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ELECTRONIC ARTICLE

Current Incidence of Retinopathy of Prematurity, 1989–1997

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ABSTRACT

Objective. To report the current incidence and the need for surgery for retinopathy of prematurity (ROP) in neonates (22–36 weeks' gestational age [GA], July 1, 1989 through June 30, 1997).

Study Design. Retrospective analyses using computerized perinatal database kept on all admissions, a review of patient charts, and eye examination log books.

Setting. Level 3 regional referral NICU.

Patients. A total of 2528 infants <37 weeks' GA were admitted during this time. Of these infants, 950 met the criteria for eye examination beginning at 4 to 6 weeks of age and repeated every 2 weeks until complete vascularization of the retina or death or discharge.

Results. The incidence of ROP was (202/950) 21.3% for any stage and 4.6% (44/950) for stage 3 ROP or greater. No ROP was noted in infants born at >32 weeks' GA. No infant born at >28 weeks needed retinal surgery. Using birth weight (BW) criteria, stage 3 ROP was not noted in infants with BWs >1500 g; retinal surgery was not needed in infants with BWs >1000 g. A number of perinatal factors were associated with ROP on univariate analysis. However, using multiple logistic regression analyses of these factors, only GA and days on supplemental oxygen therapy were associated significantly with the development of ROP. Despite increased survival of extremely low BW infants, we found a considerable reduction in incidence and severity of ROP compared with reports from an earlier chronological period. However, infants <28 weeks' GA or with BWs <1000 g were still at considerable risk for retinal surgical treatment for ROP.

Conclusion. We conclude that the incidence and severity of ROP have decreased significantly in the present era of surfactant therapy.

Key Words:

retinopathy * prematurity * incidence * morbidity * eye

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Retinopathy of prematurity (ROP) is a significant problem in low birth weight (LBW) premature infants. Before surfactant became available for clinical use in the neonatal intensive care unit (NICU), an incidence of 11% to 60% was reported in the LBW population.[1,,2] The last major report of the incidence of ROP was published from the cryotherapy–retinopathy of prematurity (CRYO–ROP) study completed in 1987,[3] which was conducted before surfactant use was approved for treatment of respiratory distress syndrome (RDS). A decade of continued advances in neonatal management, including the use of surfactant therapy and new methods of mechanical ventilation has improved most neonatal outcomes, but scarce data are available regarding the current incidence of ROP. It is also not clear whether the increased survival of smaller and sicker infants has resulted in an increased proportion of infants needing retinal surgery because of ROP.[4,,5] In their recent comprehensive review of ROP, Siatkowski and Flynn[6] noted that "we are as lacking in basic epidemiologic data of varying rates of incidence [of ROP] in geographic areas … as we were in the 1940s and 1950s." The goals of the present study are 1) to report the current incidence of ROP and the need for retinal surgery for severe ROP from a regional NICU and 2) to evaluate the contribution of various perinatal and neonatal factors to the risk for ROP.

METHODS

Subjects

The John Dempsey Hospital of the University of Connecticut Health Center is a high-risk perinatal center and a regional referral NICU for the northern two thirds of Connecticut. It is the largest of three tertiary care units for this region of Connecticut. The population profile of infants admitted reflects that of other similar centers in the United States with 75% white, 13% black, and 9% Hispanic infants.[7] There were no significant changes in referral patterns or the proportion of premature infants admitted over the study period. This was a retrospective study of all 22 to 36 weeks' gestational age (GA) premature infants who were admitted to the NICU between July 1, 1989 and June 30, 1997. Surfactant became available in this center in 1989 as an investigational drug initially and then for routine use after Food and Drug Administration approval in 1991. Of the 5526 infants admitted during the 9-year study period, 2528 were ≤36 weeks' GA. Of these infants, 950 neonates met the criteria to have their eyes examined by pediatric ophthalmologists to detect ROP. Data were collected on these infants from a combined review of a computerized database kept on all admissions to the NICU, from a review of patient records, and from log books kept to record the results of eye examinations by ophthalmologists.

Eye Examination Schedule

The eye exams were performed for all infants who met the following criteria: 1) infants <30 weeks' GA or <1300 g at birth; 2) infants <35 weeks' GA or <1800 g at birth who received supplemental oxygen for >1 week; and 3) any newborn who remained in supplemental oxygen for >60 days. Infants first were examined by the ophthalmologists at 4 to 6 weeks of age. They then were followed by eye examinations every 1 to 2 weeks until death or discharge or until retinal vascularization was complete.

Eye Examination Method

The pupils were dilated with 0.5% tropicamide and 2.5% phenylephrine, the infant was swaddled, and the ophthalmic fundus was examined by indirect ophthalmoscopy with a +30 diopter aspheric lens. An infant eye speculum and scleral indentation were used as needed to view the retinal periphery. Observations were classified according to the International Classification of Retinopathy of Prematurity.[8] In brief, the stages of ROP were:

- Stage 1. Demarcation-line separating the avascular retina anteriorly from the vascularized retina posteriorly with abnormal branching of small vessels immediately posterior to this.

- Stage 2. Intraretinal ridge: the demarcation line has increased in volume, but this proliferative tissue remains intraretinal.
- Stage 3. Ridge with extraretinal fibrovascular proliferation.
- Stage 4. Partial retinal detachment.
- Stage 5. Total retinal detachment.

The zone of vascularization was noted. The number of total and contiguous clock hours of ROP and the presence or absence of Plus disease (tortuosity of veins) were important determinants of management.

Results of eye examinations were entered into a log book and a computerized database. The same team of 3 experienced pediatric ophthalmologists performed all of the examinations. Infants who were transferred back to the referring hospital were examined at least once by the same group of ophthalmologists in >90% of the cases. No infant with significant active ROP was back transferred until regression of ROP was noted. The few infants who were transferred out of the NICU with immature zone 2 were followed up by the same group of ophthalmologists (none of these infants developed threshold ROP subsequently). The maximum severity of ROP in any one eye for an individual infant was recorded for analysis. In infants with severe disease, the same group of ophthalmologists and retinal surgeons who confirmed the need for retinal ablative surgery (cryotherapy or laser surgery) performed the procedure and were responsible for the infant's subsequent follow-up.

Monitoring and Management of Infants at Risk for ROP

Monitoring

If no ROP was noted, eye examinations were continued every 2 weeks until retinal vascularization extended to zone 3. The threshold for treatment was determined by the protocol that was used for the CRYO-ROP trials.[3] Briefly, prethreshold ROP was zone 1 ROP of any stage less than threshold; zone 2 stage 2 ROP or greater; zone 2 ROP stage 3 without Plus disease; and zone 2 stage 3 ROP or greater with fewer than the threshold number of sectors of stage 3 or greater. This was observed closely until resolution or until progression to threshold ROP. Threshold ROP needing surgery was 5 or more contiguous or 8 cumulative clock hours of stage 3 ROP or greater in either zone 1 or zone 2.

Management

All premature infants were given vitamin E 25 international units per day from the time full enteral feeds were established until 36 weeks' postmenstrual age or until discharge. Infants were cared for in a low illumination environment with cloth covers over isolettes. No eye shields were used except when infants were receiving phototherapy. At all times during NICU care, supplemental oxygen was given to maintain pulse oximetry between 90% and 95%, and no increase or decrease in target pulse oximetry was made with the identification of any stage of ROP. All infants on supplemental oxygen during the period of observation were monitored by continuous pulse oximetry.

Identification of Risk Factors

The following perinatal-neonatal variables were reviewed for their association with the risk and severity of ROP and the need for retinal ablative surgery: GA, birth weight (BW), race, type of delivery, small for GA (SGA) status, presence of RDS, use of surfactant, presence of confirmed sepsis, intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), severe bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), days on mechanical ventilation, days on continuous positive airway pressure (CPAP), days on oxygen, and length of stay in the hospital.

Definitions

GA at birth was assessed as completed weeks using obstetric estimates based on the date of the last menstrual period of the mother confirmed by clinical evaluation of early uterine size and ultrasonography of the fetus early in gestation and/or at admission. The majority (70%) of pregnancies in this study had an early gestation ultrasound for confirmation of dates. Postnatal assessment of maturity was not relied on in this study because of its known inaccuracies in extremely premature infants.[9] Ethnicity was determined based on maternal race. Infants were deemed SGA if BWs were <10 percentiles from the 3rd revision of growth charts by Gairdner and Pearson[10] (Castlemead Publications, Hertfordshire, UK). RDS was defined by the presence of clinical features and chest radiographic findings. The occurrence of IVH and PVL were determined by cranial ultrasonography at least two times within the first 10 days of birth and at least once before discharge. Sepsis was established by the growth of organisms in blood culture. NEC was diagnosed based on clinical features and abdominal radiographic changes as described by Bell.[11] Severe BPD was defined as the need for supplemental oxygen along with radiographic lung changes beyond 36 weeks' postmenstrual age.

Statistical Analysis

Univariate comparisons of risk factors between the two groups with or without ROP were evaluated using the Student's *t* test and the χ^2 test as appropriate with statistical significance at $P < .05$. Using multiple logistic regression analyses with a step-up methodology using variables that were significant on univariate comparisons, the correct classification rate was determined with the SAS/STAT package (SAS Institute Inc, Cary, NC).[12] The correct classification rate quantifies how well the models of multiple logistic regression analyses discriminate between ROP and non-ROP groups.

RESULTS

Between July 1, 1989 and June 30, 1997, 5526 infants were admitted to the NICU at John Dempsey Hospital of the University of Connecticut Health Center. The selection of patients from this population is shown in Fig 1. Of the 950 infants who met the criteria for evaluation, ROP of any degree was diagnosed in 202 (21.3%) infants, and 44 (4.6%) infants had severe stage 3 ROP or greater.

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Fig. 1.

Schematic diagram of the distribution of infants in the study.

Demographic and Perinatal Factors

In Table 1, demographic and perinatal factors in the infants who met the criteria for eye exams are summarized. Maternal race, male gender, SGA status at birth, and length of stay were not significantly different among infants who developed any stage of ROP and those who did not. Immaturity reflected by lower BW and GA at birth was a significant factor in infants who developed ROP. Severity of respiratory disease, reflected by the number of infants who developed RDS or needed the use of surfactant or required ventilatory, CPAP, or supplemental oxygen support, was also significantly higher in those who developed ROP. Infants who were diagnosed with ROP also developed more IVH and PVL and had a significantly higher incidence of

sepsis. A lower rate of vaginal delivery in the ROP group probably reflects the high-risk perinatal status of these immature infants near the time of their delivery and the perinatologist's decision not to deliver by this route.

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Table 1.

Population Characteristics and Comparison of Variables*

Relative Proportions of Infants Dead, Alive, and Those With ROP

Because infants who died before 6 weeks of age could not be examined for ROP, it is important to show the relative proportions of infants who lived or died along with those who developed ROP. This is shown in Fig 2. Infants born at ≤25 weeks' GA had high mortality rates, and the proportion of infants with ROP remained between 30% and 40% of all live-born infants. In infants born at ≥26 weeks' GA, even as the mortality remained relatively low, the proportion of infants developing ROP declined with increasing GA, thus no infant born at >32 weeks' GA developed ROP.

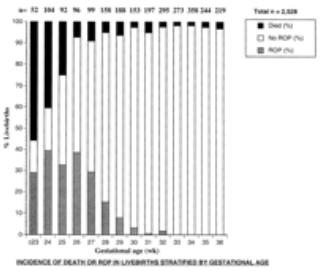

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Fig. 2.

Relative percentage of live-born infants who died, lived, or developed ROP stratified by completed weeks' GA. Data from University of Connecticut Health Center from July 1989 to June 1997. Sample size is shown at the top of each bar.

Distribution of Stages of ROP by GA

Figure 3A shows the relationship between GA and severity of ROP (percent of infants studied) including its sequelae. The incidence of ROP in survivors at 23 completed weeks was 71.4%; at 24 weeks was 70.7%; at 25 weeks was 45.5%, at 26 weeks was 44.6%; at 27 weeks was 35.4%; and at 28 weeks was 18.6%. Among all infants ≤28 weeks' GA, the incidence of any stage of ROP was 40.1% (176/439) and of severe ROP (stage 3 or greater) was 9.8% (43/439). Infants with a GA of 23 to 24 weeks were represented disproportionately in this group. Beyond 28 weeks' GA, severe ROP was virtually nonexistent. Fig 3B shows the absolute numbers of infants with mild or severe ROP and the number who needed surgical treatment (threshold disease) stratified by GA at birth in completed weeks. Of the infants examined at >60 days of oxygen requirement, there were none who were >36 weeks' GA.

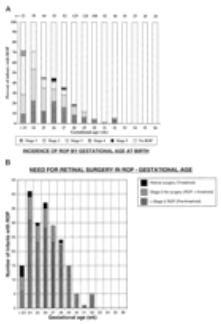

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Fig. 3.

A, Distribution of percent incidence and severity of ROP stratified by GA (22–36 weeks) from 1989 to 1997. Sample size is shown at the top of each bar. B, Absolute number of infants with ROP who required retinal surgery (threshold, needing retinal ablative surgery) compared with less severe disease stratified by GA (22–36

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weeks) from 1989 to 1997.

Distribution of Stages of ROP by BW

Similarly, Fig 4A illustrates the relationship between BW and severity of ROP as a percentage of the infants studied. For infants with BWs <1000 g, the incidence of ROP of any degree was 46% (160/347) and of severe ROP stage 3 or greater was 12% (42/347). The 2 infants with BWs >1000 g who developed stage 3 ROP did not reach the threshold for retinal surgery with laser or cryotherapy.

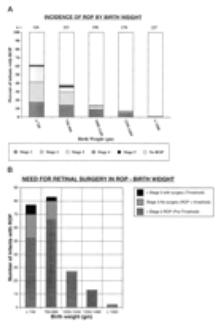

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Fig. 4.

A, Distribution of percent incidence and severity of ROP stratified by BW (in 500-g increments) from 1989 to 1997. Sample size is shown at the top of each bar. B, Absolute number of infants with ROP who required retinal surgery (threshold, needing retinal ablative surgery) compared with less severe disease stratified by BW (<750 to >1500 g) from 1989 to 1997.

Figure 4B shows the absolute number of infants with mild or severe ROP and the number who required surgery stratified by 500 g BW categories.

Multiple Logistic Regression Analysis

Because most of the risk factors are functions of immaturity, a multiple logistic regression model was designed with BW, GA, days on oxygen, surfactant use, and the incidence of sepsis to study the independent contribution of these factors to the development of ROP. Results are shown in Table 2. Only GA and days on supplemental oxygen entered the model. The chances of not developing ROP in the whole population were 78.7%; and GA by itself could discriminate this group at 81.6% correct classification rate. The addition of information on days on supplemental oxygen increased this to 82.34%. The statistical addition of surfactant use and/or episodes of confirmed sepsis to GA did not improve further the correct classification rate.

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Table 2.

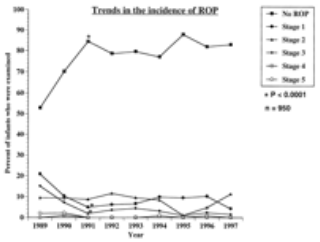
Correct Classification Rate to Discriminate Significant Factors That Help Categorize ROP After Multiple Logistic Regression Analysis

Changes in Incidence of ROP With Time

Figure 5 shows that there was an increase in the percentage of non-ROP infants with a concomitant decrease in stage 1 and 3 ROP between 1989 and 1991 (χ^2; P <.0001). This was noted despite an improvement in survival of smaller infants.[13] The notable change in care of premature infants that occurred during 1991 was the introduction of surfactant replacement with Survanta (Ross Products, Columbus, OH) for treatment of RDS. Some infants were given surfactant under an investigational new drug protocol between 1989 and 1990.

Fig. 5.

Changing trends in the percent



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incidence and severity of ROP during each year of the study period. The asterisk indicates χ^2. $P < .0001$.

DISCUSSION

This report represents the first comprehensive study of the incidence and severity of ROP, since surfactant use has become common clinical practice for the treatment of RDS in the United States.

The impact of ROP on vision in the premature infant has been well appreciated since the early report by Terry.[14] Its changing incidence has been related to changes in clinical practice.[15] Recent reports from Europe and Australia suggest a decreasing incidence of severe ROP, but data on the different stages of ROP and on the relative occurrence of different stages are not reported.[2,,5] The CRYO-ROP multicenter study (1986–1987)[3] showed that among infants with BWs <1251 g, 65.8% developed ROP to some degree, and the incidence was 81.6% in infants <1000 g. This study also analyzed the incidence stratified by GA in a separate report.[16] Since that large study, there have been no major reports published on the incidence of ROP from the United States, although it is well recognized that the recent changes in the care of premature infants (surfactant, improved understanding of physiology, improved technology, and better modalities of neonatal ventilation) may impact the incidence and severity of this condition.[17]

The present study shows a significant decrease in the incidence and severity of ROP from previous reports.[3,,16] The overall incidence in infants with BWs <1251 g was 34% (187/545), and the incidence among infants with BWs <1001 g was 46% (160/347), which is approximately half of the incidence reported in the CRYO-ROP study.[3] Moreover, none of the infants in our study with BWs >1000 g reached the threshold for laser or cryotherapy.

Similarly, the incidence of ROP of any degree in infants <28 weeks' GA was decreased from 70% (CRYO-ROP)[3,,16] to 38.7% in this study. The incidence of ROP that required surgery also was reduced by half. This reduced incidence and severity has occurred despite an increase in the survival rates of the smallest and the most vulnerable infants.[13,,18]

In this study, we also report demographic factors that may be important in the development of ROP. The population distribution of white and black individuals was similar to the national demographics of the United States.[7] However, an earlier report stating that non-black individuals were more vulnerable to ROP[19] was not confirmed by this study (Table 1). There were also no significant gender differences in incidence of ROP. This confirms the observations of previous investigators.[2,,3]

It has been reported that infants who are born SGA may be more likely to develop ROP.[20] This could not be confirmed by the analysis of our data. We believe that the cause rather than the condition of growth retardation may be a more important factor. This association needs to be studied in a larger population base stratified by the causes of growth retardation before any conclusions can be drawn.

A recent report linked an increased incidence of ROP to candidal sepsis.[21] Univariate analysis of our data showed that culture-positive sepsis of any etiology was associated significantly with ROP but that multiple logistic

regression analysis with BW, GA, and days on supplemental oxygen failed to show its independent or additional contribution to the risk of ROP. The association between sepsis and ROP needs to be studied in greater detail to delineate any independent influence of infection.

Respiratory immaturity with RDS along with the longer duration of use of mechanical ventilation, CPAP, and supplemental oxygen were related significantly to the incidence and severity of ROP in our study. These factors have been implicated from the earliest reports that linked ROP to oxygen use. Multiple regression analysis of these variables along with GA or BW in our data showed that only days on supplemental oxygen with GA could enter the model and predict the risk for ROP independently.

There are variable reports regarding the use of surfactant and incidence of ROP. Repka et al[17] suggested that surfactant prophylaxis will not change the incidence of ROP, and Rankin et al[22] reported that surfactant therapy was not associated with an increased incidence or severity of ROP. The higher use of surfactant in infants with ROP probably represents the greater pulmonary immaturity of this population. Moreover, the decrease in mortality of premature infants with this therapy probably contributes to the increase in the number of infants at risk. In our study, a multiple logistic regression analysis with BW, GA, days on supplemental oxygen therapy, and use of surfactant failed to show an independent contribution by this treatment. However, it is worth noting that in our analysis of the changing incidence of ROP during the years of our study, a significant (χ^2; $P < .0001$) decrease in incidence and severity of ROP occurred between 1989 and 1991 (by which time oxygen saturation monitoring was already routine in our center) that coincides with the Food and Drug Administration–approved introduction of surfactant replacement therapy for treatment of RDS in 1991. There seems to have been no additional change in the decreased incidence or severity of ROP from 1991 to the present.

A recent retrospective report of infants born between 1990 and 1996 by Wright et al[23] from a single center in the United States shows an incidence of ROP that was much higher than our study reports; however, the trend toward a decrease in incidence from previous reports is similar. The details of management of ROP are not provided in this report, and therefore, it is difficult to comment on the possible factors involved.

In our set-up, we take care of a large population of premature infants of various ethnicity and socioeconomic backgrounds who are given a similar pattern of care in a single tertiary center. There have been no significant changes in population or in referral patterns of the premature infants admitted over the 9 years that these data were collected. Therefore, we believe that the significant decrease in the incidence and severity of ROP that we report, which has been consistent over a number of years, reflects a true change and would be corroborated from similar reports from other centers.

CONCLUSION

We conclude that the incidence and severity of ROP have considerably decreased in the present times. It is possible that the primary determinant in this decrease in incidence of ROP is the improved understanding of the pathophysiology of premature infants and the various means of improved supportive care, such as the surfactant replacement therapy, that contribute to better stabilize the immature organ systems of premature infants and to decrease the wide fluctuations in homeostasis that recently have been shown to impact on retinal vascular development.[24,,25]

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ROP =
retinopathy of prematurity ·
LBW =
low birth weight ·
NICU =
neonatal intensive care unit ·
RDS =
respiratory distress syndrome ·
GA =
gestational age ·
BW =
birth weight ·
SGA =
small for gestational age ·
IVH =
intraventricular hemorrhage ·
PVL =
periventricular leukomalacia ·
BPD =
bronchopulmonary dysplasia ·
NEC =
necrotizing enterocolitis ·
CPAP =
continuous positive airway pressure

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