Recently, we have demonstrated the efficacy of the algorithm using weight development only.^{5,6} This retrospective study was conducted to validate WINROP using weight development only in infants born with a gestational age (GA) of 32 weeks or less in a developing country where poor early weight gain had previously been reported to be associated with severe ROP.⁷

METHODS

PATIENTS

The study group comprised all children admitted to Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil, during April 2002 through October 2008 who were screened for ROP, had weekly weight measurements, and survived

from the initial ophthalmologic examination at 4 to 6 weeks of age to 45 weeks' PMA.

Hospital de Clínicas de Porto Alegre is a university-based tertiary hospital located in Porto Alegre, a city with a total population of approximately 3 million inhabitants in southern Brazil. All of the admitted patients were from an urban and cosmopolitan population in the region surrounding Porto Alegre, the main city in the state of Rio Grande do Sul. The Hospital de Clínicas de Porto Alegre neonatal intensive care unit cares for about 130 very low-birth-weight (≤ 1500 g) preterm babies per year. At the time of the study, survival rates were 88.7% for babies with a birth weight (BW) of more than 1000 g and 1500 g or less and 47.8% for those with a BW of 1000 g or less,⁸ while some stage of ROP occurred in 24.7% with BW of 1500 g or less or GA of 32 weeks or less.⁹ The weight measurements were given to us as weekly weights, ie, we had no information on exact dates. An approximation was performed and we entered each weekly weight into WINROP as if it had been measured at exactly 1, 2, 3, and so on weeks after the infant's birth date.

The GA for each infant was determined by the neonatologists according to clinical criteria, early obstetric ultrasonography, and last menstrual date. The registered GA, in all of the patients, was approximated to the nearest GA week, for example, 27 weeks plus 5 days was recorded as GA 28 weeks; 27 weeks plus 3 days was recorded as GA 27 weeks.

ROP SCREENING AND TREATMENT

Ophthalmologic examinations consisted of binocular indirect ophthalmoscopy after pupillary dilatation with tropicamide, 0.5%, and phenylephrine, 2.5%, using a 28-diopter lens and a blepharostat. Scleral depression was used, when necessary, to better identify peripheral retinal alterations. Assessments were repeated periodically, according to the Brazilian guidelines for examining and treating ROP,¹⁰ which recommend screening for all babies born with a BW of 1500 g or less or GA of 32 weeks or less and for those babies with risk factors such as respiratory distress syndrome, sepsis, intraventricular hemorrhage, need for blood transfusions, and multiple gestation. The initial ophthalmologic examination should be performed between the fourth and sixth weeks of life and repeated weekly or more frequently according to the findings until full vascularization of the peripheral retina is observed or until 45 weeks' PMA. Retinopathy was classified according to the International Classification of Retinopathy of Prematurity (stage 1-5).¹¹ The indications for treatment were changed during the study period when the results of the Early Treatment for Retinopathy of Prematurity study¹² were published and will not be described in detail because the aim of the study was to study whether WINROP could predict proliferative ROP. However, no patient had ROP with zone 1 disease, and all laser-treated patients had stage 3 disease with plus disease. All ophthalmic examinations were performed by the same experienced pediatric ophthalmologist (J.B.F.F.).

WINROP SCREENING

The first step of the WINROP algorithm was developed using the methods of online statistical surveillance.¹³⁻¹⁵ Briefly, the algorithm using data from preterm infants with no ROP or with stage 1 ROP calculates the expected "safe" weight for each individual child. Then, the difference between expected weight gain and observed values of postnatal weight development at each point is calculated and accumulated. If the accumulated sum reaches a threshold limit, an alarm occurs.³

Data were retrospectively retrieved from the files regarding weight once every postnatal week until 35 to 36 postmenstrual weeks; these data, including GA at birth and BW, were entered

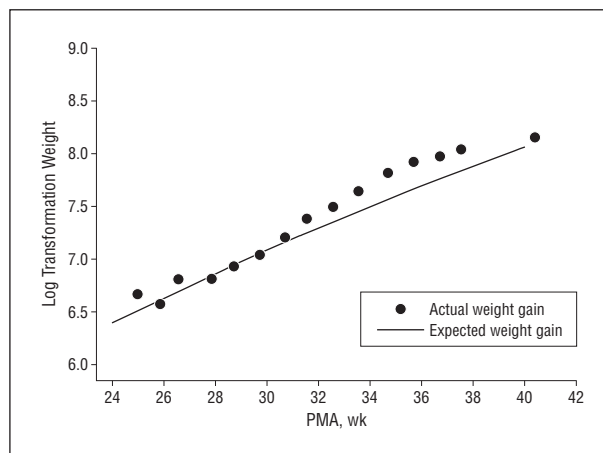


Figure 1. An example of actual weight gain in relation to expected weight gain in 1 girl born in gestational week 24 + 4 days with a birth weight of 788 g with no alarm who had no retinopathy of prematurity.

into the surveillance algorithm by a person unaware of the maximum ROP stage. Weight had been measured according to clinical practice on a digital scale. One weight per week was recorded in WINROP. In the first step of the algorithm, an alarm statistic was calculated for each child to judge whether there was enough evidence to conclude that a significant slow down in growth had occurred. **Figure 1** and **Figure 2** show examples of actual weight gain in relation to expected weight gain in 1 infant with no alarm (Figure 1) and in 2 infants with high-risk alarms (Figure 2).

When the system gives an alarm for a growth slow down, the next step takes into account GA at birth and BW to test for indications that the child is at low or high risk for ROP. If the infant had a GA more than 29 weeks and/or BW more than 850 g, he or she was automatically classified as a low-risk infant. However, if both GA was less than 29 weeks and BW was less than 850 g, he or she was classified as a high-risk infant. For each child, weekly WINROP evaluations were at 1 of 3 levels: (1) no alarm, (2) alarm at low risk, and (3) alarm at high risk.³ In the case of an alarm (low or high risk), the PMA (week) was registered, as displayed by the system. After the WINROP analysis, the results were correlated with the maximum ROP stage for each child as extracted from the child's files.

For the test characteristics, prior to the study we had hypothesized that all children with an alarm at high risk and/or an alarm at low risk before 32 weeks' PMA, ie, before the age when proliferative ROP is likely to occur, would need eye examinations while those with no or low-risk alarm (more than 32 + 0 weeks' PMA) would not.

STATISTICAL ANALYSIS AND ETHICS

The surveillance system using the variables weight gain, GA, and BW was evaluated regarding sensitivity (probability that an alarm occurs, given that the child develops stage 3 ROP) and specificity (probability that an alarm does not occur, given that the child will not develop stage 3 ROP). The negative and positive predictive values were calculated using the sensitivity, specificity, and prevalence in the present study group. We calculated 95% confidence intervals for estimated binary proportions (sensitivity and specificity) using the exact method from Clopper-Pearson.¹⁶ The study protocol regarding postnatal weight gain and ROP was approved by the Research Ethics Committee of Hospital de Clínicas de Porto Alegre (No. 03-248). The protocol also conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh, Scotland, 2000).

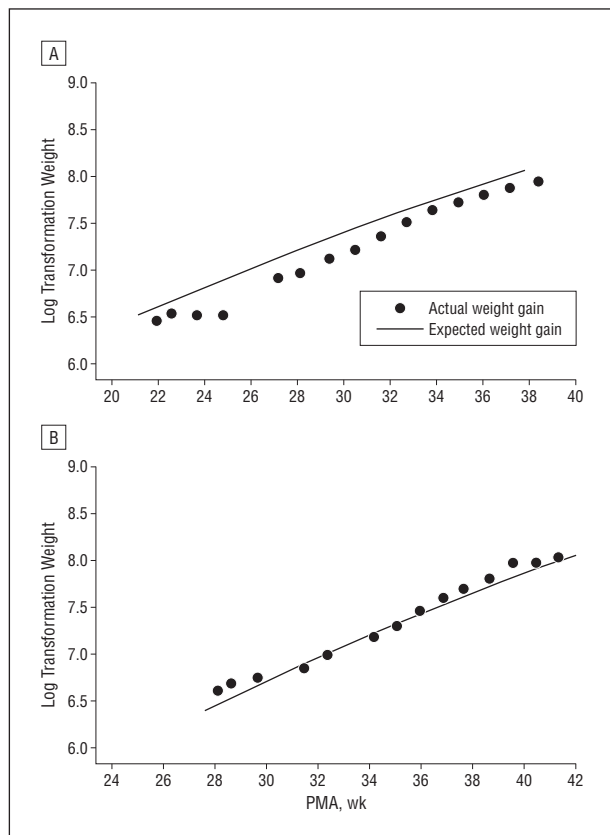


Figure 2. Examples of actual weight gain in relation to expected weight gain in 1 boy with stage 3 retinopathy of prematurity born in gestational week 25 + 2 days with a birth weight of 638 g with a high-risk alarm in gestational week 27 (A) and in 1 girl with stage 3 retinopathy of prematurity born in gestational week 24 + 1 day with a birth weight of 740 g with a high-risk alarm in gestational week 32 (B).

RESULTS

ROP OUTCOME

In total, 455 children were screened for ROP and had weekly weight measurements at Hospital de Clínicas de Porto Alegre. Forty-nine children with low BW had a GA of 33 weeks or more and were excluded from analyses because WINROP was not developed for GA more than 32 weeks. None of these children developed proliferative ROP. One child had known nonphysiologic weight gain (hydrocephalus) and 39 children had incomplete weight data, and thus, 366 children composed the final study group. The participating children had a median GA of 30 weeks (range, 24-32 weeks) at birth and their median BW was 1215 g (range, 505-2000 g). Infants with a GA of 32 weeks were included because of the approximation to full weeks, ie, a GA of 31 weeks + 4 to 6 days was classified as 32 weeks.

Among the 366 children in the study group with a GA of 32 weeks or less, 19 had developed stage 3 ROP or more, resulting in an incidence of 5.7%, and of whom all but 1, who missed the treatment appointment, had been treated with laser retinal ablation. One of the treated patients showed progression to stage 4A ROP despite 2 prior laser photocoagulations and required scleral buckling to

stop ROP progression. In addition, the patient who missed the appointment for treatment developed stage 5 ROP.

WINROP OUTCOME

For all 366 infants, weekly weights had been registered and were entered into the online surveillance system. For 192 children (53%), no alarm or alarm at low risk after 32 weeks' PMA was given (**Table 1**). Two of these infants (boys) developed stage 3 ROP and were treated. One of the boys with sepsis and pneumothorax had a GA of 32 weeks at birth and a BW of 1315 g and received an alarm in week 33 PMA; thus, in this case, the alarm could not have come earlier. The other boy, also with sepsis, who had a GA of 28 weeks at birth and a BW of 1260 g, received an alarm in week 34 PMA.

The median GA at birth in this group was 30 weeks (range, 24-32 weeks). For 174 infants (47%), an alarm at high risk or alarm at low risk at or before 32 weeks' PMA was given. In this high-risk group, 21 (12%) had developed stage 3 ROP or more and all but 1 had had laser ablation for their proliferative retinopathy.

The median GA at birth in the treated group (n=20) was 27 weeks (range, 25-32 weeks) and the median BW was 860 g (range, 620-1500 g).

TEST CHARACTERISTICS

Using a high-risk alarm or a low-risk alarm before 32 weeks' PMA to predict stage 3 ROP, the sensitivity of the WINROP algorithm was 90.5% (19 of 21; 95% confidence interval, 70%-99%) and the specificity, 55% (190 of 345; 95% confidence interval, 50%-60%).

The negative and positive predictive values in the studied population with a 5.7% (21 of 366) incidence of stage 3 ROP were 99% and 11%, respectively (**Table 2**).

In the worst-case scenario, according to confidence intervals, with a sensitivity and specificity of 70% and 50% and an incidence of 5%, 10%, and 20%, the negative predictive values would be 96.9%, 93.8%, and 87%, respectively, and the positive predictive values would be 6.9%, 13.5%, and 25.9%, respectively.

COMMENT

In this retrospective study of a Brazilian population of preterm infants, WINROP correctly identified 19 of 21 children (90.5%) who had developed proliferative ROP. In previous studies from Sweden and North America, 100% of subjects developing stage 3 ROP were identified. There may be several reasons for this discrepancy.

WINROP is based on data from infants with no or stage 1 ROP at a single neonatal intensive care unit in Sweden. In the Swedish study of the use of weight only in the WINROP algorithm, no child with a GA of 28 weeks or more developed stage 3 ROP, in contrast to the Brazilian population where 10 of 21 infants who developed proliferative ROP had a GA of 28 to 32 weeks. It is well known that more mature infants get ROP in developing countries and that screening criteria have to be modified accordingly.¹⁷ One of the "missed" infants had an ap-

Table 1. Alarm Signal in Relation to ROP Stage and Birth Characteristics in a Brazilian Population

	No. (%)						Birth Characteristics, Mean (SD)	
	Infants	No ROP	ROP Stage					
			1	2	3	4 and 5	GA, wk	BW, g
No alarm and no risk	13 (3.5)	12	0	1	0	0	29.2 (2.65)	1503 (347)
Alarm >32 wk PMA and at low risk	179 (48.9)	152	20	5	2	0	31.2 (1.04)	1381 (195)
Alarm ≤32 wk PMA and at low risk	136 (37.2)	96	19	12	8	1	29.3 (1.30)	1077 (156)
Alarm at high risk	38 (10.4)	12	3	13	9	1	26.8 (1.25)	717 (101)
Total	366	272	42	31	19	2	30.0 (1.87)	1199 (288)

Abbreviations: BW, birth weight; GA, gestational age at birth; PMA, postmenstrual age; ROP, retinopathy of prematurity.

Table 2. Sensitivity, Specificity, and Positive and Negative Predictive Values in Diagnosing Proliferative ROP (Stage 3)

Test	Reference Method		Total	PPV	NPV
	ROP ≥ Stage 3	ROP < Stage 3			
Alarm at high risk or alarm <32 wk PMA and at low risk	19	155	174	10% (19/174)	
No alarm or alarm ≥32 wk PMA and at low risk	2	190	192		99% (190/192)
Total	21	345	366		
Sensitivity	90.5% (19/21)				
Specificity		55% (190/345)			

Abbreviations: NPV, negative predictive value; PMA, postmenstrual age; PPV, positive predictive value; ROP, retinopathy of prematurity.

proximated GA of 32 weeks at birth and an alarm at week 33 PMA. In this case, an alarm before or at 32 weeks was not possible. So theoretically, because alarm levels have been set for the Swedish population, having no infant with proliferative ROP after a GA of 29 weeks, the method could not have been more sensitive. In the Swedish and North American studies, GA as well as dates of weight measurements were determined and registered more exactly using full gestational weeks plus days, while in this study, approximation to full weeks was performed. This might have influenced the results in the second “missed” infant with a GA of 28 weeks where an alarm was given at 34 weeks’ PMA. If this infant’s GA was 29 weeks, an alarm was given at 32 weeks and he would thus have been correctly identified.

Despite that WINROP appeared to be somewhat less efficient in this Brazilian population than in populations from Sweden and the United States, it correctly identified 90.5% of infants who had developed proliferative ROP and 55% of those with no or only mild ROP.

The purpose of ROP screening at present is to identify infants who need treatment with laser or cryotherapy to prevent blindness. Of those infants currently subjected to repeated eye examinations, less than 10% will need any treatment; in the rest, the disease will never develop or will regress spontaneously.

WINROP provides a tool to identify infants at risk for sight-threatening ROP. Although it has to be modulated to function optimally in countries where more mature infants develop ROP, it is in this context that it can be most useful since it is entirely based on weight measurements that are already performed as part of clinical practice all over the world. We believe that additional neo-

natal intensive care unit data from developing countries will help in modifying the algorithm for these populations. Until then, information from this population helps determine how weight measurements and GA estimation can be standardized to make the algorithm more universally applicable. As previously suggested, the close association between poor neonatal weight development and ROP^{5-7,18,19} indicates that optimizing growth may be one way to reduce ROP.

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