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**Early Weight Gain Predicts Retinopathy in Preterm Infants: New, Simple, Efficient Approach to Screening**

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**What’s Known on This Subject**

To identify children who need treatment for ROP, 1.5% of all infants (~60,000 infants per year in the United States) are repeatedly examined by ophthalmologists. Selection of infants deemed at risk involves the child’s GA and/or weight at birth.

**What This Study Adds**

With only serial weight measurements, the WINROP algorithm predicted all infants who later developed proliferative ROP requiring treatment and correctly identified 76% of those who did not develop proliferative ROP and thus would not need any ophthalmologic screening.

**ABSTRACT**

**BACKGROUND.** The risk for sight-threatening retinopathy of prematurity is predicted by using gestational age and/or weight at birth. All infants below a threshold undergo serial ophthalmologic examinations for identification of those who would benefit from treatment (~10%). We hypothesized that factoring in postnatal weight gain could identify children at risk for sight-threatening retinopathy of prematurity more specifically and earlier.

**METHODS.** Weekly weights from birth to postmenstrual week 36 were retrospectively entered into a surveillance system that gave an alarm when the rate of weight gain decreased to a certain level. For all children (N = 354) screened and/or treated for retinopathy of prematurity at Sahlgrenska University Hospital in 2004–2007, weekly weights were recorded. One child was excluded because of known nonphysiologic weight gain (hydrocephalus).

**RESULTS.** For 127 (36%) of 353 children, no alarm was given; for 40%, alarm at low risk was given after postmenstrual week 32. None of those children developed retinopathy of prematurity requiring treatment. Of the remaining 24% of children who received alarm at high or low risk before 32 postmenstrual weeks, 41% developed proliferative retinopathy of prematurity and 29% were treated because of sight-threatening disease. The median time from alarm to treatment was 9 weeks.

**CONCLUSIONS.** The weight, insulin-like growth factor, neonatal retinopathy of prematurity algorithm detected early 100% of infants who developed retinopathy of prematurity requiring treatment and correctly predicted the majority who did not require treatment. With this simple postnatal evaluation, costly stressful eye examinations can be markedly reduced (~75% of infants). In addition, early identification of children at risk may lead to the initiation of interventions and possibly prevent sight-threatening retinopathy of prematurity. Pediatrics 2009;123:e638–e645

**Abbreviations**

ETROP—Early Treatment for Retinopathy of Prematurity
IGF—insulin-like growth factor
GA—gestational age
PMA—postmenstrual age
CI—confidence interval

**Key Words**

retinopathy of prematurity, screening, weight gain

**R**etinopathy of Prematurity (ROP) is a vasoproliferative disease of the retina that is associated with preterm birth. It is a major cause of preventable blindness in both developing and developed countries.1-3 Most vascular changes in lower stages of ROP regress with time, but some may progress to total retinal detachment and blindness. Premature infants deemed to be at risk for ROP, on the basis of low birth weight or gestational age (GA) (often <1500 g or <32 weeks), with neonatal factors considered only for more-mature infants,4-8 are screened routinely and repeatedly with eye examinations from postmenstrual age (PMA) of ~30 to 32 weeks until the retina is fully vascularized (PMA of ~40 weeks). These examinations are performed to identify the ~10% of infants who need laser therapy or cryotherapy to help prevent retinal detachment.9,10 All ophthalmologic examinations are diagnostic rather
than predictive, to identify infants with sight-threatening, proliferative retinopathy. Even when the examinations are performed by experienced ophthalmologists, they often are stressful for the infants.11–13 Moreover, ~90% to ~95% of those examined never need any treatment,10,14 according to current recommendations, and thus do not benefit from screening except for learning that they do not have disease and do not need treatment. More cost-effective programs are needed to identify, before the development of ROP, infants at high and low risk for disease. The present screening criteria do not take into account postnatal clinical factors that are likely to influence the risk of ROP.5,15 Children with greater GA and weight at birth in middle-income and low-income countries develop more sight-threatening ROP than do those in industrialized countries,15 which indicates the importance of postnatal factors. In addition, it is generally known that infants with other morbidities have increased risk of ROP.16,17 Therefore, it seems appropriate to consider postnatal factors in an attempt to improve screening efficacy.

We reported previously on the weight, insulin-like growth factor (IGF), neonatal ROP (WINROP) algorithm, which was developed to detect early indications of ROP on the basis of the postnatal longitudinal patterns of weight and serum levels of IGF-I and IGF-binding protein for 79 patients.18 With this surveillance system, only 23% of the participating infants (GA of <32 weeks) were considered to be at risk of needing ROP treatment: all infants who required treatment (n = 6) were identified ≥5 weeks before they fulfilled the standard criteria for treatment. The surveillance system recently was validated successfully with a new population from another area of Sweden.19

The WINROP algorithm is an online surveillance system that is based on weekly postnatal recording of weight and serum IGF-I levels. If repeated blood sampling could be eliminated, however, excluding IGF-I levels from analysis, then there would be large reductions in costs and stress on the infants and a simplified screening procedure. In addition, use of weight measurements only as a simple tool for ROP screening would be of clear benefit in developing countries. Therefore, the aim of this retrospective study with a new population was to test the hypothesis that, with the use of the previously developed algorithm without changes, postnatal weight gain alone could efficiently detect a slowdown in growth that might indicate the risk for proliferative ROP requiring treatment in infants born at a GA of <32 weeks.

**METHODS**

**Patients**

The level III NICU at Sahlgrenska University Hospital in Gothenburg, Sweden, cares for preterm infants from the entire Västra Götaland region. Expected, extremely preterm deliveries (before 27–28 gestational weeks) are referred to Sahlgrenska University Hospital, where the deliveries take place and the infants receive their initial care. In addition, all ROP treatments in the region take place at Sahlgrenska University Hospital. The population of the region is ~1.5 million, and 70,806 live births were reported from 2004 through 2007; 719 of those infants were born before GA of 32 weeks, thus fulfilling the Swedish criteria for ROP screening.8

The study group comprised all children born with a GA of <32 weeks in 2004 through 2007 who were screened and/or treated for ROP at the Sahlgrenska University Hospital. One child with treated ROP (stage 3) who had shunt-requiring hydrocephalus causing a non-physiologic excessive weight increase was excluded from the weight algorithm analysis.18 Therefore, a total of 353 infants participated in the study (Fig 1).

The median GA at birth among the children from the Gothenburg area (n = 321) was 30 weeks (range: 23% to 31% weeks), and the median birth weight was 1310 g (range: 425–2210 g). The children who were referred from the other hospitals in the region (n = 32) were less mature, with a median GA at birth of 25 weeks (range: 23% to 31% weeks) and a median birth weight of 743 g (range: 450–1635 g). The 9 infants who were not referred for screening had a median GA of 31% weeks (range: 30% to 31% weeks) and a median birth weight of 1760 g (range: 1148–2375 g).

**ROP Screening and Treatment**

All infants were examined according to a routine protocol consisting of dilated ocular fundus examinations once every other week to twice per week, depending on the severity of the disease, from chronological age of 5 or 6 weeks until the eyes were fully vascularized or the condition was considered stable (PMA of ~40 weeks). ROP was classified according to the International Classification of Retinopathy of Prematurity (stage 1–5),20 and the recommendations of the Early Treatment for Retinopathy of Prematurity (ETROP) study21 were followed for treatment. No patient had stage 4 or 5 ROP or ROP with zone 1 disease, and all treated patients had stage 3 disease. Because this was a retrospective review, the infants were examined by different ophthalmologists, and the diagnosis of plus disease is known have large interobserver variability; we chose not to report on plus disease.

**WINROP Screening**

The first step of the WINROP algorithm was developed by using the methods of online statistical surveillance.22–24 In short, the algorithm, using data for preterm infants with no ROP or with stage 1 ROP, calculates the expected “safe” weight and IGF-I development for each individual child in 2 different systems. The differences between expected weight gain and IGF-I development and observed values of postnatal weight and serum IGF-I levels at each time point are calculated and accumulated. If the accumulated sum reaches above an alarm limit, then an alarm is called.18 In this study, however, only postnatal weight gain was used.

Data were retrieved retrospectively from the files regarding weight measured once every postnatal week until 35 to 36 postmenstrual weeks; these data, including GA at birth and birth weight, were entered into the
surveillance algorithm by a person unaware of the maximal ROP stage. Weight was measured 3 times per week on a digital scale, according to clinical practice, but only 1 value for each postmenstrual week was used. In the first step of the algorithm, an alarm statistic is calculated for each child, to determine whether there is enough evidence to conclude that a significant slowdown in growth has occurred. When the system gives an alarm for a growth slowdown, the next step takes into account GA at birth and birth weight, to test for indications that the child is at low or high risk for ROP. If the infant has a GA of >29 weeks and/or birth weight of >850 g, then he or she is classified automatically as a low-risk infant. If the GA is <29 weeks and the birth weight is <850 g, however, then the infant is classified as a high-risk infant. For each child, weekly WINROP evaluations were at 1 of 3 levels, that is, (1) no alarm, (2) alarm at low risk, or (3) alarm at high risk. In cases of an alarm (low or high risk), the PMA was recorded, as displayed by the system. Later, the maximal ROP stage for all children was extracted from the files. Before the study, we hypothesized that all children with an alarm at high risk

![Flowchart](https://www.pediatrics.org/)

**FIGURE 1**
Flowchart of the study population and WINROP outcomes. SU Hospital indicates Sahlgrenska University Hospital.
and/or an alarm at low risk before PMA of 32 weeks (ie, an age that would meet the Swedish screening criteria) would require screening, whereas those with no alarm or alarm at low risk at PMA of $\geq 32$ weeks would not require screening.

**Statistical Analysis**

The surveillance system using the variables of weight gain, GA, and weight at birth was evaluated with respect to sensitivity (probability that an alarm would be called, given that the child develops stage 3 ROP) and specificity (probability that an alarm would not be called, given that the child does not develop stage 3 ROP). The negative and positive predictive values were calculated by using the sensitivity, specificity, and prevalence for the present study group. We calculated 95% confidence intervals (CIs) for estimated binary proportions (sensitivity and specificity) by using the exact method by Clopper-Pearson.

**RESULTS**

**ROP Outcome**

Of the 353 children in the study group with GAs of $< 32$ weeks, 35 developed stage 3 ROP, resulting in a prevalence of 9.9%; 25 were treated with laser retinal ablation.

**WINROP Outcome**

For all 353 infants (145 girls), weekly weights had been recorded and were entered into the online surveillance system. The maximal ROP stage in relation to GA at birth is presented in Fig 2.

For 127 children (35.9%), no alarm was given; none of those children developed more than stage 2 ROP, and none fulfilled the ETROP requirements for treatment of ROP (Table 1). The median GA at birth in this group was $30 \pm 1$ weeks (range: $23 \pm 3$ to $31 \pm 7$ weeks).

For 156 children (44.1%), an alarm at low risk was given, at a median PMA of 34 weeks (range: 29 –36 weeks) (Table 1 and Fig 3A). In this group, 2 children (1.3%) with an alarm at PMA of $31 \pm 7$ weeks developed stage 3 ROP that was treated.

Sixty-nine infants (19.5%) had an alarm at high risk, at a median PMA of 27 weeks (range: 26 –34 weeks) (Fig 3B). In this high-risk group, 33 infants (47.8%) developed stage 3 ROP and 23 (33.3%) underwent laser ablation for their proliferative ROP. The median GA at birth in the treated group ($n = 25$) was $24 \pm 9$ weeks.

**TABLE 1** Alarm Signal in Relation to ROP Stage and Birth Characteristics

<table>
<thead>
<tr>
<th></th>
<th>No alarm and no risk</th>
<th>Alarm at PMA of $\geq 32$ wk and low risk</th>
<th>Alarm at PMA of $&lt; 32$ wk and low risk</th>
<th>Alarm at high risk</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>127 (36)</td>
<td>141 (40)</td>
<td>16 (4)*</td>
<td>69 (20)*</td>
<td>353</td>
</tr>
<tr>
<td>No ROP</td>
<td>105</td>
<td>114</td>
<td>9</td>
<td>11</td>
<td>239</td>
</tr>
<tr>
<td>Stage 1 ROP</td>
<td>7</td>
<td>14</td>
<td>1</td>
<td>7</td>
<td>29</td>
</tr>
<tr>
<td>Stage 2 ROP</td>
<td>15</td>
<td>13</td>
<td>4</td>
<td>18</td>
<td>50</td>
</tr>
<tr>
<td>Stage 3 ROP</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>33</td>
<td>35</td>
</tr>
<tr>
<td>Treated</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>23</td>
<td>25</td>
</tr>
<tr>
<td>GA, Median (Range), wk</td>
<td>30 (23–31)</td>
<td>30 (25–31)</td>
<td>29 (25–31)</td>
<td>25 (23–29)</td>
<td>29 (23–31)</td>
</tr>
<tr>
<td>Birth Weight, Median (Range), g</td>
<td>1550 (745–2210)</td>
<td>1335 (755–1820)</td>
<td>980 (605–1120)</td>
<td>695 (425–850)</td>
<td>1290 (425–2210)</td>
</tr>
</tbody>
</table>

* In total, 24% needed screening (alarm at high risk or alarm at PMA of $< 32$ weeks).
(range: 23% to 27½ weeks), and the median birth weight was 690 g (range: 425–930 g).

**Time From Alarm to Proliferative ROP and Treatment**

For the 35 children with proliferative ROP, the median time from birth to the alarm was 3.1 weeks (range: 2–10 weeks). The time from the alarm to the time when proliferative ROP was first observed by an ophthalmologist (diagnosis) was 7.7 weeks (range: 1–16 weeks). The median time from the alarm to treatment of ROP for the 25 treated children was 9 weeks (range: 4–18.3 weeks) (Fig 4).

**Test Characteristics**

With the use of a high-risk or low-risk alarm before PMA of 32 weeks to predict stage 3 ROP, the sensitivity of the WINROP algorithm was 100% (95% CI: 90%–100%; 35 of 35 infants) and the specificity was 84.5% (95% CI: 81%–88%; 268 of 318 infants). The negative and positive predictive values in the studied population, with a 9.9% prevalence (35 of 353 infants) of stage 3 ROP, were 100% and 41%, respectively (Table 2). In the worst-case scenario, according to CIs, with sensitivity of 90%, specificity of 81%, and prevalence values of 5%, 10%, and 20%, the negative predictive values would be 99%, 97%, and 97% and the positive predictive values would be 20%, 35%, and 54%, respectively.

**WINROP Screening Reduces the Need for Eye Examinations**

With traditional Swedish screening guidelines, preterm children with GA of <32 weeks are examined repeatedly (every other week to twice per week) by an ophthalmologist, from PMA of 30–32 weeks. Children screened in Gothenburg in 2007 underwent a mean of 5 ophthalmologic examinations per infant. On the basis of the results of this study, only preterm children with a high-risk alarm or a low-risk alarm before PMA of 32 weeks and children with hydrocephalus would need an eye examination. With the surveillance system using weight only, 86 (24%) of 354 infants in the study population...
would need ophthalmologic examinations, and the number of infants needing eye examinations would thus be reduced by 76%.

**DISCUSSION**

The surveillance system (WINROP) using weekly weight measurements was shown to identify accurately the infants who several weeks to months later did develop proliferative ROP requiring treatment according to ETROP criteria. It also correctly identified a majority of the participating infants who were not at risk for sight-threatening ROP (76%). With the use of this algorithm that is based on a simple, safe, noninvasive, and already routinely performed measurement, we can design individualized screening programs to identify infants who need intervention for their ROP. Presently, all screening examinations are performed by ophthalmologists, and current criteria result in examinations with low cost-effectiveness and in many unnecessary, stressful examinations of fragile infants. In 2007, infants who fulfilled the present Swedish screening criteria underwent a mean of 5 ophthalmologic examinations. Therefore, ~3170 detailed ophthalmologic examinations were performed in 2004–2007 in the Västra Götaland Region to identify the 27 infants who needed treatment for ROP. With the use of this algorithm, ~2377 screening examinations could have been avoided during these years.

In the development of the online surveillance algorithm, the expected weight gain was estimated from data for a group of preterm infants who did not develop ROP or developed only stage 1 ROP. An alarm system that indicates deviations from the expected development and a need for an eye examination was devised. The algorithm was calibrated to detect all infants at risk of developing ROP requiring treatment according to ETROP criteria, and the sensitivity was considered to be more important than the specificity. Currently there is no corresponding screening system, although the Cryotherapy for Retinopathy of Prematurity Study has developed an algorithm to assess the risk for progression to blindness once there is proliferative disease. That algorithm has been used to select subjects for inclusion in random-
ized trials; however, it is not useful as a screening tool, because the child needs to have prethreshold disease to be included in the analysis.

The timeliness of the alarms is important. With the present surveillance system, alarms are usually given many weeks, sometimes several months, before the development of proliferative ROP. The pathogenesis of ROP is still largely unknown. A number of risk factors and comorbidities have been identified. In the present study, the infants who developed proliferative disease had a median chronological age after birth of 3 weeks when the alarm was given and of 8.4 weeks before the first sign of proliferative disease was seen. The fact that very early weight deviations are associated with proliferative ROP may help to provide new insights into the nature of the disease. A few literature reports showed a relationship between poor postnatal weight gain and an increased risk of ROP development.28,29 In addition, several reports on preterm children showed a strong association between poor postnatal growth and weight gain and low serum IGF-I levels.30–33 This is consistent with our previous work that showed a strong association between low serum IGF-I levels and the severity of ROP.34,35 Promoting postnatal growth and weight gain through, for example, optimal nutritional supplementation and/or supplementation with growth factors such as IGF-I, levels of which are known to be low in infants with ROP, may improve the condition of infants and prevent the development of proliferative ROP.

It has been reported that infants are kept at high levels of NICU care for prolonged periods because of lack of specialized ophthalmologists outside hospitals.36 With the present surveillance system, infants at risk could be identified earlier, and unnecessary and prolonged treatment of infants at high levels of NICU care could be reduced. The system also could be used to alert physicians to high-risk patients, to avoid the rare cases of ROP requiring treatment developing after discharge.37 Evaluation of weekly weight development is likely to result in fewer cases to screen and thus reduced workload but also reduced training for pediatric ophthalmologists. It also would require a more-active role for neonatologists in the screening process, including improved communication between neonatologists and ophthalmologists. It should be noted that preterm infants with nonphysiologic weight increases (eg, severe hydrocephalus or excessive edema) must be excluded from screening with the algorithm.

There is a need to explore alternative approaches to current screening that are feasible, safe, and cost-effective and have high sensitivity for identifying infants who are developing ROP severe enough to warrant the expert opinion of an ophthalmologist.15 We think that we have found such an approach. Before new screening guidelines can be constructed, however, further validation of the surveillance system must be performed with other populations of infants, which might have different expected weight gains than the studied population.

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