

# Prediction of Retinopathy of Prematurity Using the Screening Algorithm WINROP in a Mexican Population of Preterm Infants

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**Objective:** To retrospectively validate the WINROP (weight, insulin-like growth factor I, neonatal, retinopathy of prematurity [ROP]) algorithm in identification of type 1 ROP in a Mexican population of preterm infants.

**Methods:** In infants admitted to the neonatal intensive care unit at Hospital Civil de Guadalajara from 2005 to 2010, weight measurements had been recorded once weekly for 192 very preterm infants (gestational age [GA] <32 weeks) and for 160 moderately preterm infants (GA ≥32 weeks). Repeated eye examinations had been performed and maximal ROP stage had been recorded. Data are part of a case-control database for severe ROP risk factors.

**Results:** Type 1 ROP was found in 51.0% of very preterm and 35.6% of moderately preterm infants. The

WINROP algorithm correctly identified type 1 ROP in 84.7% of very preterm infants but in only 5.3% of moderately preterm infants. For infants with GA less than 32 weeks, the specificity was 26.6%, and for those with GA 32 weeks or more, it was 88.3%.

**Conclusions:** In this Mexican population of preterm infants, WINROP detected type 1 ROP early in 84.7% of very preterm infants and correctly identified 26.6% of infants who did not develop type 1 ROP. Uncertainties in dating of pregnancies and differences in postnatal conditions may be factors explaining the different outcomes of WINROP in this population.

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**R**ETINOPATHY OF PREMATURITY (ROP) is a major cause of life-long blindness; its frequency is strongly associated with the quality of health care. In high-income countries, where many very immature babies survive, severe ROP affects the most immature, and screening and treatment programs make blindness rare. In middle-income countries, health care is good enough for survival of some extremely premature and more mature babies<sup>1</sup> but is insufficient in preventing ROP, leading to an increased prevalence of ROP in more mature babies; an epidemic of ROP-related blindness is presently seen in these countries. In the poorest parts of the world, where immature babies do not survive, ROP is not a problem.<sup>2</sup>

Current screening programs are based on gestational age (GA) and/or birth weight (BW) but, because of national differences in socioeconomic status and quality of care, different countries need different screening criteria.<sup>2</sup> The disadvantage of using GA for national screening criteria was recently shown in a study<sup>3</sup> from Rio de Janeiro. Two clinics with high survival rates had no infants with type 1 ROP whose GA was more

than 32 weeks, while in 5 other clinics with poorer survival rates, infants with GA 35 weeks or less required screening.

In high-income countries that screen infants with GA less than 32 weeks, only 5% to 10% of the infants need treatment,<sup>4</sup> and many fragile babies who will never develop sight-threatening ROP undergo repeated painful and stressful eye examinations.<sup>5</sup>

Based on the finding of the association between poor early weight gain,<sup>6</sup> low serum insulin-like growth factor I, and ROP and in an attempt to refine ROP screening, the algorithm WINROP (weight, insulin-like growth factor I, neonatal, ROP) was developed and validation of its ability to predict severe ROP was performed.<sup>7,8</sup> Later, WINROP was found to function well using only weights,<sup>9</sup> allowing blood sampling and analyses to be omitted. Studies validating WINROP in 3 different populations with GA less than 32 weeks have been published. In one Swedish<sup>9</sup> and one US population,<sup>10</sup> sensitivity of 100% and specificity of 84.5% and 81.7%, respectively, were found, and in a Brazilian study,<sup>11</sup> sensitivity was 90.5% and specificity was 55.0%.

The aim of this study was to validate WINROP regarding its ability to predict

severe ROP, defined as type 1 ROP, in a Mexican population of preterm infants.

## METHODS

### PATIENTS

The study group comprised a case-control database of infants (N = 377) who were screened and/or treated for ROP at the Hospital Civil de Guadalajara, Mexico, from April 20, 2005, to April 15, 2010, and had weekly weight measurements. The infants included had survived from the initial ophthalmologic examination at 3 to 6 weeks to the final ROP examination. Fifteen infants were referred for treatment from Hospital Materno Infantil Esperanza Lopez Mateos in Guadalajara.

Hospital Civil de Guadalajara is a university hospital located in Guadalajara, a city with a total population of approximately 5 million inhabitants. Guadalajara is the main city in the state of Jalisco. All admitted patients were from the low-income urban population in the Guadalajara region. The neonatal intensive care unit ROP program screens approximately 220 preterm babies per year. Each weekly weight was entered into WINROP.

The neonatologists determined the GA for each infant on the basis of the mother's report of the date of her last menstrual period.

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 lid speculum; when necessary, a depressor (Flynn Scleral) was used to better identify peripheral retinal alterations. Retinopathy was classified according to the International Classification of Retinopathy of Prematurity (stages 1-5).<sup>12</sup> The indications for treatment were type 1 ROP according to the recommendations of the ETROP (Early Treatment for Retinopathy of Prematurity) study.<sup>13</sup> The same ROP-experienced pediatric ophthalmologist (L.C.Z.R.) performed all ophthalmic examinations.

### WINROP SCREENING

The first step of the WINROP algorithm was developed using the methods of online statistical surveillance.<sup>14-16</sup> Briefly, the algorithm, using data on preterm infants with no ROP or with ROP stage 1, calculates the expected "safe" weight for each child. The difference between the expected weight gain and documented values of postnatal weight development at each time point is calculated and accumulated. If the accumulated sum reaches a threshold limit, an alarm is triggered.<sup>7</sup> Data were retrieved from the files regarding weight once every postnatal week until 35 to 36 postmenstrual weeks; a person unaware of the maximum ROP stage entered these data, including GA at birth and BW, into the surveillance algorithm. Weight was measured every morning before feeding, and the weight on every 7th day was recorded in WINROP. In the first step of the algorithm, an alarm statistic is calculated for each child to judge whether there is enough evidence to conclude that a significant slowing of growth has occurred.

In previous studies, WINROP evaluations were at 1 of 3 levels: (1) no alarm, (2) alarm at low risk, and (3) alarm at high risk.<sup>7,8</sup> Risk level was based on GA and BW. Because classifying alarms as either high risk or low risk before 33 weeks' postmenstrual age (PMA) or no alarm or low risk after 33 weeks' PMA has been used successfully in previous studies, we decided to simplify classification into alarms before 33 weeks' PMA or no alarms before 33 weeks' PMA. In case of an alarm, 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.

## STATISTICAL ANALYSIS

The surveillance system using the variable *weight gain* was evaluated regarding sensitivity (probability that an alarm is triggered given that the infant develops type 1 ROP) and specificity (probability that an alarm is not triggered given that the infant will not develop type 1 ROP). The negative and positive predictive values were calculated using the sensitivity, specificity, and prevalence in the present study group. We calculated 95% CIs for estimated binary proportions (sensitivity and specificity) using the exact method of Clopper-Pearson.<sup>17</sup>

## ETHICS

The Research Ethics Committee of the Hospital Civil de Guadalajara approved the study protocol regarding postnatal weight gain and ROP. The protocol also conforms to the provisions of the Declaration of Helsinki in 1995 (as revised in Edinburgh, 2000).

## RESULTS

### ROP OUTCOME

A total of 362 infants had been screened for ROP and had weekly weight measurements performed at Hospital Civil de Guadalajara and 15 at Hospital Materno Infantil Esperanza Lopez Mateos in Guadalajara. Because WINROP was developed for infants with GA less than 32 weeks, separate analyses were performed for infants with GA less than 32 weeks (very preterm) and for those with GA 32 weeks or more (moderately preterm).

#### Infants With GA Less Than 32 Weeks

There were 206 very preterm infants, 14 of whom were excluded (12 owing to hydrocephalus, which may cause non-physiologic weight gain, and 2 because of unspecified ROP stage), leaving a study group of 192 infants (median GA, 30 weeks; range, 25-31 weeks). The type of ROP in relation to WINROP alarm in very preterm infants is given in **Table 1**. In this group, 163 infants had ROP (84.9%) and more than half (51.0%) had type 1 ROP. The ROP stages of these infants are also given in Table 1. Of the 192 infants, 102 (53.1%) were diagnosed as having plus disease.

#### Infants With GA 32 Weeks or More

There were 171 moderately preterm infants. Two of them were excluded because of unspecified stage of ROP, 4 because of hydrocephalus, and 5 for an insufficient number of weight measurements. The moderately preterm study group thus comprised 160 infants (median GA, 33 weeks; range, 32-35 weeks). The type of ROP in relation to WINROP alarm in moderately preterm infants is provided in **Table 2**. In this group, 103 infants (64.4%) had ROP and more than one-third had type 1 ROP. The ROP stages of these infants are also provided in Table 2. Of the 160 moderately preterm infants, 63 (39.4%) had plus disease.

### WINROP OUTCOME

For all 352 infants, weekly weights had been registered and were entered into the online surveillance system.

**Table 1. Type of ROP in Relationship With WINROP Alarm in Infants With GA Less Than 32 Weeks**

ROP Type	No Alarm or Low-Risk Alarm $\geq$ 33 wk	Low-Risk Alarm Before PMA 33 wk	High-Risk Alarm	Total, No. (%)
1	15	66	17	98 (51.0)
2	1	9	0	10 (5.2)
Less severe than 2	11	41	3	55 (28.6)
No ROP	13	16	0	29 (15.1)
<b>Total</b>	<b>40</b>	<b>132</b>	<b>20</b>	<b>192 (100.0)</b>

Abbreviations: GA, gestational age; PMA, postmenstrual age; ROP, retinopathy of prematurity; WINROP, weight, insulin-like growth factor I, neonatal, ROP.

**Table 2. Type of ROP in Relationship With WINROP Alarm in Infants With GA 32 Weeks or More<sup>a</sup>**

ROP Type	No Alarm or Low-Risk Alarm $\geq$ 33 wk	Low-Risk Alarm Before PMA 33 wk	High-Risk Alarm	Total, No. (%)
1	54	3	0	57 (35.6)
2	5	0	0	5 (3.1)
Less severe than 2	34	7	0	41 (25.6)
No ROP	52	5	0	57 (35.6)
<b>Total</b>	<b>145</b>	<b>15</b>	<b>0</b>	<b>160 (100.0)</b>

Abbreviations: GA, gestational age; PMA, postmenstrual age; ROP, retinopathy of prematurity; WINROP, weight, insulin-like growth factor I, neonatal, ROP.

<sup>a</sup>Indicates having a GA greater than 31 weeks, 6 days.

Details follow on the outcome of using the WINROP screening tool.

#### Infants With GA Less Than 32 Weeks

For 40 children (20.8%), no alarm was triggered (Table 1). Fifteen of these infants developed type 1 ROP. The median GA of these 15 patients was 31 weeks (range, 28-31 weeks), and the median BW was 1420 g (range, 1180-1510 g). Six of the 15 infants with type 1 ROP with no alarms had stage 2+ ROP in zone II. For 152 infants (79.2%), an alarm was triggered. In this group, 83 (54.6%) developed type 1 ROP. The sensitivity with which WINROP predicted type 1 ROP in the infants with GA less than 32 weeks was 84.7%, and the specificity was 26.6%.

#### Infants With GA 32 Weeks or More

No alarm was generated for 145 of the infants (90.6%) in this group, although 54 of them had type 1 ROP. Of the 5 infants with type 2 ROP without alarms, none developed type 1 ROP. Fifteen infants had alarms, and 3 of them developed type 1 ROP. The sensitivity of WINROP in predicting type 1 ROP in infants with GA 32 weeks or more was 5.3%, and the specificity was 88.3%.

### COMMENT

In this retrospective study on a Mexican population of preterm infants, the WINROP algorithm correctly identified type 1 ROP in 83 of 98 very preterm infants (84.7%) (GA <32 weeks) but only in 3 of 57 of moderately preterm infants (5.3%) (GA  $\geq$ 32 weeks). In previous studies from Sweden<sup>9</sup> and North America,<sup>10</sup> 100% of infants developing stage 3 ROP have been identified. There may be several reasons for this discrepancy.

In the previous studies,<sup>9,10</sup> GA calculations were based on ultrasound measurements during early pregnancy; in this study, the mother's report on her last menstrual period was the basis of GA estimation, making it less accurate.

In previous studies, we have tested WINROP's ability to predict proliferative ROP, and we decided not to include plus disease because it is difficult to evaluate retrospectively. For the population of the present study, data on plus disease were provided, and because future prospective studies will aim to predict ROP that needs to be treated according to the criteria recommended by the ETROP study,<sup>13</sup> we set out to determine the ability of WINROP to predict type 1 ROP in this population. Thus, some infants with proliferative ROP without plus disease or in zone III are not included among the patients we wanted to identify.

Before the study, we had hypothesized that all infants with an alarm before 33 weeks' PMA, ie, before the age when proliferative ROP is likely to occur, would need eye examinations, while those without such alarms would not.

According to present treatment criteria, patients should be treated if they have stage 2+ ROP in zone II that is not proliferative. A total of 31 infants (10 with GA <32 weeks) in this study had stage 2+ ROP in zone II. In the Swedish experience, stage 2+ ROP in zone II is very rare and was not found in any patient in the Gothenburg study.<sup>9</sup> In the ETROP study,<sup>13</sup> only 66 of 828 infants (8.0%) with BW less than 1251 g and prethreshold disease had stage 2+ ROP in zone II compared with 31 of 352 (8.8%) of all screened infants in the present study. A high frequency of stage 2+ ROP in zone II has also been found in India, according to A. Vinekar, MD, PhD (e-mail communication, April 2011).

The fact that a different kind of ROP affecting more mature babies is seen in developing countries has led to different screening criteria in terms of GA and BW in differ-

ent populations ( $\leq 34$  weeks weight for GA and  $\leq 1750$  g BW in Mexico).<sup>18</sup> The finding of severe ROP in comparatively mature infants and the finding of more stage 2+ in zone II in this Mexican population and an Indian population may indicate different quality of neonatal care, with risk factors and causative mechanisms that result in different progression of ROP in different populations. In the present study, we know that oxygen monitoring was insufficient and that the antenatal care could be improved,<sup>19-21</sup> and there is reason to believe that other differences exist between this population and those of high-income countries that could be improved by better care. Because WINROP gives very early indications of poor growth that is related to later morbidity, one may anticipate that it can be used as an indicator of the need for better early care long before information on ROP outcome is available, possibly at a stage when morbidity may be prevented.

Considering the possible differences in ROP progression in this population compared with those of high-income countries, one cannot be confident that treatment criteria necessarily should be the same as those based on US infants with BW less than 1251 g, as in the ETROP study. One intriguing factor for this and other populations is the importance of plus disease as a criterion for type 1 ROP and the inconsistencies found between observers regarding plus disease, making overdiagnosis a possible problem.<sup>22</sup>

In the present study of a Mexican population, teenage pregnancies were common, GA estimates were less accurate than in other WINROP studies, and prenatal and postnatal care were different.

It is not surprising that WINROP, which was developed for use in infants with GA less than 32 weeks and initiates an alarm before 33 weeks' PMA, was not able to predict type 1 ROP in infants with GA 32 weeks or more. Of those with GA less than 32 weeks, 84.7% received an alarm. We do not know to what extent inaccurate dating contributed to WINROP's poorer ability to predict ROP in very preterm infants in this study compared with previous studies. The exact date of birth is necessary, and one must know whether the baby is born before 32 weeks' GA. Of the 15 infants with type 1 ROP and no alarms, 12 had GA 30 weeks or more, making inappropriate dating of 2 weeks significant. The results from the moderately preterm infants show that WINROP is not useful for infants for whom it was not developed.

Early weight gain is a marker for conditions that later may lead to ROP and possibly other morbidities. Because WINROP generates early alarms regarding later morbidity, its use as a monitor of quality of early care of infants with GA less than 32 weeks should be explored. Early alarms may lead to interventions preventing disease. Discrepancies could reflect the excess of ROP in these settings that is a result of differences in the quality of neonatal care.

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