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IMPORTANCE OF BIRTH WEIGHT AS A RISK FACTOR FOR SEVERE RETINOPATHY OF PREMATURITY WHEN GESTATIONAL AGE IS 30 OR MORE WEEKS

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Abstract

Purpose—To determine whether birth weight less than 1,500 grams is a relevant guideline indicating the need for examination for retinopathy of prematurity (ROP) when gestational age at birth is 30 or more completed weeks.

Design—A retrospective observational cohort study.

Methods—266 infants in a single institutional neonatal intensive care unit (NICU), whose gestational age at birth was 30 or more weeks but whose birth weight was less than 1,500 grams, were examined according to published guidelines. Infants with lethal congenital anomalies or major ocular abnormalities were excluded. Outcomes were vascularization in retinal zone III without a prior need for treatment, or ROP warranting treatment.

Results—A study outcome was reached by 212 infants. Two hundred and eleven (99.5%) became vascularized through zone III without needing treatment. Only 1 (0.5%) required

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treatment for ROP. The 95% confidence interval for the occurrence rate of ROP requiring treatment in this cohort was 0.01 to 2.60%.

Conclusion—Our results suggest that the occurrence rates of ROP requiring treatment in infants with gestational age 30 or more weeks and birth weight less than 1,500 grams is very low, and could indicate the need to revise examination guidelines for this subgroup of infants.

Introduction

Current guidelines for examination of neonates who may require treatment for retinopathy of prematurity (ROP) have continued to evolve.¹⁻⁶ While guidelines may vary worldwide, the criteria in the United States, and applicable to our neonatal intensive care unit (NICU) population during the period of this study, include gestational age 30 or fewer completed weeks, or birth weight less than 1,500 grams.

We have observed that infants born at gestational age 30 weeks or later often have birth weights that call for examination under the guidelines, but only occasionally do they show even mild degrees of ROP. We undertook this study to determine the number of our highest gestational age neonates, considered to require examination for ROP under the criterion for birth weight, who developed ROP calling for intervention as recommended under the guidelines prevailing at the time.

Our results may form the basis for exploring, with more rigorous studies, whether existing guidelines should be re-evaluated to allow fewer examinations of members of this high gestational age subgroup, without holding them exempt from all scrutiny.

Patients and Methods

The design and execution of this retrospective observational study was approved prior to initiation by the Icahn School of Medicine at Mount Sinai Program for the Protection of Human Subjects and conformed to the requirements of the United States Health Insurance Portability and Privacy Act and the Declaration of Helsinki.

We reviewed the records of infants born during the period January 1, 2001 through December 31, 2010 who were cared for in our single-center institutional level IIIC NICU. As is standard in neonatology practice and research, we ascertained gestational age by best obstetrical estimate, a combination of menstrual dating and first trimester sonography; this was corroborated by physical examination at birth. Fractional days beyond the estimated number of completed weeks of gestation were not “rounded up”. Exclusion criteria were those of the CRYO-ROP and ET-ROP studies, ie, infants with lethal congenital anomalies or major ocular abnormalities in one or both eyes.^{2,4} We recorded the postmenstrual age, in completed weeks, and results of each examination on all infants, without considering racial groups separately.

Examination was performed after topical administration of a cycloplegic/mydriatic agent by binocular indirect ophthalmoscopy and scleral indentation. A fellowship-trained pediatric ophthalmologist (XXX) performed approximately 85% of the examinations over the entire

10-year period. The remaining examinations were provided by a vitreoretinal surgeon (YYY) and a subspecialist in medical retinal disorders (ZZZ), both having broad experience with childhood ophthalmologic conditions within their fields of interest and with ROP examination.

After initial evaluation at 4-5 weeks of chronologic age, examinations were performed at 2-week intervals if no ROP was present and at 1-week intervals if any degree of ROP was detected and had not yet resolved spontaneously. Infants requiring ophthalmologic follow up after discharge from the NICU received those examinations in our outpatient facility.

Our outcome measures were the occurrence of either ROP warranting treatment or confirmed retinal vascularization present in zone III, with or without prior spontaneously resolved milder ROP.^{2,4,5} We discontinued follow up when one of these outcomes was present. We assumed that eyes once reaching the need for treatment would not later show spontaneous regression to the point of no detection, so that the absence of examinations between those at planned intervals would not have revealed severe ROP.

Statistical comparisons were made with Fisher's exact test or Student's t-test (2-tailed) as appropriate. Our chosen level for statistical significance was $p < 0.05$. We ascertained the 95% confidence interval for our observed occurrence rate of severe ROP from the analysis-one proportion module of the NCSS statistical software model, version 9.0; Kaysville, Utah.

Results

Of 780 neonates examined for ROP during our 10-year study period, there were 332 who met study gestational age and birth weight criteria. Nine of these died or were transferred for care at other institutions prior to any examination. An additional 57 eligible infants did not undergo ophthalmologic examinations at our institution.

Complete medical records including ophthalmologic examination history were available for 266 infants. There were 128 male and 138 female infants; this is not significantly different ($p = 0.73$) from an equal gender distribution. Their gestational ages at birth are listed in Table 1, and their birth weights in Table 2.

One of our two defined study outcomes was reached by 212 infants. Only 1 (0.5%) required treatment for ROP. This infant was born at 32 weeks of gestation weighing 905 grams. He was transferred to our NICU for unrelated surgical care, and did not show any ROP on examination at postmenstrual age 34 weeks. His diagnosis of ROP and need for treatment was reached following transfer back to the original facility. Because he received care and both pre- and post treatment ophthalmologic examinations at our institution, he is included in our cohort.

Two hundred and eleven (99.5%) babies were observed to become vascularized in zone III. The postmenstrual ages at which this was first noted are shown in Table 3. Of these, 168 of the 211 (79.6%) reached zone 3 at or prior to 38 weeks postmenstrual age.

We have excluded from consideration 54 other examined neonates for whom we have only incomplete information. Of these, 25 showed normal vascularization in zone II at 36 postmenstrual weeks or later. None of the remaining 29 with shorter follow up had any degree of ROP,

Of the 211 neonates without ROP warranting treatment, 202 showed no ROP at all. Nine showed evidence of mild ROP, no more severe than stage 2 without plus disease in zone II on any examination. No infant with mild ROP had involvement in zone I. There was documented regression without reaching treatment criteria in 5 of these neonates; only these are included among the 211 who reached full vascularization.

Birth weight (mean, SD) for the 10 infants in the cohort with ROP was 1,188+227 grams, and 1,287+165 grams for those without ROP, (2-tailed t-test, $p = 0.08$).

Discussion

The goal of examination for ROP is to identify preterm infants at risk for serious permanent visual loss that can be reduced or prevented by timely intervention. In an effort to not overlook any affected infant, for some the guidelines result in examinations that are stressful to both the fragile neonates and their families and that involve substantial effort and financial cost, and that do not improve patient care. Evidence of reduced risk in infants beyond a certain gestational age regardless of birth weight would allow a lesser level of scrutiny of those infants.

The most recent iteration of the guidelines⁶ includes revised recommendations directed at neonates at the early portion of the range of gestational ages. Previous studies, as antecedents for the guidelines, have not concentrated separately on patients at the upper limit of the recommended range. The observations reported here, informed by the results of our study, are identical even beyond the 10-year period we scrutinized. While only those infants born at gestational ages beyond 30 completed weeks have been considered outside the sphere of risk for severe ROP except when having a birth weight below 1,500 grams, we extended our study entrance criteria to include gestational age to 30 weeks to further emphasize our conclusion. Although there have been anecdotal reports of infants older than 30 weeks at birth requiring treatment, sporadic individual cases do not facilitate the establishment of an occurrence rate for that outcome.

Our tertiary care NICU population resembles those in other ROP studies.⁷⁻¹⁰ The overall appearance of any degree of ROP in 780 infants across all gestational ages and birth weights (19%) parallels the 20.5% over essentially the same range of gestational ages reported from a comparable medical environment in the Northeastern United States.⁹ Similarly, the 7.5% of our examined infants of any gestational age who needed treatment approximates the 8.1% reported in an extensive Canadian study.¹⁰ These investigations, like ours, were done from the standpoint of gestational age, whereas other studies²⁻⁴ do not allow similar comparisons as they were primarily stratified by birth weight, or were confined to neonates weighing less than 1,251 grams at birth, below which limit these occurrence rates for severe ROP are expected to be higher.

Recognizing that our sample size is small, we do not offer our results as definitive. That only 1 of 212 infants in a single-center retrospective study developed ROP severe enough to warrant treatment cannot be taken as the rate of severe ROP for the universal population of older gestational age premature neonates. In our study, it establishes a 95% confidence interval of 0.01 to 2.60%, within which limits the true occurrence rate for our institution's population lies. Our results do not justify conducting a randomized clinical trial in which some infants, as controls, would be denied examinations. We have calculated that if a similar cohort of approximately 1,300 premature infants showed the same occurrence rate for development of severe ROP as in our sample, this would reduce the upper limit of the 95% confidence interval to not less than 1%. A pooled retrospective study of that number of infants would not be difficult to conduct. It should be noted that approximately 106,000 subjects, in whom the same rate were to be observed, would be required to reduce the upper limit of the 95% confidence limit to our observed 0.47%. This is grossly impractical and could not result in a zero incidence that would obviate all scrutiny.

There are prior reports that advocate limiting the scope of ROP screening.^{11,12} Some studies¹³⁻¹⁵ have scrutinized postnatal factors, such as weight gain, as predictors of the risk of developing severe ROP. We did not attempt to address these questions within our limited sample. Analysis of the effect of additional parameters is left to a more extensive study.

We are aware that other investigations^{12,13} have cautioned, that independent corroboration in our and in other environments is necessary. Most important, we do not advocate risking the failure to identify even a single infant who warrants treatment by discontinuing all scrutiny of neonates born at gestational ages of 30 weeks and later. Other studies¹⁶ have that same goal, but approach the question of implementation based more on birth weight than gestational age. As Palmer has pointed out, with respect to ROP the practical goal is to employ the fewest possible examinations at times most likely to detect the highest number of cases.¹⁷

In addition to our limited sample size, we are aware that, as in many retrospective studies, follow up was not uniform. Of the 54 infants for whom we had only partial information, 25 were without any degree of ROP through their 36Th postmenstrual week or later. This is insufficient to conclude that their retinal vascularization would have continued to proceed normally, although it suggests that they were not severe co-morbidities that might predispose to the development of ROP warranting treatment. Although we cannot include them in our principal result, they provide information that can contribute to the establishment of a limited but strategic examination protocol.

Similarly, for the eligible neonates for whom we found no examination data, the occurrence rates of several major co-morbidities (severe anemia, neonatal sepsis, necrotizing enterocolitis, and intracranial hemorrhage) that might indicate an unstable course suggesting an increased susceptibility to severe ROP⁵ were not significantly different from those with complete ophthalmologic documentation, so that their unintentional exclusion was not a clear source of bias in favor of either a higher or lower rate of severe ROP.

Our experience indicates that, although not necessarily for other settings, birth weight may be a much less relevant factor for the development of ROP requiring treatment when gestational age is at least 30 completed weeks. We have included patients of 30 weeks gestational age and point out that our finding holds even within the upper limit of the present guideline. Accordingly, for such infants, a schedule that calls for fewer examinations might be equally effective, if strategic times for them can be identified. The information in Table 3 may contribute to the development of such a strategy. This is a question that should be addressed by wider experience than our study provides. Our intent is to call attention to this possibility.

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Table 1

Distribution of gestational ages at birth for 266 neonates born at 30 or more completed weeks and examined for retinopathy of prematurity

<u>Gestational Age (Weeks)</u>	<u>No. of Patients</u>
30	99
31	67
32	57
33	22
34	11
35	5
36-42	5
Total	266

Table 2

Distribution of birth weights for 266 neonates with gestational ages of 30 or more weeks and birth weights below 1,500 grams and examined for retinopathy of prematurity

<u>Birth Weight (grams)</u>	<u>No. of Patients</u>	<u>Patients with Retinopathy of Prematurity</u>
1,401-1,499	75	0
1,301-1,400	68	4
1,201-1,300	50	3
1,101-1,200	39	0
1,001-1,100	18	1
< 1,001	16	2
Total	266	10

Table 3

Postmenstrual ages at first notation of vascularization in zone III in neonates examined for retinopathy of prematurity.

<u>Postmenstrual Age (weeks)</u>	<u>No. of Patients</u>
34 (or earlier)	51
35	37
36	37
37	24
38	19
39	15
40	13
41 or later	15
Total	211