

Ocular findings in low birthweight and premature babies in the first year: Do we need to screen?

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PURPOSE. *There is no standardized approach for the ophthalmic care follow-up of children screened for retinopathy of prematurity (ROP). The authors report the ocular findings at 12 months in preterm and low birthweight babies screened for ROP over a 5-year period (1998–2003).*

METHODS. *The case notes of 211 babies were retrospectively reviewed for birth details, maternal details, presence of ROP, and findings at follow-up screening which included visual acuity, refraction at 12 months, presence of squint, and any other ocular problems.*

RESULTS. *At 1 year follow-up, 16.6% of ROP positive children failed a screening visit because of squint (6.66%), refractive error (6.66%), and optic nerve abnormalities (3.33%). At 1 year follow-up, 10% of ROP negative children had failed a screening visit because of squint (3.75%), refractive error (3.75%), and other pathology (2.5%).*

CONCLUSIONS. *The authors recommend screening all babies with ROP at 12 months to identify amblyogenic factors such as squint and refractive error. Parents of infants who do not develop ROP should be advised of the increased risk of visual problems in their children and to have their child examined in the preschool period. (Eur J Ophthalmol 2008; 18: 104-11)*

KEY WORDS. *Retinopathy of prematurity, Screening, Squint, Refractive error, Myopia*

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INTRODUCTION

Preterm birth

Preterm birth is defined as birth before 37 completed weeks of gestation. In developed countries, iatrogenic delivery is responsible for almost half of the births between 28 and 35 weeks; hypertension and pre-eclampsia are the major pathologies (1). Delivery before 28 completed weeks, extreme prematurity, has multiple etiologies including premature rupture of membranes, spontaneous preterm labor, multiple pregnancy, cervical incompetence, and others. It is likely that anthropometric and environmental risk factors in combination with inherent genetic susceptibilities contribute to an increased risk of preterm labour for certain women (2). The preterm delivery rate in the United Kingdom is currently 7% and rising (3).

Retinopathy of prematurity

Apart from cerebral visual impairment, retinopathy of prematurity (ROP) is the most serious ocular complication for these babies in the neonatal period. The Multicentre Trial of Cryotherapy for ROP showed conclusively that cryotherapy for threshold disease reduces the risk of an unfavorable outcome by 50% (4). The Royal College of Ophthalmologists issued guidelines for ROP screening in 1996 (5) and these have been universally adopted throughout the United Kingdom. Currently these guidelines are under revision, re-examining the timing of initial examinations and the criteria for treatment (6, 7). Advances in neonatal care over the past decade have resulted in increased survival rates amongst preterm infants, with 88% survival for 27/28 weeks, and 21% for 24 weeks (depending on birthweight) (3, 8). This increased

survival rate means potentially more babies are at risk of developing ROP.

Visual deficit as a result of ROP in premature babies continues to be a severe disability in some of the survivors of neonatal intensive care. Recently published data from the United Kingdom report that 233 preterm babies between December 1997 and March 1999 developed stage 3 ROP: 59% of these were treated and 13% had a severe visual deficit at 1 year (9). The incidence of refractive error, strabismus, and reduced visual acuity is increased in children with and without ROP (10-15).

The Royal College of Ophthalmologists advises follow-up during the preschool years for all babies with stage 3 ROP but there is no clear consensus on follow-up screening for children with mild ROP or no ROP (16, 17).

It has been the policy at our unit to provide follow-up screening for these children at 6 months and 1 year following discharge from hospital. This article reviews the findings during the first year and evaluates the need for ophthalmic care follow-up in this group.

METHODS

An audit of screening outcomes for all babies born at the Ipswich Hospital and screened for ROP over the 5-year period 1998-2002 was undertaken. Cases were identified from a register on the neonatal unit and from records kept by the orthoptic department.

All babies were screened in accordance with the guidelines issued by the Royal College of Ophthalmologists, i.e., all babies ≤ 1500 g birthweight and ≤ 31 weeks gestational age. Pupils were dilated with gutt. 0.5% cyclopentolate and gutt. 2.5% phenylephrine and the retinas examined using a speculum and scleral indentation. ROP screening was undertaken by two consultant ophthalmologists in the department, R.G. and S.H.L.

Babies who developed threshold disease were transferred to a tertiary centre for treatment.

All follow-up screening was undertaken at the hospital. At 6 months children were screened by the orthoptist and an ophthalmologist, who carried out a further dilated funduscopy. Visual acuity was assessed using Keeler cards or the Cardiff Acuity cards. Ocular movements were assessed and the presence of squint recorded. The MTI Photoscreener™ was also employed, although not routinely to detect refractive errors at 6 months. Stereopsis was also checked although not recorded for the purposes

of this review. At 12 months children were screened by the orthoptist and an optometrist recorded a cycloplegic refraction. The majority of children were reviewed again at 2 years.

Case notes were reviewed for the following information: sex, ethnic origin, gestational age, birthweight, maternal age, multiple births, mode of delivery, maternal steroid, findings on cranial ultrasound, findings on hearing screening, duration in the neonatal intensive care unit, and the presence of ROP. Ocular findings were recorded as +/- family history of squint/amblyopia, visual acuity, fundus findings, presence of squint or abnormal eye movements, refraction.

Statistics

Logistic regression was used to decide which neonatal and maternal characteristics significantly differ when a baby is ROP positive or negative. Initially each factor was investigated individually. If the Wald test statistic generated a p value < 0.1 then this variable was included in the multiple logistic regression model. The final model which indicates those factors that best predict whether a baby is likely to be ROP positive or negative was selected using backwards elimination with the likelihood ratio test.

RESULTS

There were 239 babies identified from our records who underwent ROP screening between March 1998 and May 2003. Twenty-eight of these babies fell outside the ROP screening guidelines from the Royal College of Ophthalmologists in London. None of these 28 babies developed ROP. Two of the 211 babies remaining were deceased by the 6-month follow-up. All but one of the 211 babies included in this study were screened for ROP by a single examiner (R.G.).

Retinopathy of prematurity

The population screened was 91.5% (193) white. The remaining 8.5% (18) comprised Asian, African, Afro-Caribbean, and mixed race. There were similar numbers of male and female babies. The overall incidence of ROP was 15.2% (32 babies) of which 11 babies had stage 1 ROP, 16 babies had stage 2 ROP, and 3 babies had stage 2 ROP with plus disease. Two babies (0.95%) developed

threshold ROP (stage 3 plus) and were transferred to a tertiary unit for retinal laser ablative treatment. These children returned to our unit following treatment. The three children with stage 2 and plus disease resolved fully. Table I shows the birthweight, gestation, and numbers of multiple births. Twenty-six percent of all children were from multiple births. Those who developed ROP were the most premature and lowest birthweight.

Maternal details

The mean maternal age at delivery was 28 years with a range from 16 to 51 years (Tab. II). Children who developed ROP tended to be born to younger mothers. Sixty-three percent of births were by caesarean section, the

majority as emergency cases due of a range of both maternal and fetal factors. Pre-eclampsia was diagnosed in 28.9% of mothers and 7.1% of mothers were pyrexial prior to delivery. Maternal steroid was given in over 83% of deliveries.

Neonatal unit screening

Overall 22% of cranial ultrasound scans showed some degree of ventricular hemorrhage. One quarter of those who developed ROP had an abnormal cranial ultrasound and 30% of ROP-positive babies also failed their hearing test. Those children who developed ROP spent longer in the neonatal intensive care unit, almost twice as long as ROP negative children.

TABLE I - CHARACTERISTICS OF NEONATES

	Total	ROP negative	ROP positive
Male	103	86	17
Female	108	93	15
Birthweight, g			
Mean ± SD	1304.36±339.64	1361.62±325.32	984.09±221.19
Range	530–3110	645–3110	530–1400
Gestation weeks			
Mean ± SD	29.83±2.22	30.30±1.91	27.16±1.97
Range	24–36	26–36	24–32
Multiple births			
Single	156	137	19
Twin	45	33	12
Triplet	10	9	1

TABLE II - MATERNAL CHARACTERISTICS

	Total	ROP negative	ROP positive
Maternal age, yr			
Mean ± SD	28.8±6.47	29.20±6.42	26.56±6.44
Range	16–51	16–51	17–40
Maternal health			
NAD	138	114	24
PET	61	56	5
Pyrexia	15	13	2
Other	7	6	1
Maternal steroid			
Yes	176	148	28
No	35	31	4
Delivery			
Vaginal	77	58	19
C-section elective	18	18	0
C-section emergency	116	103	13

NAD = No abnormality detected; PET = Pre-eclamptic toxemia

Logistic regression analysis: Factors significantly associated with retinopathy of prematurity

Results suggest that birthweight, gestational age, mode of delivery, multiple birth, maternal age, and duration in special care baby unit are all significantly associated at the 10% level with whether a baby is ROP positive or negative (Tab. III). Following from these results a logistic regression equation was constructed with the outcome variable being ROP positive or negative and the explanatory variables being those listed above. This equation was then reduced using backwards elimination with the likelihood ratio test and a final model was obtained which best describes the data given. The reduced model is shown in Table IV. Gestational age and duration spent in the special care baby unit were significantly associated with ROP.

Follow-up screening visit at 6 months

Two children were deceased and 29 of 209 (13.9%) children did not attend their first follow-up visit. There were 15 children who failed the screening visit

in the ROP-negative group. Findings were as follows: three had nystagmus (optic atrophy, congenital idiopathic motor nystagmus, and suspected ocular albinism), five had esotropia, five had greater than 4 D of hypermetropia (working distance [-1.50 D] subtracted), one had anisometropic myopia (-8.5 D right, -1.0 D left), and one child was diagnosed with Crouzon's condition.

In the ROP-positive group three children failed their screening: one child had cicatricial changes related to ROP in one eye, one had an optic nerve hypoplasia, and one was highly myopic (-8.0 D right, -7.5 D left).

There was no standardized approach to the detection of refractive errors at the 6 month visit. Some refractive errors were picked up by the orthoptists using the MTI Photoscreener™ and in some cases clinical suspicion prompted a request for cycloplegic refraction.

Follow-up screening at 1 year

Table V illustrates the ocular findings in ROP negative and positive babies who failed their screening test at 1 and 2 years.

TABLE III - LOGISTIC REGRESSION ANALYSIS: FACTORS ASSOCIATED WITH RETINOPATHY OF PREMATUREITY

Variable	Contrast	Wald	df	p value	OR (95% CI)
Sex	Female vs male	0.28	1	0.597	0.82 (0.38, 1.73)
Constant	-	37.30	1	<0.001	0.20
Ethnicity	Other vs white	1.27	1	0.260	0.31 (0.04, 2.40)
Constant	-	71.15	1	<0.001	0.19
Birthweight	-	29.88	1	<0.001*	1.00 (0.99, 1.00)
Constant	-	17.93	1	<0.001	104.11
Gestational age	-	35.29	1	<0.001*	0.41 (0.30, 0.55)
Constant	-	32.14	1	<0.001	3.1x10 ¹⁰
Delivery	C-section vs normal	8.02	1	0.005*	0.33 (0.15, 0.71)
Constant	-	17.83	1	<0.001	0.33
Multiple birth	Yes vs no	4.01	1	0.045*	2.23 (1.02, 4.90)
Constant	-	65.12	1	<0.001	0.14
Maternal age	-	4.42	1	0.035*	0.94 (0.88, 1.00)
Constant	-	0.04	1	0.846	1.19
Maternal steroid	-	0.45	1	0.502	1.47 (0.48, 4.48)
Constant	-	14.86	1	<0.001	0.13
Cranial US	Fail vs pass	0.74	1	0.390	1.45 (0.62, 3.40)
Constant	-	65.02	1	<0.001	0.16
Hearing screen	Fail vs pass	0.52	1	0.469	1.35 (0.60, 3.07)
Constant	-	61.69	1	<0.001	0.16
Duration in SCBU	-	34.23	1	<0.001*	1.06 (1.04, 1.08)
Constant	-	55.23	1	<0.001	0.01

*Factors significantly associated with retinopathy of prematurity.
SCBU = Special care baby unit

At 2 years the types of squint detected in the ROP negative group were as follows: esotropia (8), Browns syndrome (1), and exotropia (1). Refractive errors included hypermetropia $\geq +4.00$ D (5) and anisometropia of greater than 1.00 D (2). One case with 9.5 diopters anisometropia was picked up at 6 months and was treated with a contact lens. Causes of nystagmus were as follows: optic atrophy, ocular albinism, and congenital idiopathic motor nystagmus. Other pathologies included Crouzon syndrome and optic nerve hypoplasia.

Squint types in the ROP positive group at 2 years were as follows: exotropia (1), esotropia (1), and one Duane syn-

drome. Refractive errors included myopia (<0.0 D), hypermetropia (>4.0 D) with astigmatism (≥ 1.0 D), and anisometropia (>1.0 D).

There were results available on 161 refractions at 12 months shown in Table VI. In total there were 14 (8.7%) myopic children, i.e., a spherical equivalent of less than zero in one or both eyes. In the ROP positive group just one child was highly myopic at 1 year with a refraction of -7.5 D right and -8.0 D left. One child had 2 diopters of anisometropia and one child had 2 diopters of astigmatism. In the ROP negative group five children were prescribed glasses.

TABLE IV - MULTIPLE REGRESSION ANALYSIS: FACTORS ASSOCIATED WITH RETINOPATHY OF PREMATURITY

Variable	Wald	df	p Value	OR (95% CI)
Maternal age	4.00	1	0.046	0.92 (0.85, 1.00)
Gestational age*	15.29	1	<0.001	0.53 (0.38, 0.73)
Duration in SCBU*	13.25	1	<0.001	1.04 (1.02, 1.06)
Constant	10.44	1	<0.001	11,683,517**

*Factors significantly associated with retinopathy of prematurity.

SCBU = Special care baby unit

** This figure is generated from the statistical equation

TABLE V - FINDINGS IN RETINOPATHY OF PREMATURITY (ROP) POSITIVE AND ROP NEGATIVE CHILDREN WHO FAILED SCREENING AT 1 AND 2 YEARS

Ocular morbidity	ROP negative, n=160, 1 yr	ROP positive, n=30, 1 yr	ROP negative, n=160, 2 yr	ROP positive, n=30, 2 yr
Squint	6 (3.75)	2 (6.7)	10 (6.25)	3 (10)
Refractive error	6 (3.75)	2 (6.7)	7 (4.38)	3 (10)
Nystagmus	2 (1.25)	—	2 (1.25)	—
Other	2 (1.25)	1 (3.3)	2 (1.25)	1 (3.3)
Total	16 (10.0)	5 (16.7)	21	7 (23.3)

Values are n (%).

N = Total numbers screened

TABLE VI - DISTRIBUTION OF REFRACTIVE ERRORS AT 12 MONTHS (RIGHT EYE DATA ONLY*)

MSE (D)	Total,* n=161	ROP positive,* n=26	ROP negative,* n=135
$\geq +3.00$	15	2	13
≥ 0.00 and $\leq +3.00$	132	19	113
<0.00 and ≥ -3.00	12	4	8
< -3.00	2	1	1
Overall MSE (D)		Left +0.99 SD 1.97 Right +0.79 SD 2.74	Left +1.39 SD 1.1 Right +1.29 SD 1.44

MSE = Mean spherical equivalent; D = Diopters; SD = Standard deviation

Children outside the ROP screening criteria

There were 28 children screened who did not fulfill the criteria for ROP screening. At 1 year, one child had an esotropia with anisometropic hypermetropia, one had hypermetropia of +6.00 D each eye, and one child was referred to a specialist Sticklers Clinic for follow-up because of a positive family history. The refractive state of this child is not known.

DISCUSSION

Our review supports the view that the incidence of severe ROP is in decline despite reductions in birthweight and gestational age (18, 19). We found that just 15.2% (32) of babies screened had any degree of ROP and just 1.4% (2) had stage 3 or over. Much of this has been attributed to overall improvements in maternal and neonatal care, in particular the use of maternal steroids and more controversially the introduction of surfactant (8, 20, 21). We found that lower gestational age and a long duration spent in the special care baby unit was significantly associated with ROP. The most premature and ill babies, however, may not be born in a district general hospital or may be transferred to a tertiary unit after birth and perhaps this reflects our low incidence of ROP. Much of the ocular morbidity was detectable at the first follow-up visit at 6 months and continued to increase at subsequent visits. Many would argue against screening at such an early age since intervention is unlikely. We repeated the fundus examination at the 6-month visit and in this series a subtle optic nerve abnormality was picked up in the ROP positive group although the visual significance of this finding is not yet apparent.

Saunders et al (27) examined refractive development in a group of preterm infants without ROP and found that these infants demonstrated significantly higher levels of anisometropia and myopia at birth compared with term infants but concluded that most astigmatic and anisometropic errors are lost during the first year of life in a process called emmetropization. Many studies have shown approximately twice the rate of myopia following acute ROP compared with the absence of ROP (22, 23). Myopia of prematurity is explained by a highly curved cornea, shallow anterior chamber, and relatively short axial length than would be expected for its dioptric

power (24, 25). Myopia is also more common in the more immature infants, i.e., lowest gestational age and birthweight (26).

Refractive status at 12 months does not necessarily predict refractive status later on and some premature infants may demonstrate a more erratic refractive development (27). The spherical equivalents from this study demonstrate a myopic trend which was more pronounced in the ROP positive group. Snir et al reported the refractions of 33 premature babies at 40 weeks corrected age (mean birthweight 1694 grams). The spherical equivalents for the right eye were 1.36 D (SD 1.16 D) and left eye 1.39 D (SD 1.22 D) (25). These figures are similar for our ROP negative group refractions at 12 months of age although our babies were more immature at 30.3 weeks gestation vs 32 weeks gestation and had lower birthweight (1362 g vs 1694 g).

O'Connor et al have recently reported a one diopter shift in mean spherical equivalent towards myopia over the first decade in a cohort of low birthweight babies. ROP was found to increase the likelihood of developing anisometropia by sixfold (28). The prevalence of refractive errors at 11 years of age in this group was myopia (18.9%), high hypermetropia (6.6%), astigmatism (13.7%), and anisometropia (9%).

Atkinson et al screened over 8,000 infants aged 9 to 11 months and found the prevalence of hyperopia to be 5%, manifest strabismus 0.3% at 9 months and 1.5 to 2% by school age (29). In this series the ROP positive babies have an increased incidence of squint (6.7%) and refractive error (6.7%) at 12 months while ROP negative babies probably do not differ significantly from the general population at this age.

Our figures show additional refractive errors and squints being detected or requiring treatment at 2 years. At 2 years 4.38% of ROP negative children required spectacle correction versus 10% of ROP positive children and 6.25% of ROP negative children had a squint compared with 10% of ROP positive children. There was a family history of squint in 3 of 10 squints in the ROP negative group and 2 of 3 squints in the ROP positive group at 2 years.

Ocular morbidity was overall almost twice as likely in the ROP positive group: 23.3% versus 13.1% in the ROP negative group. Not all abnormal ocular findings in our series can be directly attributed to prematurity, such as optic nerve hypoplasia, Crouzon syndrome, and ocular albinism, and indeed the functional visual signifi-

cance is difficult to determine at such an early age. Many studies have reported the increase in strabismus in premature infants and this has been attributed to many factors, some interrelated, such as ROP, birthweight, increase in refractive errors/anisometropia, family history, general development quotient, neurologic insult, maternal age, and smoking (10, 30-32).

Strabismus in low birthweight children may develop shortly after birth but many cases develop after infancy (31). Amblyopia in the preterm infant may differ from that of the full term infant with regard to severity and treatability. The high incidence of amblyogenic factors in low birthweight and premature infants raises the issue of whether such children should be assessed in the preschool period (17). It has been suggested that perhaps the most useful intervention for low birthweight children would be to refract them between 6 months and 1 year to identify high refractive errors. Early detection of visual impairment in these children is also useful in informing developmental and educational strategies (33).

CONCLUSIONS

We recommend based on our findings that all babies found to have ROP should have follow-up screening from

the age of 12 months. Parents of other children who were ROP negative should be advised that their children are at increased risk of squint, amblyopia, and refractive error and these children should at least be screened in the preschool period either in an established community or hospital based screening program or by their local optometrist.

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