RETINAL VASCULAR DEVELOPMENT IN PREMATURE INFANTS

ALAN M. ROTH, M.D.
Davis, Califomia

Previous reports on retinal vascular maturation in premature infant eyes have had variable conclusions because of the criteria used for determining fetal age and the type of material studied. Fletcher[1] clinically determined that retinal vessels usually matured by the time fetal weight reached 2 kg. All other studies have been based on pathologic specimens. Mann[2] stated that retinal vessels reached the ora serrata by the eighth lunar month. Using his flat mount trypsin digest technique, Cogan[3] concluded that retinal vascular remodeling continued for several months after birth. Foos and Kopelow[4] did the most extensive study based on autopsy material. They found that an increasing percentage of babies' eyes had mature vasculature beginning at seven months' gestation; by the tenth lunar month, 100% were vascularized. The age of these infants was determined from the body weight at the time of autopsy. Kushner and co-workers[5] also examined eyes removed at autopsy and determined age from birth weight and crown to heel length. They found that four cases considered premature by these criteria had completely vascularized retinas, while seven cases they considered mature births had incomplete vascularization. They concluded that there is an inherent variability between gestational maturity and retinal vascularization.

Pediatricians, repeatedly point out the need for accurate assessment of gestational age in the newborn infant, particularly to differentiate preterm infants from those who are merely small at term. They have described methods for such evaluation based on such clinical factors as neurologic development and external characteristics.[6] Birth weight and size are unreliable criteria of gestational age and are dependent on many factors, including intrauterine environment and state of the mother's health (for example, high birth weights of infants of diabetic mothers). I undertook this study to evaluate by clinical examination the maturity of the retinal vasculature of newborn infants and to clarify the various reports regarding its relationship to gestational age determined by the pediatric clinical criteria. Additionally, I obtained new information about fetal remnants and their relationship to retinal vascular maturity. I also observed the morphology of the optic nerve heads in these paranatal eyes.

SUBJECTS AND METHODS

I studied a total of 654 eyes from 327 babies in the high-risk and premature infant nurseries here. The examination consisted of indirect ophthalmoscopy through pupils dilated with 1% tropicamide and 10% phenylephrine (babies considered at risk with a high concentration of phenylephrine received a 2.5% solution instead). The infants were selected at random by neonatologists. The infants had had variable amounts of oxygen therapy, ranging from none to several days of therapy.

For each infant, I recorded sex, race, birth weight, estimated gestational age at birth (Dubowitz method[6]), number of days since birth, use of oxygen therapy with respirator settings and arterial blood

From the Departments of Ophthalmology and Pathology, University of California, Davis, and the University of California, Davis, Sacramento Medical Center, Sacramento, California.

Reprint requests to Alan M. Roth, M.D., Room 251, UCD Professional Building, 4301 X St., Sacramento, CA 95817.

gases, as well as the babies' systemic disease and details of pregnancy and birth. I also recorded details of the ocular examination, including the clarity of the media, presence of fetal vasculature, type of optic cup (Elschnig's classification as modified by Portney[7]), condition of the macula, vessels, and peripheral fundus. In particular, I examined the peripheral retina with emphasis on the extent of vascularization and the presence or absence of signs of retrolental fibroplasia. If the ora serrata was not visualized by oblique viewing, I used gentle scleral depression to see it. I included in the results only infants without signs of retrolental fibroplasia and those I had examined within four weeks of birth. The majority of cases were studied less than one week after birth. Of these, 17 cases had retrolental fibroplasia of some degree and will not be considered in this report.

RESULTS

The number and percentage of eyes with mature retinal vasculature in each week of paranatal life is shown (Fig. 1). I first observed maturation in the 31st week and its frequency increased steadily until the 38th week, when all infants had mature retinal vasculature. In no case was the vasculature immature in one eye and mature in the other. In one case of 34-week-old twins, both eyes of the firstborn were vascularized and incompletely vascularized in the second. There were no differences in the eyes of multiple-birth babies as compared to those singly born. While the birth weights of twins and triplets were generally lower than those of single-birth infants, neither their age range, nor the percentage of retinal vascularization at any given age was significantly different. If the retinal vascularization is compared to birth weight, there is also a steady increase in vascularization until, at 3-kg weight, all infants have mature vessels (Fig. 2). However, this is an artifact of grouping infants of similar birth weights together, as was done in previous studies[4,5]; if the groups are separated into single kilogram segments, the

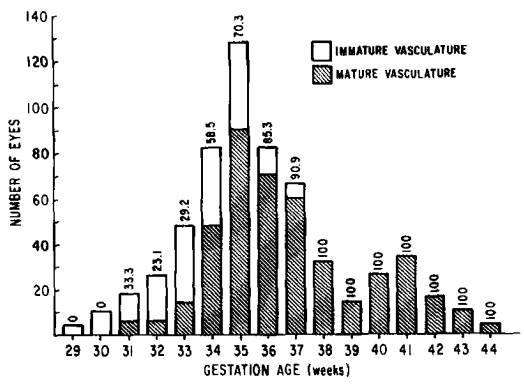

Fig. 1 (Roth). Extent of retinal vascularization in eyes of infants of different gestation ages. Percentages of eyes with mature vasculature indicated over bars.

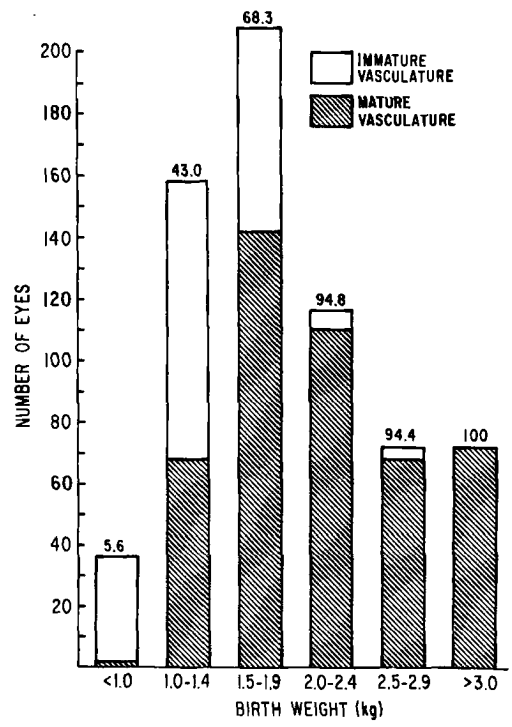

Fig. 2 (Roth). Extent of retinal vascularization in eyes of infants of different birth weights. Percentages of eyes with mature vasculature show steady increase with weight-related grouping of cases.

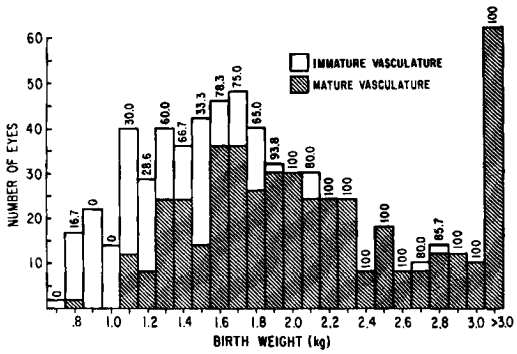

Fig. 3 (Roth). Same cases as in Figure 2, showing variability of percentages fully vascularized when cases are not grouped.

percentage varies (Fig. 3); the lowest weight infant with complete vasculature was 840 gm, but was small for age (31 weeks). No differences in maturation were seen between male and female infants, nor were differences related to presence or amount of oxygen therapy.

There was a positive relationship between the presence of fetal vascular remnants and nonvascularized retinas. Some degree of pupillary membrane was present in infants between the ages of 30 and 36 weeks. I observed this structure in 29 of the 80 infants in this age range who had incomplete retinal vascularization; the age distribution is shown (Fig. 4). No infant who had complete retinal vascularization had this structure. When present, the membrane was always bilateral and usually symmetrical in the two eyes. The other fetal remnants observed were those of the hyaloid system, seen in 82 of the 247 infants who were between the ages of 29 and 38 weeks. Of the 85 infants in this age range who had incompletely vascularized retinas, 52 had some remnant of the hyaloid system; of the 162 infants with mature retinal vasculature, 30 had hyaloid remnants. The age distribution of this group of patients is shown (Fig. 5). Almost half of the cases with incomplete retinal vasculature (23 of 52) had both pupillary membranes and hyaloid remnants. One case with incomplete retinal vascularization had the hyaloid remnant in one eye only, there were six cases of unilateral hyaloid remnants in infants with mature retinal vasculature. The extent of the hyaloid system varied from a small segment posteriorly (most common) to a complete system including the posterior tunica vasculosa lentis (least common). While the more complete systems tended to be in infants with incomplete retinal vasculature and the smaller remnants in those with mature retinal vessels, this was not a statistically significant correlation. The presence and extent of the fetal vascular remnants were not related to the presence, amount, or duration of oxygen therapy. In no case did the pres-

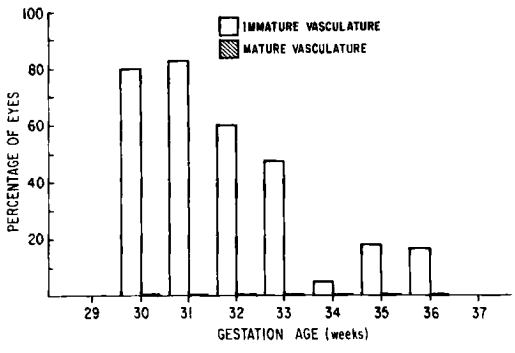

Fig. 4 (Roth). Incidence of pupillary membranes in infant eyes studied. No eye with mature retinal vasculature had pupillary membrane.

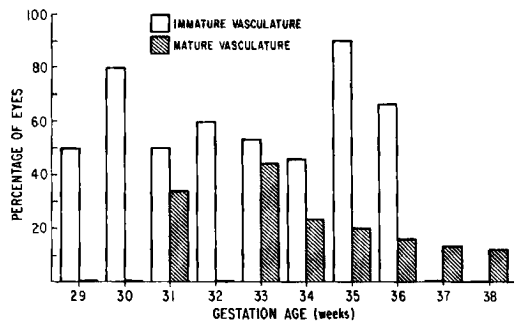

Fig. 5 (Roth). Incidence of hyaloid remnants in eyes studied.

ence of the anterior vascular remnants interfere with visualization of the peripheral retina.

Optic cup types (based on the modified Elschnig classification[7]) were recorded for 306 of the babies (Table). Sixteen cases had cups that were markedly asymmetric in the two eyes, the remaining cases were symmetrical.

DISCUSSION

The incompletely vascularized retina is recognized clinically by a barely discernible blend of the transparent, vascularized posterior retina with the gray, relatively opaque, non-vascularized anterior zone. This transition, although subtle, was easily seen by indirect ophthalmoscopy, even when pupillary membranes or hyaloid structures, or both, were still present. Hazy media, which Cantolino and coauthors[8] reported obscured visualization of the retina for several weeks after premature birth, were not a problem in this study. While anterior fetal remnants rarely caused some obscuration of the posterior fundus, the peripheral retina could always be seen clearly.

The data are generally in agreement with Foos and Kopelow's[4] observation that the percentage of infants with mature vasculature increases progressively from the seventh lunar month until term. However, the gestational age in this study was determined to the nearest week by an experienced neonatologist using clinical assessment of neurologic signs and external characteristics.[6] This method is more accurate than that used in autopsy cases,[9] which uses fetal length and weight but cannot allow for factors causing infants to be either small or large for their gestational age. Thus, Kushner and colleagues'[5] observation of variability in the time relationship between retinal vascularization and gestational maturity is based on less-accurate ages, and the present study shows a variability only as might be expected in any physiologic process. All infants 38 weeks of age and older had completely vascularized retinas, an observation I confirmed by prospective study of nearly 60 infants after these data were obtained.

The presence of fetal vascular remnants, both from the hyaloid system and the pupillary membrane, has been studied previously. Roper-Hall[10] correlated hyaloid remnants with birth weight. He noted progressively smaller percentages of infants having such remnants as birth weight increased from 0.9 to 2.7 kg. He also stated that, at all weights, pupillary membrane remnants were more common. Jones[11] noted hyaloid remnants in 95% of infants under 2.2 kg, and no remnants in 97% of infants over 3 kg. Gans[12] stated that an obvious pupillary membrane is present in the majority of premature infants, and almost always in those whose weight is less than 1.5 kg. He further observed that some "small, although relatively mature, infants" had no pupillary membrane. Hornblass[13] concluded that

TABLE

INCIDENCE OF PHYSIOLOGIC CUP TYPES IN PARANATAL INFANTS

Elschnig Type	No. of Cases	(%)	No. of Bilaterals	(%)	No. of Eyes	(%)
Flat	15	(4.9)	13	(86.7)	28	(4.8)
I	220	(71.9)	212	(96.4)	432	(73.2)
II	13	(4.3)	9	(69.2)	22	(3.7)
III	57	(18.6)	50	(87.8)	107	(18.1)
IV	1	(0.3)	0	(0.0)	1	(0.2)

there is a relationship between remnants of pupillary membrane and oxygen therapy, with duration of oxygen supplementation playing an important role in the extent of the membrane. My observations indicate that both of these fetal vascular remnants are more common in eyes that have immature retinal vasculature. Pupillary membrane remnants, in particular, were seen only in eyes with incompletely vascularized retinas; there was no correlation with the level or duration of oxygen therapy. This finding may aid the clinician who is inexperienced in assessing the maturity of retinal vasculature with the ophthalmoscope, such as the neonatologist, in clinically identifying those infants at risk for oxygen toxicity to the retinal vasculature.

Long-term interest at our center in morphology of the optic cup stimulated an additional area of observation. While highly detailed classification of the cup requires use of contact lens and slit lamp,[14] general classification into Elschnig types[7] could easily be done with the ophthalmoscope. The infant population had a distribution of cup types similar to an adult population. Those cases designated as "flat" cups were mostly caused by abundant glial tissue on the surface of the nerve head and could not be classified into one of the Elschnig types. These findings suggest that physiologic cup morphology is determined developmentally and does not change significantly with increasing age.

SUMMARY

I studied the degree of maturation of the retinal vasculature in 654 eyes of premature and high risk infants. I determined gestational age of the infants by neurologic and physical findings, instead of by the less accurate method of using birth weight and length determinations. Vascular maturation first appeared in 31-week-old infants and was seen in an increasing percentage of eyes until age 38 weeks when I saw it in all eyes. I found a positive correlation between the presence of pupillary membranes and hyaloid remnants and the immaturity of the retinal vessels. This may allow examiners inexperienced in the use of the indirect ophthalmoscope to detect infants with incomplete retinal vascularization. The variation in morphology of the optic cups in this newborn population was similar in distribution to that seen in adult populations.

REFERENCES

1. Fletcher, M. C.: Retrolental fibroplasia role of oxygen. In Report of the 16th Ross Pediatric Research Conferences, Columbus, Ohio, Ross Laboratories, 1955, pp. 34-38.

2. Mann, I.: The Development of the Human Eye, 3rd ed. London, Brit. Med. Assoc. 1964, pp. 228-229.

3. Cogan, D. G.: Development and senescence of the human retinal vasculature. Trans. Ophthalmol. Soc. U. K. 83:465, 1963.

4. Foos, R. Y., and Kopelow, S. M.: Development of retinal vasculature in paranatal infants. Surv. Ophthalmol. 18:117, 1973.

5. Kushner, B. J., Essner, D., Cohen, I. J., and Flynn, J. T.: Retrolental fibroplasia. 2. Pathologic correlation. Arch. Ophthalmol. 95:29, 1977.

6. Dubowitz, L. M. S., Dubowitz, V., and Goldberg, C.: Clinical assessment of gestational age in the newborn infant. J. Pediatr. 77:1, 1970.

7. Portney, G. L.: Qualitative parameters of the normal optic nerve head. Am. J. Ophthalmol. 76: 655, 1973.

8. Cantolino, S. J., O'Grady, G. E., Herrara, J. A., Israel, C., Justice, J., and Flynn, J. T.: Ophthalmoscopic monitoring of oxygen therapy in premature infants. Am. J. Ophthalmol. 72:322, 1971.

9. Potter, E. L.: Pathology of the Fetus and Infant, 2nd ed. Chicago, Yearbook Medical Publishers, 1961, pp. 11-12.

10. Roper-Hall, M. J.: The eye of the premature baby. Br. Med. J. 2:231, 1960.

11. Jones, H. E.: Hyaloid remnants in the eyes of premature babies. Br. J. Ophthalmol. 47:39, 1963.

12. Gans, B.: The pupillary membrane in premature infants. Arch. Dis. Child. 34:292, 1959.

13. Hornblass, A.: Persistent pupillary membrane and oxygen therapy in premature infants. Ann. Ophthalmol. 3:95, 1971.

14. Portney, G. L.: Photogrammetric analysis of three-dimensional geometry of normal and glaucomatous optic cups. Trans. Am. Acad. Ophthalmol. Otolaryngol. 81:239, 1976.