Importance of Early Postnatal Weight Gain for Normal Retinal Angiogenesis in Very Preterm Infants

A Multicenter Study Analyzing Weight Velocity Deviations for the Prediction of Retinopathy of Prematurity

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Objective: To assess WINROP (https://winrop.com), an algorithm using postnatal weight measurements, as a tool for the prediction of retinopathy of prematurity (ROP) in a large geographically and racially diverse study population.

Methods: WINROP analysis was performed retrospectively on conventionally at-risk infants from 10 neonatal intensive care units. Weight measurements were entered into WINROP, which signals an alarm for an abnormal weight gain rate. Infants were classified into categories of no alarm (unlikely to develop type 1 ROP) and alarm (at risk for developing type 1 ROP). Use of WINROP requires that an infant has (1) gestational age less than 32 weeks at birth, (2) weekly weight measurements, (3) physiologic weight gain, and (4) absence of other pathologic retinal vascular disease.

Results: A total of 1706 infants with a median gestational age of 28 weeks (range, 22-31 weeks) and median birth weight of 1016 g (range, 378-2240 g) were included in the study analysis. An alarm occurred in 1101 infants (64.5%), with a median time from birth to alarm of 3 weeks (range, 0-12 weeks) and from alarm to treatment of 8 weeks (range, 1 day to 22 weeks). The sensitivity of WINROP was 98.6% and the negative predictive value was 99.7%. Two infants with type 1 ROP requiring treatment after 40 weeks' postmenstrual age did not receive an alarm.

Conclusion: The WINROP system is a useful adjunct for ROP screening that identifies high-risk infants early to optimize care and potentially reduce the overall number of diagnostic ROP examinations.


Retinopathy of prematurity (ROP) is a leading cause of preventable childhood blindness.1-3 Most cases of ROP are mild and regress spontaneously; however, severe ROP can lead to retinal detachment and permanent vision loss. Currently, birth weight (BW) and gestational age (GA) are used as selection criteria to examine infants for treatable disease;4 postnatal factors that may help to predict or prevent ROP are not considered. Retinopathy of prematurity is diagnosed only later in the disease process by serial ophthalmoscopic examinations.

Serial ROP examinations are labor-intensive for clinicians and stressful on infants.5,6 In the United States, more than 85,000 live births per year are very preterm and/or very low BW.7 Estimating an average of 5 examinations per infant,8 as many as 425,000 or more screenings are performed each year, with more than 90% of infants examined never developing ROP that requires intervention.9,10 There is a need for earlier differentiation of infants at higher risk for severe ROP from those at lower risk.

Predicting ROP early depends on understanding early retinal vascular changes that occur after premature birth and before extensive retinal neovascularization that precipitates ROP treatment. Retinopathy of prematurity is a 2-phase disease. Phase I consists of poor postnatal retinal vascular growth leading to hypoxia, which then determines the degree of pathologic neovascularization, or phase II of ROP. Accordingly, postnatal growth factors or nutritional deficiencies that suppress retinal vascular growth may influence the later development of proliferative retinopathy. Given the biphasic nature of ROP, low levels of factors that affect vascular growth may be assessed to help predict ROP risk.

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Group Information: The members of the WINROP Consortium are listed at the end of this article.
weeks to months before the neovascular phase. These low levels of growth factors may also determine postnatal somatic growth or weight gain. Inclusion of postnatal risk factors for ROP can be used to help select premature infants for eye examinations. This may help target at-risk infants for interventions that may reduce severe ROP. Extensive clinical and animal studies have demonstrated the relationship between low serum insulin-like growth factor (IGF) I levels and associated poor weight gain with the development of more severe ROP. The WINROP (weight, IGF, neonatal ROP) algorithm was developed in Sweden to evaluate the risk of treatable ROP based on weekly postnatal measurements of these 2 parameters. Prospective and retrospective pilot studies have shown that the WINROP algorithm has the potential to identify infants who are at high risk for severe ROP early in their neonatal course. The WINROP algorithm has been further simplified as an online monitoring system (https://winrop.com) using weight gain measurements alone, allowing for use in any nursery, and has demonstrated 100% sensitivity in predicting severe ROP in 2 Swedish and US populations. The WINROP system was also validated in a Brazilian population with a sensitivity of 90.5% in predicting proliferative ROP. This population of infants had less stringently documented GA and dates for weekly weight measurements. As commonly seen in developing countries that require broadened screening guidelines, there was a higher median BW and GA in treated Brazilian infants. However, the high sensitivity in this group further supports the relationship between poor postnatal weight gain and severe ROP.

Given the very high sensitivity of these early pilot studies, we sought to evaluate the potential use of the WINROP algorithm to help predict type 1 ROP in a large, more geographically and racially diverse study population in the United States and Canada.

METHODS

PATIENTS

A review was performed of records on premature infants from level III neonatal intensive care units (NICUs) in the United States and Canada who qualified for ROP examinations according to the conventional criteria of GA and BW between 2006 and 2009. For this retrospective study, infants were excluded if they were born at a GA of 32 weeks or more, had incomplete medical records, or lacked weekly weight measurements until 36 weeks' postmenstrual age (PMA) or hospital discharge, demonstrated nonphysiologic weight gain, or had retinal disease other than ROP. Prospective use of WINROP would also exclude these infants. Follow-up of infants with ROP was required untilROP was inactive, mature retinal vascularization or immature retinal vascularization in zone III was reached, prethreshold or threshold ROP occurred, or treatment was required.

Data collected included birth date, GA, BW, weekly postnatal weight, sex, birth multiplicity, race, ROP examination results, and presence of bronchopulmonary dysplasia, intraventricular hemorrhage, hydrocephalus, and necrotizing enterocolitis. Race was classified as white, black, Asian, American Indian or Alaskan Native, Native Hawaiian/Pacific Islander, or Hispanic origin by participating investigators on the basis of data obtained from the infant’s medical record. The study was approved by the institutional review boards at all participating centers.

ROP EXAMINATIONS AND TREATMENT

Examinations for ROP were performed by qualified ophthalmologists with expertise in ROP on infants with BW less than 1500 g or GA 30 weeks or less, as well as select infants with BW between 1500 and 2000 g or GA more than 30 weeks with an unstable clinical course that was considered to place them at high risk for ROP. Infants were examined using standard binocular indirect ophthalmoscopy with scleral depression. Examinations ranged from twice per week to every 3 weeks, depending on the severity and zone of ROP. Classification of ROP was performed according to the International Classification of Retinopathy of Prematurity. The highest and lowest zone of ROP, presence of prethreshold (PT) or threshold disease, and need for ROP treatment were recorded. Prethreshold ROP was further subclassified according to Early Treatment for Retinopathy of Prematurity criteria into type 1 or type 2 ROP, as described in the next paragraph.

The maximum ROP for the worse eye was categorized into 4 groups: (1) no ROP (immature or mature retinal vascularization); (2) non-PT ROP (zone II stage 1 or 2 ROP without plus disease; zone III stage 1, 2, or 3 ROP); (3) type 2 ROP (zone I stage 1 or 2 ROP without plus disease; zone II stage 3 ROP without plus disease); and (4) type 1 ROP (any zone I ROP with plus disease; zone I stage 3 ROP without plus disease; zone II stage 2 or 3 ROP with plus disease). Retinal ablative treatment was considered for type 1 ROP.

WINROP SCREENING

The WINROP algorithm was developed using the methods of online statistical surveillance. Use of WINROP requires that an infant has (1) GA less than 32 weeks at birth, (2) weekly weight measurements, (3) physiologic weight gain, and (4) absence of other pathologic retinal vascular disease. Reference models of the expected safe weekly IGF-I levels and physiologic weight gain velocity were created using data from infants who did not develop ROP or developed stage 1 ROP. In this study, the simplified version of WINROP analysis with postnatal weight gain alone was used. Deviations between observed and reference weight gain values were calculated and accumulated. When the accumulated sum exceeded a limit, an alarm was signaled in infants with a GA less than 30 weeks and BW less than 850 g. An alarm was signaled in infants with a GA 30 weeks or more and BW 850 g or more if the limit was exceeded at 32 or fewer weeks’ PMA. Additionally, birth weights that were very low for a given GA could result in an immediate alarm at week 0.

The WINROP model used in this study was developed with the derivation sample data on the basis of weekly physiologic weight gain and was not modified on the basis of data collected for this or any previous validation study. Infants with evidence of nonphysiologic weight gain do not qualify for WINROP analysis. Any weekly weight gain of more than 450 g was identified by WINROP as an indicator for excessive, nonphysiologic weight gain. Additionally, infants with hydrocephalus or excessive edema on physical examination, representing nonphysiologic weight gain, would also require exclusion from WINROP use. Given the retrospective design of this study, these infants could be identified only on post hoc review of medical records. With prospective use, WINROP queries the presence of nonphysiologic weight gain based on physi-
A total of 1965 infants from 10 centers were screened for ROP. For WINROP assessment, 259 infants did not meet inclusion criteria, since 187 were born at a GA of 32 weeks or more, 58 had missing medical data or weekly weight measurements, 12 had nonphysiologic weight gain, and 2 underwent treatment for familial exudative vitreoretinopathy, a genetic disease causing retinopathy that mimics ROP (eTable 1; http://www.archophthalmol.com). Of the 187 infants who were born at a GA of more than 32 weeks, 179 did not develop ROP. Only 1 infant developed PT ROP and received a WINROP alarm. Most of the infants with missing data were transferred from outside institutions to the study center; therefore, early weight measurements were unavailable. No or only mild ROP developed in the premature infants with familial exudative vitreoretinopathy, but treatment was performed for persistent avascular retina. Familial exudative vitreoretinopathy was diagnosed in these infants on the basis of clinical, angiographic, and genetic testing.

A total of 1706 infants were included in the study analysis (Figure 1). The median GA at birth was 28 weeks (range, 22-31 weeks) and the median BW was 1016 g (range, 378-2240 g). Female infants accounted for 47.9% (817 of 1706) of the study population; 1172 infants were singleton births, 436 were twin births, 90 were triplet births, and 8 were quadruplet births. The study population was 54.0% white, 27.1% black, 9.8% Hispanic, 5.3% Asian, and 3.7% other races (Table 1). The racial distribution of premature infants born at a GA of less than 32 weeks in the United States is approximately 42.9% non-Hispanic white, 29.0% non-Hispanic black, 21.7% Hispanic, 4.6% Asian or Pacific Islander, 1.3% American Indian or Alaskan Native, and 0.5% other races.

There was a trend for a higher rate of complicating comorbidities, such as bronchopulmonary dysplasia, intraventricular hemorrhage, hydrocephalus, and necrotizing enterocolitis, in infants with more severe ROP (Table 2).

**RPO AND WINROP OUTCOME**

The maximal ROP attained by the worse eye was type 1 ROP in 146 infants (8.6%), type 2 ROP in 75 infants (4.4%), and non-PT ROP in 605 infants (35.5%); 149 infants (8.7%) underwent ROP treatment. No ROP developed in 880 infants (51.6%) (Table 3).

No alarm was signaled in 605 infants and 603 of these did not develop type 1 ROP. Two infants developed type 1 ROP and underwent treatment after 40 weeks' PMA (eTable 2).

An alarm was signaled in 1101 infants; 78 of these infants (7.1%) received an alarm at week 0 based on BW alone. None of these infants was extremely preterm, with a mean (SD) GA of 29.5 (1.4) weeks. However, they were born severely small for GA, with a mean BW SD score of
−4.5 (0.7). In the alarm group, type 1 ROP developed in 144 infants, including 44 who developed zone I ROP. One infant (GA, 23 weeks; BW, 499 g) who had feeding difficulties with prolonged use of total parenteral nutrition developed zone I stage 2 ROP with plus disease requiring treatment at 32 1/7 weeks’ PMA and received an alarm at 33 weeks’ PMA. For all other infants, the median time from birth to alarm was 3 weeks (range, 0-12 weeks), from alarm to development of PT ROP was 8 weeks (range, 0-17 weeks), and from alarm to ROP treatment was 8 weeks (range, 1 day to 22 weeks) (Figure 2). Of the infants with zone I ROP, the median time from birth to alarm was 3 weeks (range, 0-10 weeks), from alarm to development of PT ROP was 7 weeks (range, 1 day to 13 weeks), and from alarm to ROP treatment was 7 weeks (range, 1 day to 16 weeks). The percentage of infants who developed type 1 ROP after receiving an alarm was also calculated and categorized by GA at birth (Figure 3).

Secondary analysis was performed on the 149 infants who underwent ROP treatment. Based on clinical judgment of the treating ophthalmologist, 10 infants who developed type 1 ROP were not treated and 13 infants were treated for less than type 1 ROP. Of these 13 infants, 11 were treated for type 2 ROP, 1 for zone III stage 3 ROP, and 1 for zone III stage 2 ROP with persistent temporal avascularity. Two additional infants in the treatment group who did not develop type 1 ROP received no alarm (eTable 3).

Prethreshold ROP developed in 221 infants. Excluding the 4 previously mentioned infants, all who developed PT ROP received an alarm.

### Test Characteristics

The overall sensitivity of the WINROP algorithm in detecting type 1 ROP was 98.6% (95% CI, 96.7%-100.5%; 144 of 146 infants) and the specificity was 38.7% (95% CI, 36.2%-41.1%; 603 of 1560 infants). The positive predictive value was 13.1% (144 of 1101 infants) and the negative predictive value was 99.7% (603 of 605 infants) (Table 4).

For secondary analysis, the overall sensitivity of the WINROP algorithm in identifying infants who required ROP treatment was 97.3% (95% CI, 94.7%-99.9%; 145 of 149 infants) and the specificity was 38.6% (95% CI, 36.2%-41.0%; 601 of 1557 infants). The positive predictive value was 13.2% (145 of 1101 infants) and the negative predictive value was 99.3% (601 of 605 infants).

The overall sensitivity of the WINROP algorithm in detecting PT ROP was 98.2% (95% CI, 96.7%-99.9%; 217 of 221 infants) and the specificity was 40.5% (95% CI, 38.0%-43.0%; 601 of 1485 infants). The positive predictive value was 19.7% (217 of 1101 infants) and the negative predictive value was 99.3% (601 of 605 infants).

### Comment

Our multicenter study validated the use of postnatal weight gain analysis by WINROP to aid early prediction of infants at high risk for type 1 ROP. The study was conducted in a large geographically and racially diverse NICU

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### Table 2. Prematurity-Related Illnesses

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (N = 1706)</th>
<th>No ROP (n = 880)</th>
<th>Non-PT ROP (n = 605)</th>
<th>Type 2 ROP (n = 75)</th>
<th>Type 1 ROP (n = 146)</th>
<th>Treated ROP (n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>687 (40.3)</td>
<td>191 (21.7)</td>
<td>315 (52.1)</td>
<td>58 (77.3)</td>
<td>123 (84.2)</td>
<td>124 (83.2)</td>
</tr>
<tr>
<td>Intraventricular hemorrhage</td>
<td>459 (26.9)</td>
<td>157 (17.8)</td>
<td>207 (34.2)</td>
<td>29 (38.7)</td>
<td>66 (45.2)</td>
<td>69 (46.3)</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>69 (4.0)</td>
<td>15 (1.7)</td>
<td>40 (6.6)</td>
<td>4 (5.3)</td>
<td>10 (6.8)</td>
<td>11 (7.4)</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>150 (8.8)</td>
<td>50 (5.7)</td>
<td>67 (11.1)</td>
<td>9 (12.0)</td>
<td>24 (16.4)</td>
<td>27 (18.1)</td>
</tr>
</tbody>
</table>

**Abbreviations:** PT, prethreshold; ROP, retinopathy of prematurity.

### Table 3. Alarm Signal in Relation to ROP Categories and Birth Characteristics

<table>
<thead>
<tr>
<th>Alarm Status</th>
<th>No Alarm</th>
<th>Alarm</th>
<th>All Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants, No. (%)</td>
<td>605 (35.5)</td>
<td>1101 (64.5)</td>
<td>1706</td>
</tr>
<tr>
<td>ROP categories, No.</td>
<td>484</td>
<td>396</td>
<td>880 (51.6)</td>
</tr>
<tr>
<td>None</td>
<td>117</td>
<td>488</td>
<td>605 (35.5)</td>
</tr>
<tr>
<td>Non-PT</td>
<td>2</td>
<td>73</td>
<td>75 (4.4)</td>
</tr>
<tr>
<td>Type 2</td>
<td>2</td>
<td>144</td>
<td>146 (8.6)</td>
</tr>
<tr>
<td>Type 1</td>
<td>4</td>
<td>145</td>
<td>149 (8.7)</td>
</tr>
<tr>
<td>Treated</td>
<td>29 (23-31)</td>
<td>27 (22-31)</td>
<td>28 (22-31)</td>
</tr>
<tr>
<td>GA, wk</td>
<td>1385 (625-2240)</td>
<td>850 (378-1720)</td>
<td>1016 (378-2240)</td>
</tr>
<tr>
<td>BW, g</td>
<td>1385 (625-2240)</td>
<td>850 (378-1720)</td>
<td>1016 (378-2240)</td>
</tr>
</tbody>
</table>

**Abbreviations:** BW, birth weight; GA, gestational age; PT, prethreshold; ROP, retinopathy of prematurity.
population in the United States and Canada, used current Early Treatment for Retinopathy of Prematurity criteria, and included infants with zone I ROP.

Severe ROP is one of the strongest predictors for death or major disability.27,28 Because the retina is part of the central nervous system, measures to prevent poor neurovascular development in the eye may also benefit the development of the brain in preterm infants. Interventions that maximize nutritional support and normalize weight gain for high-risk infants early in life may decrease the development of severe ROP and reduce the long-term neurocognitive and functional impairments associated with prematurity.

Poor weight gain is a common, multifactorial complication of premature birth. Preterm infants require protracted time to adjust to an appropriate metabolic state after birth and are characterized by hypermetabolism,29 which can hinder weight gain. Aside from IGF-I levels, other factors that affect ROP, such as hyperglycemia,30,31 poor enteral nutrition,32-34 loss of ω-3 fatty acids,35 intrauterine infection,36,37 and excessive or fluctuating oxygen levels,38 are also associated with poor postnatal growth.

We have found that poor weight gain during the first weeks of life is a marker for severe ROP risk; approximately 50% of infants who developed type 1 ROP received a WINROP alarm 2 weeks or less after birth and 75% received an alarm 3 weeks or less after birth. High-risk infants were identified a median of 3 weeks after birth and 8 weeks before ROP treatment. The WINROP system is a valuable instrument to optimize inpatient and outpatient ROP screening and follow-up. Because WINROP is a noninvasive tool to assess ROP risk with the potential to reduce ROP screenings for select infants, it is conceivable that WINROP could allow NICUs flexibility in screening programs to identify treatable ROP in their particular population of premature infants.

Advance knowledge of ROP risk might affect the transfer of infants to hospitals with limited ROP coverage, as well as modify decisions to defer examinations in medically unstable infants who may be at increased risk for ROP. Most medicolegal claims involving ROP outcomes are the result of failure to transfer care from the NICU setting to the outpatient setting.39 Identification of infants who are at high ROP risk would help to ensure timely follow-up to decrease unfavorable outcomes from missed or delayed examinations.

Conversely, infants with no alarm were very unlikely to develop significant ROP. Ophthalmologic examina-
tions might be safely reduced in frequency and numbers for these infants, keeping in mind that WINROP is an adjunct to and not a replacement for standard ophthalmologic screening.

Examination schedules with use of WINROP have been implemented in several Swedish NICUs. For infants born at a GA of more than 29 weeks who do not receive an alarm, an ROP examination is performed at 5 weeks' chronologic age. If no ROP is present, no further ROP examinations are performed. If ROP is present, routine ROP examinations continue. For infants born at a GA of 29 weeks or less who do not receive an alarm, examinations are reduced according to clinical judgment if no ROP is present. With this implementation of WINROP, the number of ROP screening examinations has been reduced by 25% in one NICU center (A.H., unpublished data, October 2011). Using this examination schedule in our study cohort would have reduced ophthalmologic examinations for almost 30% of infants and still have detected 100% of type 1 ROP, including all 3 infants who did not receive an alarm or received a late alarm. There would have been a reduction of examinations in almost 65% of infants born at a GA of more than 29 weeks and in more than 16% of infants born at a GA of 29 weeks or less GA.

Current ROP screening guidelines suggest a 1- to 2-week follow-up range for infants with immature retinal vascularization in zone I with no ROP, zone II stage 2 ROP, and regressing zone I ROP and a 2- to 3-week follow-up range for infants with immature retinal vascularization in zone II without ROP, zone III stage 1 or 2 ROP, or regressing zone III ROP. It may be possible to safely decrease the number of ROP screening examinations for infants receiving no alarm by selecting the longer follow-up date within this range. As with any decision regarding ROP follow-up and management, clinical judgment must be used and be based on an infant’s complete medical history and examination.

Special attention should be given to the identification of nonphysiologic weight gain, clinical surveillance must be emphasized and routine ROP screenings should occur for all infants with nonphysiologic weight gain, such as for hydrocephalus or edema. Use of WINROP for prospective detection of type 1 ROP is ongoing.

It is important to characterize infants who developed type 1 ROP but were not identified by WINROP in this study. No evidence of nonphysiologic weight gain was found on limited retrospective review of the medical records in the 2 infants who developed type 1 ROP and did not receive an alarm or in the infant with a late alarm; however, there was a history of feeding intolerance requiring cessation of enteral nutrition and subsequent prolonged (>6 weeks) total parenteral nutrition use. Early postnatal nutrition is an important factor for weight gain and affects ROP severity. Human milk increases infant levels of IGF-I and ω-3 fatty acids that protect against ROP. It has been shown that infants who require ROP treatment receive more parenteral nutrition and less human milk during the first postnatal month, particularly during the second postnatal week. Prolonged feeding intolerance and total parenteral nutrition use, especially early in life, may be factors that warrant standard clinical surveillance for ROP even with WINROP indicating no alarm.

No infant in this cohort who developed type 1 ROP qualified for screening on the basis of BW alone, suggesting that GA and postnatal weight gain analysis may be more reflective of ROP risk. In 2006, ROP guidelines were modified to increase the GA for screening from 28 weeks or less to 30 weeks or less, but most infants who developed type 1 ROP in our cohort were born at 28 weeks or less GA. Two infants born at 29 weeks’ GA with type 1 ROP experienced poor postnatal weight gain and were correctly identified by WINROP. Current BW guidelines for ROP screening might be reconsidered if this is borne out in other studies.

In conclusion, postnatal weight gain analysis can help identify early infants at high risk for developing treatable ROP, as well as identify those not at risk. The WINROP system is an accessible, noninvasive tool that can be used to focus care on those at high risk for ROP, optimize follow-up, and potentially reduce the overall number of stressful diagnostic eye examinations.

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Table 4. Sensitivity, Specificity, and Positive and Negative Predictive Values in Identifying Type 1 ROP

<table>
<thead>
<tr>
<th>ROP categories, No. (%) of infants</th>
<th>Alarm Status</th>
<th>% (95% CI)</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alarm No Alarm Total</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 ROP</td>
<td>144</td>
<td>2</td>
<td>146</td>
<td>98.6 (96.7-100.5)</td>
</tr>
<tr>
<td>Non-type 1 ROP</td>
<td>957</td>
<td>603</td>
<td>1560</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1101</td>
<td>605</td>
<td>1706</td>
<td></td>
</tr>
<tr>
<td>Predictive value, % (No./total No.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>13.1 (144/1101)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPV</td>
<td>. . . 99.7 (603/605)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ellipses, not applicable; NPV, negative predictive value; PPV, positive predictive value; ROP, retinopathy of prematurity.
Author Contributions: Drs Wu and Löfqvist had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Drs Wu and Löfqvist contributed equally to first authorship; Drs VanderVeen and Hellstro¨m contributed equally to last authorship.

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REFERENCES


