Longitudinal Postnatal Weight and Insulin-like Growth Factor I Measurements in the Prediction of Retinopathy of Prematurity

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Objective: To investigate whether postnatal growth and development influence retinopathy of prematurity (ROP) and may be included in screening for ROP.

Design: We developed an algorithm to predict for individual infants the risk of later ROP development requiring treatment based on the postnatal longitudinal systemic factors of insulin-like growth factor I (IGF-I) level, IGF binding protein 3 level, and postnatal weight gain. We developed the algorithm based on 79 preterm infants considered at risk for ROP by standard criteria (gestational age, 23.6-31.7 weeks) in a longitudinal study measuring weight gain and serum IGF-I and IGF binding protein 3 levels weekly from birth until discharge from the hospital. We monitored deviations from reference models for weight and IGF-I level (preterm children who developed no or minimal ROP) to detect indications for treatable ROP by Early Treatment for Retinopathy of Prematurity study criteria.

Results: This monitoring method detected 6 (100%) of 6 infants in this cohort who required treatment for ROP with a warning signal at least 5 weeks before requiring treatment and at least 3 weeks before the onset of stage 3 ROP. The majority of infants (61/73 infants) requiring no treatment were also correctly identified.

Conclusions: Monitoring the postnatal factors of weight, IGF-I level, and IGF binding protein 3 level substantially enhances the clinician's ability to identify patients who will require treatment for ROP.

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RETINOPATHY OF PREMATURITY (ROP) is a retinal vasoproliferative disease associated with preterm birth. It is a major cause of blindness in children in the developed and developing worlds[1] despite current disease treatment. The vascular changes in the early stages[2,3] most often regress with time, but stage 3 may progress and lead to total retinal detachment and blindness. Premature infants considered at risk for blindness are screened with eye examinations for ROP starting at approximately 30 weeks' postmenstrual age (PMA) primarily to identify those who will need laser therapy or cryotherapy to help prevent further progression. The current guidelines for eye screening are based on the perinatal risk factors of low gestational age (GA) at birth and low birth weight (BW), and they are intended to include close to 100% of infants requiring treatment. However, fewer than 10% of infants screened with eye examinations will develop sight-threatening ROP, subjecting many low-risk infants to stressful eye manipulations. If infants who will develop treatable ROP are identified early, it would help clinicians to plan appropriately. It is widely understood that "sicker" infants with a poor postnatal course are at higher risk for ROP, but postnatal factors are currently not taken into account in predicting retinopathy. A system that uses both perinatal factors and

For editorial comment see page 1775

growth factors may be able to predict disease early and to reduce the number of eye examinations. We have previously found that a persistent reduction in the growth factor insulin-like growth factor I (IGF-I) (and, by implication, growth) after birth is associated with subsequent development of ROP.[4] Although it is possible to calculate ROP risk scores based on IGF-I levels at a certain week for an infant,[4] we found that by following the development of the children weekly (weight and IGF-I level) and using accumulated information about their development, we get a better indication of the future development of ROP and can exclude those at low risk.

Table 1. Clinical Characteristics, Interventions, and Separate Outcome Variables of the Study Group

Variable	ROP0/ROP1	ROP2	ROP3/ROPT
Sex, M/F, No.	16/22	14/14	5/8
Postmenstrual age, median (range), wk	29.4 (24.4 to 31.7)	26.5 (23.9 to 30.9)	26.0 (23.6 to 29.9)
Birth weight, median (range), g	1180 (640 to 2015)	898 (530 to 1540)	780 (535 to 1410)
Birth weight standard deviation score, median (range)	–1.23 (–5.04 to 1.12)	–1.64 (–4.41 to 1.94)	–0.99 (–4.03 to 0.79)
NEC, No. (%)	0	0	4 (31)
BPD, No. (%)	2 (5)	13 (46)	8 (62)
IVH, No. (%)	0	3 (11)	1 (8)

Abbreviations: BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP0, no retinopathy of prematurity; ROP1, stage 1 retinopathy of prematurity; ROP2, stage 2 retinopathy of prematurity; ROP3, stage 3 retinopathy of prematurity; ROPT, treated retinopathy of prematurity.

METHODS

STUDY PARTICIPANTS

Preterm infants born at less than 32 weeks' GA at the Queen Silvia Children's Hospital, Göteborg, Sweden, between December 18, 1999, and April 8, 2002, and at Uppsala University Hospital, Uppsala, Sweden, between February 12, 2001, and April 11, 2002, were recruited to these studies. Inability to complete postnatal clinical follow-up until 40 weeks' PMA or discharge to home and conspicuous congenital anomaly were exclusion criteria. The ethics committees of the medical faculties at Göteborg University and Uppsala University approved the study (approval number Ö594-00), and the parents of the infants gave informed consent. Clinical characteristics are given in **Table 1**.

GROWTH FACTOR MEASUREMENTS

Venous blood samples (0.5 mL) were taken weekly, and the serum was stored at –20°C to –80°C until assayed. All of the samples from an individual infant were analyzed in the same assay.

The serum IGF-I level was measured using an IGF binding protein (IGFBP)–blocked radioimmunoassay (Mediagnost GmbH, Tübingen, Germany) with a large excess of IGF-II for determination of the IGF-I level.[5] For the IGF-I assay at concentrations of 36, 260, and 545 µg/L, the intra-assay coefficients of variations (CVs) were 11.1%, 5.2%, and 7.4%, respectively, and the interassay CVs were 13.5%, 7.8%, and 9.9%, respectively.

Serum IGFBP-3 levels were measured with a specific radioimmunoassay (Mediagnost GmbH).[5] For the IGFBP-3 assay at concentrations of 1800, 3790, and 5776 µg/L, the intra-assay CVs were 7.1%, 7.3%, and 7.9%, respectively, and the interassay CVs were 13.4%, 10.5%, and 14.1%, respectively.

MORBIDITY

Retinopathy of prematurity was classified according to the International Classification of Retinopathy of Prematurity[6] and subdivided into stage 1 (demarcation line), stage 2 (ridge), stage 3 (ridge with extraretinal fibrovascular proliferations), stage 4 (subtotal retinal detachment), and stage 5 (total retinal detachment). In all GA weeks, each child was classified according to the most advanced ROP stage observed. No or stage 1 ROP was designated ROP0/1, stage 2 ROP was designated ROP2, proliferative stage 3 ROP was designated ROP3, and treated ROP was designated ROPT. The infants were examined according to a routine protocol that consisted of dilated eye fundus examinations once or twice a week depending on the severity of the disease from the chronological age of 5 to 6 weeks until the eyes were fully vascularized or until the condition was considered stable. After pupillary dilatation with weak solutions of cyclopentolate hydrochloride and phenylephrine hydrochloride, the eyes were examined by indirect ophthalmoscopy by a trained pediatric ophthalmologist (A.-L.H., A.H., or Gerd Holmström, MD, PhD) who had no knowledge of the IGF-I status.

STATISTICAL DATA ANALYSIS

Determining Which Variables Best Discriminate Between ROP0/1 and ROP3/ROPT

The longitudinal data consisted of weekly measurements of weight and growth factors. We started by determining which variables best discriminated between no or mild ROP (ROP0/1) and proliferative disease possibly requiring laser treatment (ROP3/ROPT). The analysis was made using logistic regression where the ROP stage was categorized as no or minimal ROP (ROP0/1) or proliferative ROP potentially requiring treatment (ROP3/ROPT). In the logistic regression, the risk (or log odds) of proliferative ROP was modeled as a function of explanatory variables. The explanatory power of the following variables was assessed: sex, BW, change in weight, and postnatal serum IGF-I, IGF-II, IGFBP-1, and IGFBP-3 levels. For the postnatal variables with more than 1 value for each child, a mean value was used. For children with proliferative ROP, the mean was calculated from the observations up to the week before ROP3 (ending week). Thus, the ending week differed between the children (week 30-39). For the children with mild ROP, there was no natural ending week, so an ending week was set according to the same distribution as for the children with ROP3 (thus ranging from week 30-39).

Construction of Reference Model for IGF-I Level and Weight for ROP0/1

We wanted to construct a system for detecting those children who had poor weight gain and/or poor IGF-I development. One way of doing this was to follow a child's development of weight and IGF-I and continually assess whether that child's measurements were smaller than what could be expected. We used those variables that discriminated best between no or minimal ROP and proliferative ROP to construct reference models, showing the expected longitudinal development in patients who progressed to no or mild ROP (ROP0/1) (**Figure 1**A and B). We used random coefficient regression (PROC MIXED procedure in SAS version 8.02 statistical software [SAS Institute, Inc, Cary, NC]). With repeated measurements on the same individual, there is often a within-individual dependence. Therefore, ordinary regression analysis is not suitable. Instead, a random coefficient regression model can be estimated where the coefficients (a, b1, b2, etc) are allowed to vary from one individual

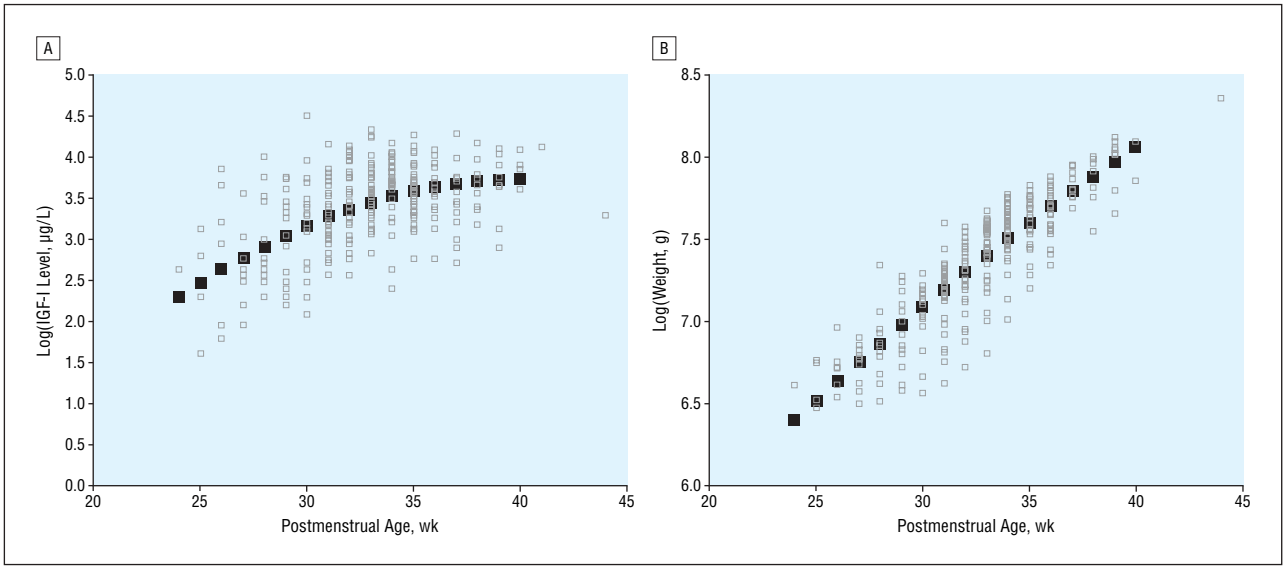

Figure 1. Reference models for weight and insulin-like growth factor I (IGF-I). A, Development of IGF-I for children with no or stage 1 retinopathy of prematurity. Solid squares indicate the expected IGF-I level at different postmenstrual ages. The IGF-I values were log-transformed to stabilize the variance. B, Weight development for children with no or stage 1 retinopathy of prematurity. Solid squares indicate the expected value of weight at different postmenstrual ages. The weight values were log-transformed to stabilize the variance.

to the next. In our model, the intercept a is individual, allowing child 1 to have a different intercept than child 2. This means that the model of the development of weight over time takes into account that each infant has his or her own starting value. The same applies to IGF-I development.

Construction of Surveillance System to Alert for Deviations From Reference Model

We followed the development of a child by measuring the weight and growth factors once a week to detect a slowdown. These measurements contained stochastic variation, so a slowdown might have been obscured. At each week, we used the accumulated weight and IGF-I measurements for each child to calculate the value of an alarm statistic that was used to judge whether the weight or IGF-I level was close enough to the expected value. The simplest form of surveillance is to use only the observation of the current week, but for gradual or small changes, it is better to accumulate the observations. A slowdown can be detected when the observations differ substantially from the expected weight or IGF-I development. This is shown schematically in **Figure 2**A. The expected development was assessed from the reference models. The surveillance system was developed according to the theory of statistical surveillance.[7] The alarm statistic was based on the likelihood function using the Shiryaev-Roberts approach.[8,9] When an infant's measurement deviated considerably from the reference model, a signal was called that this individual might be at risk for developing proliferative ROP. The alarm limit for what was to be considered a large enough cumulative deviation was set with the criterion of not missing any of the children with proliferative ROP.

Reassessment if an Alarm Is Called

If an alarm was called for a child at, for example, 29 weeks' PMA, a follow-up evaluation was required to discriminate between patients at low risk and patients at high risk for treatable ROP. At the time of the alarm, the child's levels of IGF-I and IGFBP-3 at that time as well as the child's BW and GA were analyzed. Cutoff limits were constructed for the IGF-I and IGFBP-3 levels at the alarm time as well as for PMA and BW. The cutoff limits were based on the values for the children who required treatment. Infants with values below a cutoff remained at risk. Because the levels of IGF-I and IGFBP-3 obviously vary with time (higher levels for later alarm times), the cutoff for these variables was constructed as a function of PMA (**Figure 3**).

Analyses were performed using SAS version 8.02 and SPSS version 11.0 (SPSS, Inc, Chicago, Ill) statistical software.

RESULTS

An analysis was first made to determine which growth factors best indicated proliferative ROP. Using these results, models for the longitudinal development of the relevant factors in patients who did not develop ROP were made. These reference models were used in an online surveillance system to detect slowdown in weight and IGF-I development.

DETERMINING WHICH VARIABLES BEST DISCRIMINATE BETWEEN NO ROP AND PROLIFERATIVE ROP

A logistic regression was performed with a dichotomized ROP variable as the response variable (ROP0/1 vs ROP3/ROPT). Explanatory variables were GA, BW, and the postnatal variables of weight gain and levels of IGF-I, IGF-II, IGFBP-1, and IGFBP-3. As expected, the birth indicators GA and BW were both highly associated with ROP, with R^2 values of 0.43 and 0.36, respectively (**Table 2**). The postnatal longitudinal variables that best discriminated between ROP0/1 and ROP3/ROPT were weight and IGF-I level (R^2, 0.35 and 0.29, respectively).

DEVELOPMENT OF A REFERENCE MODEL FOR LONGITUDINAL DEVELOPMENT OF IGF-I AND WEIGHT IN ROP0/1

A reference model was developed for infants with no or mild ROP for IGF-I level (Figure 1A) and weight

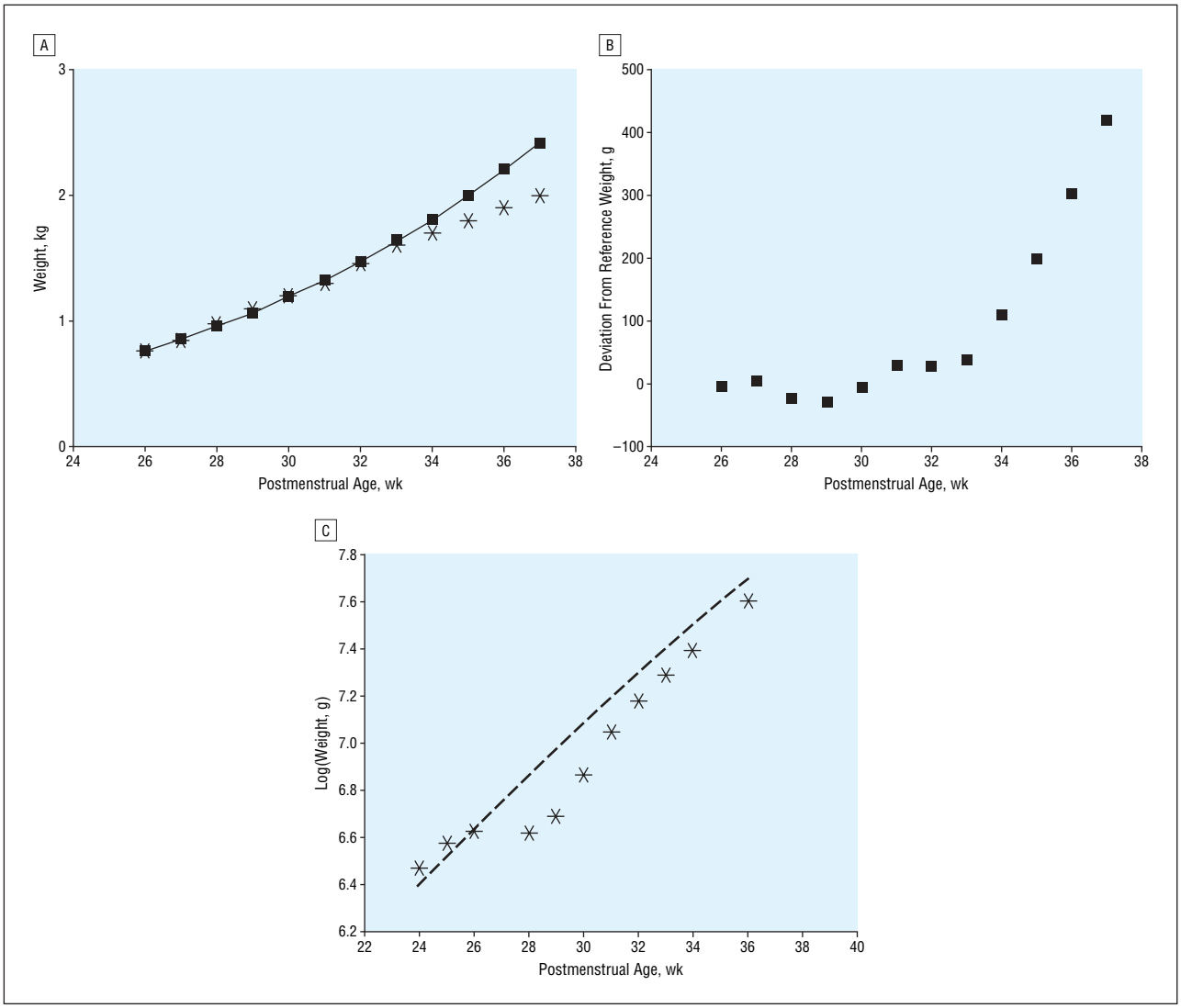

Figure 2. Schematic figure of the gradual slowdown in weight (A), the cumulative deviation from the expected weight (B), and the observed (asterisks) and expected (dashed line) log(weight) values of 1 child together with the expected weight (C).

(Figure 1B). The reference models for IGF-I level and weight were estimated using different polynomials. The variables were log-transformed to stabilize the variance. These reference models were used to calculate the expected value at each PMA. For example, the expected value for ln (weight) at week 25 is $2.8524 + 0.1738 \times 25 - 0.00109 \times (25^2) = 6.52$, and the expected value for ln(IGF-I level) at week 25 is $-5.1062 + 0.4398 \times 25 - 0.00547 \times (25^2) = 2.47$. Also, the variance was estimated here.

USING AN ONLINE SURVEILLANCE SYSTEM TO DETECT SLOWDOWN IN IGF-I DEVELOPMENT AND WEIGHT GAIN

In the surveillance, we compared each child's weight value and IGF-I level to the respective reference model to detect a slowdown in the development of either variable (or both). For each child, the deviation from the reference model was used in the surveillance algorithm as an indication of possible development of proliferative ROP.

The continual monitoring meant that new observations on weight and IGF-I level became available each week; at each PMA week, the values of 2 so-called alarm statistics were calculated for each child (1 alarm statistic for IGF-I level and 1 for weight). The alarm statistics were used to judge whether there was enough evidence to conclude that a considerable slowdown had occurred in either weight or IGF-I level for that child. The alarm statistics for each child were based on all of the differences over time between the observed values and the reference value for that respective week. At each PMA, new values of the alarm statistics for each child were compared with preset alarm limits, and an alarm was called if either alarm statistic crossed the limit. Thus, the information about possible deviations from each reference model was accumulated since birth (example in **Table 3**). In Figure 2B, we see the observed values of ln(weight) as well as the expected development. According to this reference model, the child had weight development below the expected value from 28 weeks' PMA. The actual computation was rather complex and we are developing a computer pro-

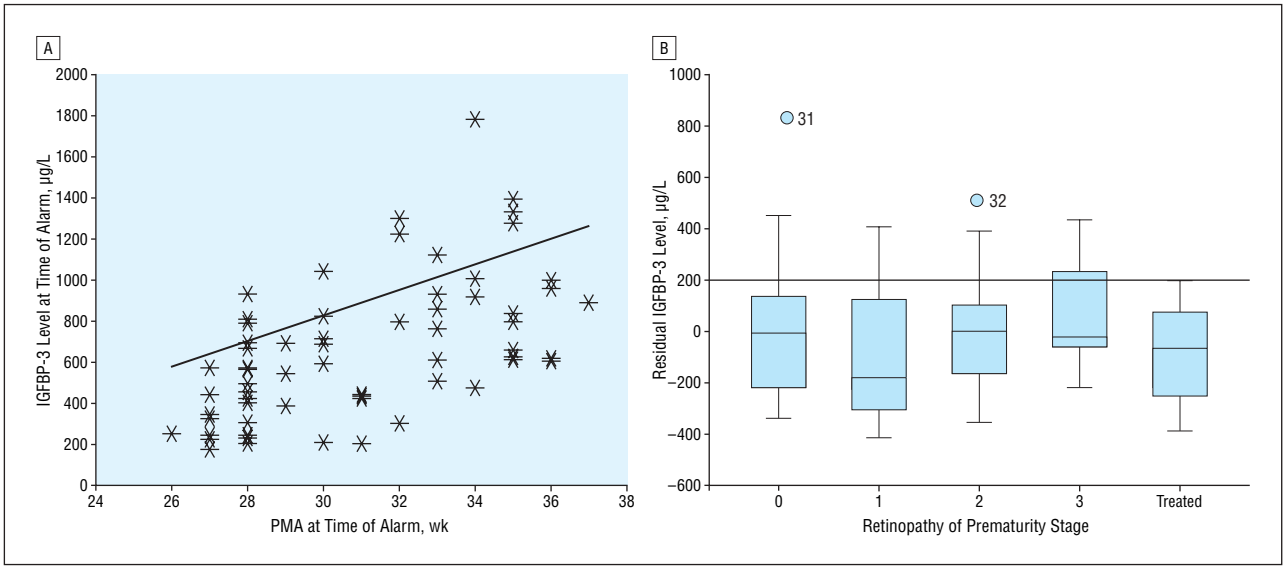

Figure 3. When an alarm is called for a child in the surveillance system, a reassessment of the values at the alarm time is made to determine whether the child is at low or high risk of needing treatment. Children with values below a cutoff are considered to be at high risk of needing treatment. A, The cutoff function for the insulin-like growth factor binding protein 3 (IGFBP-3) level is shown. Since the IGFBP-3 level increases with time, the cutoff function meant that we used a cutoff value that reflected a high IGFBP-3 level in relation to postmenstrual age (PMA). B, A child's value above the cutoff function is equivalent to the residual value being above a constant cutoff. The residual value is calculated as the difference between the observed value and the value calculated according to the regression. The error bars indicate the minimum and maximum values except when there is an outlier (circle), in which case the error bars indicate the next largest value. The numbers next to the circles indicate the number of outliers.

gram for the computation (Weight, IGF, Neonatal Retinopathy of Prematurity [WINROP] program, weight, IGF, neonatal measurements).

REASSESSMENT IF AN ALARM SOUNDED

If an alarm was called, the child's levels of IGF-I and IGFBP-3 at the alarm time as well as the child's BW and GA were analyzed. Infants with values below a cutoff remain at risk (Figure 3). After the follow-up test, 18 infants (6 of whom were treated) were followed up conventionally until they reached 40 weeks' PMA (**Table 4** and **Table 5**). Clinical characteristics are given in **Table 6**. Thus, an additional 45 (63%) of 73 infants who did not need treatment were correctly identified and cleared after 1 ophthalmologic examination. The infants were then transferred back to the surveillance (as the surveillance was constructed to detect all infants with ROP3 while the follow-up test only classified the infants at risk of needing treatment [ROPT]) (**Figure 4**). Thus, the WINROP algorithm combined with the follow-up test correctly excluded 61 (84%) of 73 infants who did not need treatment, predicted 13 (100%) of 13 infants who developed ROP of stage 3 or higher, and identified all of the infants at risk of needing treatment (ROPT).

ONLINE SURVEILLANCE REDUCED THE NEED FOR EXAMINATIONS

The benchmark rule for screening for ROP with eye examinations is that infants born before 32 weeks' GA need to be monitored by weekly eye examinations starting at age 5 weeks (this included all of the patients in our cohort). If this group had been monitored with the suggested surveillance system, all of the children who developed ROP3 or needed treatment would have been detected with a warning signal at least 4 weeks before the onset of ROP3 and 5 weeks before requiring treat-

Table 2. Logistic Regression With Dichotomized Retinopathy of Prematurity as the Response Variable and Constant Perinatal and Longitudinal Postnatal Explanatory Variables*

Variable†	Nagelkerke R^2 (Patients, No.)
Constant perinatal variable	
GA at birth	0.43 (51)
BW standard deviation score	0.004 (51)
BW	0.36 (51)
Sex	0.002 (51)
Twin	0.01 (51)
BW standard deviation score, GA at birth	0.46 (51)
BW, GA at birth	0.45 (51)
Longitudinal postnatal variable	
Weight in g	0.35 (51)
IGF-I level in µg/L	0.29 (51)
IGF-II level in µg/L	0.004 (51)
IGFBP-1 level in µg/L	0.014 (48)
IGFBP-3 level in µg/L	0.13 (51)
Weight in g, IGF-I level in µg/L	0.40 (51)

Abbreviations: BW, birth weight; GA, gestational age; IGF, insulin-like growth factor; IGFBP, IGF binding protein.

*The response variable was dichotomized as no or stage 1 retinopathy of prematurity vs stage 3 or treated retinopathy of prematurity.

†When performing the logistic regression, the mean value was used for the variables that had repeated measures for the same child. For children with proliferative retinopathy of prematurity, the mean was calculated from the observations up to the week before stage 3 retinopathy of prematurity (ending week). Thus, the ending week differed between the children (week 30-39). For the children with mild retinopathy of prematurity, there was no natural ending week, so an ending week was set according to the same distribution as for the children with stage 3 retinopathy of prematurity (thus ranging from week 30-39).

Table 3. Example of Surveillance Model for Child With First Week of Stage 3 Retinopathy of Prematurity at 34 Weeks' Postmenstrual Age and Laser Treatment at 35 Weeks' Postmenstrual Age

PMA, wk	Log(IGF-I Level, µg/L)	Log(Weight, g)	In-Control IGF-I Level, ln(IGF-I Level, µg/L)	In-Control Weight, ln(Weight, g)	Different IGF-I Level, ln(IGF-I Level, µg/L)	Different Weight, ln(Weight, g)	Alarm for IGF-I Level	Alarm for Weight
24	2.20	6.48	2.30	6.40	–0.10	0.08	No	No
25	3.33	6.53	2.47	6.52	0.86	0.01	No	No
26	2.56	6.63	2.63	6.63	–0.07	0.00	No	No
28	2.25	6.62	2.92	6.86	–0.67	–0.24	No	Yes*
29	2.08	6.68	3.05	6.98	–0.97	–0.30	No	Yes
30	3.09	6.89	3.16	7.09	–0.07	–0.20	Yes*	Yes

Abbreviations: IGF-I, insulin-like growth factor I; PMA, postmenstrual age.
*The first alarm was called.

Table 4. Result of Alarm System for Insulin-like Growth Factor I and Weight Showing Early Detection of Children With Stage 3 Retinopathy of Prematurity Who Will Need Treatment

Child No.	Maximal ROP Stage	First Week of Proliferative ROP	Week of Alarm	Week of Treatment	Time Before Treatment, wk
292	ROPT	34.6	28	35.1	7.1
320	ROPT	34.3	27	35.3	8.3
931	ROPT	40.1	30	43.9	13.9
2023	ROPT	38.0	28	38.0	10.0
2123	ROPT	40.7	28	41.7	13.7
2529	ROPT	35.1	32	37.7	5.7

Abbreviations: ROP, retinopathy of prematurity; ROPT, treated retinopathy of prematurity.

Table 5. Reassessment of 4 Variables in 63 Infants After First Alarm to Dichotomize a Child Into High or Low Risk of Retinopathy of Prematurity Requiring Treatment

Variable	Children, No.	
	Excluded From Risk	Remaining at Risk
IGFBP-3	11	52
IGF-I	15	37
PMA	13	24
BW	6	18

Abbreviations: BW, birth weight; IGF-I, insulin-like growth factor I; IGFBP-3, insulin-like growth factor binding protein 3; PMA, postmenstrual age.

ment (Table 4). With a second evaluation, a total of 61 (84%) of 73 infants who developed no ROP were correctly identified and thereby classified as being in less need of any eye examinations (Figure 4).

OTHER MORBIDITY

Although the purpose of the surveillance system with the follow-up procedure was to identify those infants who would need treatment for ROP, we investigated the incidence of other morbidity (intraventricular hemorrhage, necrotizing enterocolitis, and bronchopulmonary dysplasia) in the infants classified as being at high risk. Within the group of 18 infants classified as being at high risk for needing treatment for ROP, 16 infants either required treatment for ROP or developed other morbidity (intraventricular hemorrhage, necrotizing enterocolitis, or bronchopulmonary dysplasia) (Table 5). Of the 18 infants classified as being at high risk with the WINROP algorithm, only 2 (11%) developed no morbidity (intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, or ROPT).

COMMENT

Most clinicians believe that the clinical postnatal course of premature infants may be critical in determining ROP and other complications of prematurity. However, current screening for postnatal disease, eg, ROP, in the preterm child does not take extrauterine health into consideration. In this article, we describe a new algorithm that takes the postnatal course into consideration to predict early the risk of an individual infant developing ROP requiring treatment and to predict those infants at minimal risk requiring fewer or no eye examinations.

Screening for ROP was started in many countries at the end of the 1980s, when the Cryotherapy for Retinopathy of Prematurity[10] study based in the United States reported its first positive results of cryotherapy, which was to be performed at the time of reaching a threshold that was defined by retinal characteristics. Screening guidelines for ROP were introduced in Sweden a decade ago based on an epidemiological study[2] on the inci-

Table 6. Characteristics of 18 Children at High Risk for Retinopathy of Prematurity After First Alarm and Reassessment of 4 Variables

Child No.	Sex	GA, wk	BW, g	BWSDS	BPD	IVH	NEC	Maximal ROP Stage*
26	Female	25.00	650	–1.59	Yes	No	No	2
282	Male	28.00	625	–4.41	No	No	No	2
292	Female	23.57	590	–0.42	Yes	No	No	T
320	Male	24.86	835	0.38	Yes	No	No	T
652	Male	26.57	790	–2.11	Yes	No	No	2
931	Male	25.43	780	–0.96	Yes	No	No	T
1172	Male	26.00	700	–2.34	Yes	No	No	2
1213	Male	26.71	750	–2.57	No	No	No	2
1888	Male	24.71	530	–2.80	Yes	No	No	2
2003	Male	26.57	715	–2.73	Yes	No	No	3
2006	Male	25.57	811	–0.84	No	No	No	2
2007	Male	23.86	594	–1.03	Yes	Yes	No	2
2023	Male	24.71	535	–2.74	Yes	No	Yes	T
2123	Female	28.57	715	–4.03	No	No	No	T
2508	Female	25.14	640	–1.86	No	No	No	0
2529	Female	24.43	775	0.64	Yes	No	Yes	T
2548	Female	24.43	745	0.27	No	No	No	1
2601	Female	26.57	700	–2.70	No	No	Yes	3

Abbreviations: BPD, bronchopulmonary dysplasia; BW, birth weight; BWSDS, BW standard deviation score; GA, gestational age; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; ROP, retinopathy of prematurity.
*A retinopathy of prematurity stage of T indicates treated retinopathy of prematurity.

dence of ROP and on other international studies.[3,11] In Sweden, eye examinations are recommended for all infants born at 32 weeks' GA to detect ROP. However, screening with eye examinations is expensive, time-consuming, and stressful for the infant. It has been found that the physical manipulation of the eye causes significant changes in pulse, respiratory rate, and oxygen saturation.[12] Clarke et al[13] found that the insertion of an eyelid speculum and indentation of the globe during an eye examination produced a significant change in blood pressure. Laws et al[12] specifically studied the ROP screening process and concluded that the physical manipulation of the eye was indeed related to the greatest observed changes in oxygen saturation, blood pressure, and pulse.

Our previous studies have demonstrated that a prolonged period of a low level of serum IGF-I in children born preterm is strongly associated with ROP.[4] Hubler et al[14] and Villegas Becerril et al[15,16] have confirmed this association. Poor postnatal weight gain has also been suggested as a risk factor for the development of severe (≥stage 3) ROP.[17,18]

We found that the longitudinal postnatal factors of weight gain, IGF-I level, and IGFBP-3 level as well as the neonatal factors of GA at birth and BW were the most effective factors in the algorithm to predict risk for vision-threatening ROP in infants. The 2 single-best discriminators for ROP were longitudinal weight and IGF-I level changes, although all of the parameters used in the algorithm contributed to the final predictive power. The WINROP algorithm based on postnatal factors can be modified as other longitudinal factors are found to be predictive. Using WINROP in a clinical setting requires weekly measurements of weight and serum IGF-I level beginning at birth and continuing until hospital discharge.

For IGF-I level determination, we found a good correlation between different IGF-I assays, which is in agreement with findings from other groups.[19,20] The comparison of serum IGFBP-3 levels measured with various assays has shown mostly poor correlation.[21] However, the slope for IGFBP-3 level has generally shown little variability

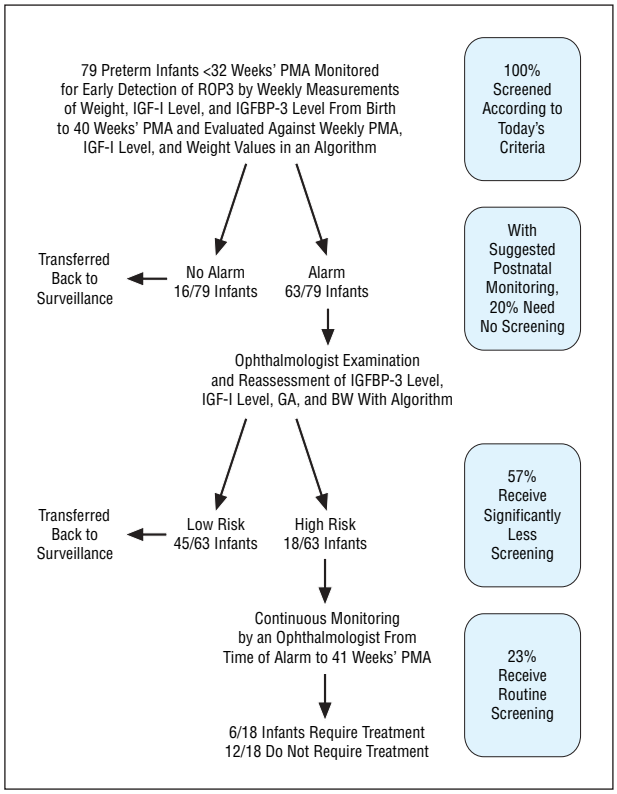

Figure 4. All of the infants requiring treatment were correctly detected. Twelve of 79 infants were monitored with eye examinations without requiring treatment. Sixty-two of 79 infants were correctly predicted to not develop stage 3 retinopathy of prematurity (ROP) or to be at low risk of needing treatment for ROP. PMA indicates postmenstrual age; IGF-I, insulin-like growth factor I; IGFBP-3, insulin-like growth factor binding protein 3; GA, gestational age; BW, birth weight.

around the regression line. Nevertheless, it is important for laboratories to determine whether their assays give IGF-I and IGFBP-3 measurements similar to the measurements obtained with the Mediagnost assays or whether a conversion factor is required. For all assays, reproducibility may be affected by factors such as the quality of sample collection and the use of proper internal and external standards.

To summarize, the surveillance model based on our study population of 79 infants defined as being at high risk for ROP by current criteria was able to show that 16 infants (20%) did not deviate from the expected curves for IGF-I level or weight and were unlikely to develop severe ROP. Of the infants who deviated from the control curves significantly enough for either IGF-I level or weight to trigger an alarm, further evaluation of the IGF-I level, IGFBP-3 level, BW, and GA at the time of the alarm was undertaken with the algorithm. Forty-five (71%) of these 63 infants were considered to be at low risk of needing treatment. Thus, of the original 79 infants, only 18 (23%) were considered to be at high risk of needing ROP treatment and would be screened according to the standard protocol of eye examinations starting at 32 weeks' PMA. Thus, all of the infants (6/6 infants) actually requiring treatment were identified at least 5 weeks before requiring laser therapy by Early Treatment for Retinopathy of Prematurity study criteria, and 61 (84%) of 73 infants not requiring treatment were also identified.

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Correction

Omissions in End Matter. In the Clinical Sciences article titled "Longitudinal Postnatal Weight and Insulin-like Growth Factor I Measurements in the Prediction of Retinopathy of Prematurity" by Löfqvist et al, published in the December 2006 issue of the ARCHIVES (2006; 124:1711-1718), the "Funding/Support" and "Acknowledgment" sections were omitted from the end matter. They should have appeared as follows.

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