Retinopathy of Prematurity in Very Low Birth Weight Infants

J K Chye,* *FRACP, DCH (Otago), FAMM*, C T Lim,** *FRCP (Land), FRCPE, FAMM*, H L Leong,** *FRCOphth (UK)*, P K Wong,*** *FRCS (Edin)*

Abstract

This study aims to determine theprevalence of and riskfactors associated with retinopathy ofprematurity (ROP) in very low birth weight (VLB W) infants. All premature VLB W infants, admitted into the neonatal intensive care unit of the University Hospital Kuala Lumpur, were screenedfrom 4 weeks of life. Perinatal and neonatal data were retrieved from the infants' medical notes. Between August 1994 and July 1996,100 infants had their eyes examined serially. Of the 15 (15%) infants with ROP, all were less than 31 weeks gestation, and only 1 infant had birth weight above 1250 g. Five (5%) infants had severe ROP; 4 infants underwent cryotherapy for stage 3 threshold disease. Infants with ROP, as compared to infants without ROP, had lower birth weight [mean (SEM) 993 (50) g versus 1205 (22) g, P <0.001], lower gestational age [mean (SEM) 28.0 (0.4) weeks versus 30.1 (0.2) weeks, P <0.001], higher rates of patent ductus arteriosus and chronic lung disease, greater number of radiographic examinations and episodes of late-onset suspected/confirmed sepsis, and required longer duration of supplemental oxygen, ventilation, xanthine, antibiotics and intralipid use, but were slower to establish full enteralfeeds. On multivariate logistic regression analysis, birth weight ≤1000 g [OR 2.38, 95% CI 1.25, 4.55, P = 0.009] and gestational age ≤28 weeks (OR 2.86, 95% CI 1.47, 5.56, P = 0.002] were significantpredictors of increased risk of this disease. In conclusion, ROP is strongly associated with smaller, more immature and sicker neonates. Prevention of prematurity would help reduce the incidence of this disease.

***Ann Acad Med Singapore 1999;* 28:193-8**

Key words: Malaysia, Neonates, Oxygen, Risk factors

Introduction

Retinopathy of prematurity (ROP), which could lead to visual impairment and blindness,[1-2] is a recognised serious morbidity amongst surviving premature infants. The inverse relationship between the risk of this disease with birth weight and gestational age had been well-documented, in particular, in infants with birth weight ≤1500 g[1-7] (very low birth weight or VLBW infants) and infants ≤28 weeks gestation.[1,8] Other multifactorial risk factors associated with this disease had also been well reviewed.[9]

This study aims to establish the prevalence of ROP and associated risk factors in our population of VLBW infants.

Materials and Methods

Infants who were admitted to the Special Care Nursery (SCN), University Hospital Kuala Lumpur, which is a level 3 neonatal intensive care unit, received indirect ophthalmoscopic assessment if they meet the following criteria: VLBW, born before 32 weeks gestation, or had required ventilatory support or oxygen therapy for more than one week. These eye examinations were carried out in the SCN by 2 ophthalmologists, using the binocular indirect ophthalmoscope, 30 dioptre lens, eyelid speculum and scleral indentation. Each examination was preceeded by the instillation of mydriatic drops (tropicamide 1% and phenylephrine HCl 2.5%) every half hourly for 2 to 3 times to fully dilate the pupils, and local anaesthesia (amethocaine 0.5%). The first ophthalmologic assessments were performed from 28 days of life, when the conditions of the infants were stable, and thence screened once to twice-weekly until full maturity of retinal vascularisation was reached, complete regression of retinopathy attained or retinal cryotherapy indicated.[10] This was followed after hospital discharge by regular outpatient eye clinic review until the first year of corrected age. Infants with documented ROP were seen past their first birthday. The grading of ROP was based on the International Classification of ROP.[11]

Between August 1994 and July 1996, medical records of all VLBW infants in the SCN were retrieved. Data on some perinatal and neonatal events were reviewed, as were the number, severity and treatment of any ROP.

* *Lecturer*
** *Professor*
Department of Paediatrics
*** *Lecturer*
Department of Ophthalmology
Faculty of Medicine
University of Malaya, KL, Malaysia
Address for Reprints: Dr Joon-Kin Chye, Department of Paediatrics, Faculty of Medicine, University of Malaya, 50603 Kuala Lumpur, Malaysia

During this study period, the oxygen status of the infants was monitored by continuous pulse oximetry, and regular arterial blood gas measurement of blood sampled from indwelling arterial catheters or obtained via percutaneous punctures of peripheral arteries. The inspired oxygen concentration had been regulated to keep the pulse oximeter (Nellcor) oxygen saturation readings between 88% and 95%,[12] and the arterial PO_2 between 6.5 kPa and 11 kPa.

As of February 1995, exogenous surfactant (Survanta, Ross Laboratories) was administered to ventilated infants with severe respiratory distress syndrome (inspired oxygen concentration greater than 40% and a/A ratio less than 0.22). Postnatal steroids were not used to wean infants off the ventilators or supplemental oxygen. Replacement blood transfusion (10 to 15 ml/kg/day) was given when the haematocrit dropped below 40% in ventilated infants or greater than 10% of blood volume has been removed for blood tests. Enteral feeds were commenced in the first 3 to 5 days of life, and total parenteral nutrition and intralipids via central venous lines were added within the first week. Where the gestational age by dates of the infants were doubtful, the results of the clinical assessment (Ballard's scores[13]) were used. Prophylaxis or treatment with vitamin E was not practised.

The following definitions were adopted for this study: severe ROP for stage 3 disease or greater (the stage of the more severely affected eye was used), chronic lung disease as ongoing supplemental oxygen requirement beyond 28 days of life; patent ductus arteriosus as diagnosed clinically, with echocardiographic confirmation in some cases; respiratory distress syndrome diagnosed on both clinical and radiographic criteria; late-onset sepsis for suspected and confirmed (blood culture proven) episodes of infections occurring beyond 48 hours of life; and antenatal dexamethasone if ≥2 doses were given at least 12 hours before delivery.

Data were analysed with the Statistical Package for the Social Sciences (Windows version, Release 6.1), SPSS Inc, Chicago, Ill.[14] The Chi-square statistics, Fisher's exact test and Student's t-test were used for univariate analyses. Multivariate logistic regression analysis using the backward likelihood ratio method was performed to determine any predictive factors for ROP. Statistical significance was considered at $P<0.05$.

Results

Over the 2-year study period, 184 VLBW infants were admitted to the SCN (including 3 out-born infants, but excluding 3 infants with lethal congenital malformations). Of these, 33 (18%) infants had died before their eyes could be examined; 51 (28%) were lost to follow-up (discharged home prior to any eye assessment and failed to attend the outpatient eye clinic). One hundred infants (54%) had their eyes examined. The mean (standard error of mean, SEM) postnatal age for first eye examinations was 4.9 (0.2) weeks of life, which corresponded to a mean (SEM) corrected age of 34.7 (0.3) weeks.

Fifteen (15%) infants had ROP (Tables I & II). The severity of ROP and the number of infants affected (in parentheses) are as follows: bilateral stage 1 (3), stage 2 (3) and stage 3 (4); unilateral stage 1 (1) and stage 2 (2); and mixed stages 1 and 2 (1), and stages 2 and 3 (1). The trend for increasing rates of ROP with decreasing birth weight and gestational age is statistically significant. Except for an infant with unilateral stage 2 disease (birth weight of 1500g, received IPPV for 4 days, and then head box oxygen for 1 day), all the other 14 infants had birth weights <1250 g. No ROP was noted in any infants greater than 30 weeks gestation. All the 5 (5%) cases of severe ROP had occurred in infants with birth weight 11000 g (extremely low birth weight or ELBW infants) and gestational age 128 weeks. Of these, 4 infants with stage 3 threshold disease underwent cryotherapy, which resulted in regression of the disease. The bilateral stage 3 ROP in the remaining infant, as with the other retinal lesions, had resolved spontaneously. No stage 4 or greater severity was noted. The mean (SEM) corrected ages for first detection of any ROP and severe ROP were 34.1 (0.3) weeks and 35.4 (1.2) weeks respectively. Only in 1 of the 5 infants with severe ROP was the lesion found during the first eye examination at 32 weeks corrected age.

TABLE I: RETINOPATHY OF PREMATURITY AND BIRTHWEIGHT

Birth weight (g)	No. of infants admitted	No. of survivors (%)	No. of infants with eyes examined	ROP stage*				No. of infants with ROP (%)**
				1	2	3	4	
1750	15	3 (20)	3			1		1 (33)
751 to 1000	37	24 (65)	24	2	3	4		9 (38)
1001 to 1250	53	46 (87)	34	2	2			4 (12)
1251 to 1500	79	78 (99)	39		1			1 (3)
Total	184	151 (82)	100	4	6	5		15 (15)

ROP: retinopathy of prematurity

* In bilateral asymmetrical disease, the stage of the more severely affected eye is shown.

** The trend for increasing rates of ROP with decreasing birth weight is statistically significant (χ^2 15.0, df 3, $P = 0.002$).

TABLE II: RETINOPATHY OF PREMATURITY AND GESTATIONAL AGE

Gestation (weeks)	No. of infants admitted	No. of survivors (%)	No. of infants with eyes examined	ROP stage*				No. of infants with ROP (%)**
				1	2	3	4	
23 to 26	18	6 (33)	6	2		1		3 (50)
27 to 28	34	23 (68)	22	1	3	4		8 (36)
29 to 30	55	51 (93)	39	1	3			4 (10)
31 to 32	38	34 (89)	23					0
33 to 35	39	37 (95)	10					0
Total	184	151 (82)	100	4	6	5		15 (15)

ROP: retinopathy of prematurity

* In bilateral asymmetrical disease, the stage of the more severely affected eye is shown.

** The trend for increasing rates of ROP with decreasing gestational age is statistically significant (χ^2 21.4.0, df 4, P <0.001)

Infants with ROP, as compared to infants without ROP, had lower birth weight and gestational age; had greater number of radiographic examinations (chest and abdomen) and episodes of late-onset sepsis; needed longer duration of supplemental oxygen, ventilation, theophylline, antibiotics and intralipid use; and were slower to start and to attain full enteral feeds (Table III). They were also more likely to have birth weight ≤1000 g, gestational age ≤28 weeks, and higher rates of patent ductus arteriosus and chronic lung disease (Table IV).

There were no significant differences in the Apgar scores, number of blood transfusions, days of phototherapy, peak levels of serum bilirubin, and days of total parenteral nutritional support (Table III), nor the need for intubation at birth, respiratory distress syndrome, need for ventilation, antenatal dexamethasone use, mode of delivery (vaginal versus Caesarean section), infants' gender or race (Table IV) between the infants with and without ROP. Amongst the 55 infants who were intubated and ventilated for respiratory distress syndrome, no significant difference in the rate of ROP was noted between those who were and were not given surfactant replacement therapy [6 (22%) versus 4 (14%), OR 1.71, 95% CI 0.43, 6.91, P = 0.5031. On logistic regression analysis, using the covariates with P values < 0.30 (Table IV), birth weight 11000 g [adjusted OR2.38, 95% CI 1.25, 4.55, P = 0.0091 and gestational age 128 weeks [adjusted OR 2.86, 95% CI 1.47, 5.56, P = 0.0021 were the only predictive factors of increased risk of this disease.

TABLE III: RISK FACTORS FOR RETINOPATHY OF PREMATURITY (UNIVARIATE ANALYSIS WITH STUDENT'S t-TEST)

	ROP* (n = 15)	No ROP* (n = 85)	*P* values
Birth weight (g)	993 (50)	1205 (22)	<0.001
Gestational age (weeks)	28.0 (0.4)	30.1 (0.2)	<0.001
Number of radiographs	6.1 (1.2)	3.5 (0.4)	0.02 1
Number of late-onset sepsis**	2.3 (0.4)	1.1 (0.1)	0.001
Supplemental oxygen (days)	32.6 (6.2)	13.7 (2.6)	0.006
IPPV (days)	13.3 (4.1)	5.9 (1.3)	0.036
Theophylline therapy (days)	49 (7.5)	17 (1.9)	<0.001
Antibiotics therapy (days)	25.9 (3.1)	16.3 (1.9)	0.044
Intralipids (days)	23.1 (4.4)	10.4 (2.0)	0.016
First oral feed started (days)	5.0 (1.0)	3.2 (0.3)	0.038
Full oral feed established (days)	26.9 (4.0)	12.5 (1.2)	co.00 1
Apgar score at 1 minute	6.1 (2.0)	6.0 (2.2)	0.916
Apgar score at 5 minutes	8.5 (1.6)	8.5 (1.7)	0.953
Number of blood transfusions	4.7 (1.3)	2.6 (0.5)	0.075
Phototherapy (days)	6.9 (1.0)	5.1 (0.4)	0.069
Peak serum bilirubin level (μmol/l)	180 (12)	187 (7)	0.658
Total parenteral nutrition (days)	15.8 (3.8)	8.8 (2.0)	0.166

ROP: retinopathy of prematurity; IPPV: intermittent positive pressure ventilation

* Values are expressed as mean (standard error of mean).

** Episodes of clinical infections (suspected or blood-culture proven).

There was also a trend towards higher rates of ROP with increasing duration of oxygen therapy (Table V). However, 1 infant who was born at 30 weeks gestation and weighed 830 g, required only a brief period of manual bagging with oxygen at birth and had an uneventful postnatal period, developed stage 1 ROP in the right eye and stage 2 disease in the other eye.

In contrast to the study infants, the 51 infants who did not have ophthalmologic examination were heavier and more matured at birth, and had a less complicated SCN stay (Table VI). None of them had birth weight 11000 g, patent ductus arteriosus or chronic lung disease. In a subgroup of 12 infants with birth weight ≤1250 g (range 1100 g to 1250 g), only 1 infant was born at 28 weeks gestation, and who had an uncomplicated neonatal course. One infant received IPPV support (for 3 days), multiple blood transfusions and 54 days of theophylline therapy (for recurrent apnoea), another infant had nasal continuous positive airway pressure support (for 2 days), and 5 other infants needed head box oxygen (inspired concentration ≤30%) for less than 24 hours. Similarly, amongst the 39 infants with birth weight above 1250 g, only 2 infants received IPPV support (for ≤2 days) and another 12 infants had needed supplemental oxygen (inspired concentration ≤30%) for less than 48 hours.

TABLE IV: RISK FACTORS FOR RETINOPATHY OF PREMATURITY (CHI-SQUARE STATISTICS AND FISHER'S EXACT TEST)

	ROP* (n = 15)	No ROP* (n = 85)	OR (95% CI)	*P* values
Birth weight ≤1000 g	10 (67)	17 (20)	8.00 (2.41, 26.50)	<0.001
Gestation 128 weeks	11 (73)	17 (20)	11 .oo (3.11, 38.85)	<0.001
Patent ductus arteriosus	10 (67)	25 (29)	4.80 (1.49, 15.47)	0.005
Chronic lung disease	8 (53)	14 (17)	5.80 (1.81, 18.58)	0.004
Late-onset sepsis**	10 (67)	25 (29)	4.80 (1.49, 15.47)	0.008
Intubation at birth	6 (40)	24 (28)	1.69 (0.54, 5.82)	0.372
RDS	11 (73)	49 (58)	2.02 (0.59, 6.86)	0.253
Need for ventilation	10 (67)	51 (60)	1.33 (0.42, 4.24)	0.625
Antenatal dexamethasone	4 (27)	28 (33)	0.74 (0.22, 2.53)	0.769
Vaginal delivery	8 (53)	24 (28)	2.90 (0.95, 8.89)	0.073
Male gender	5 (53)	41 (48)	1.23 (0.41, 3.68)	0.716
Race				
Malay	8/58 (14)			
Indian	2/19 (11)			0.553
Chinese	5/23 (22)			

ROP: retinopathy of prematurity; RDS: respiratory distress syndrome; OR: odds ratio; 95% CI: 95% confidence interval

* Number of infants (percentages)

** Two or more episodes of clinical infections (suspected or blood-culture proven)

TABLEV: DURATION OF OXYGEN THERAPY AND RISKS OF RETINOPATHY OF PREMATURITY

Postnatal days of supplemental oxygen	nil	≤7	8-14	15-21	22-28	>28
	No. (%)					
Infants with ROP	1 (6)	2 (5)	2 (17)	0	2(33)	8(36)
Infants without ROP	15(94)	38(95)	10 (83)	4(100)	4(67)	14(64)
Total	16	40	12	4	6	22

ROP: retinopathy of prematurity

The trend towards an increasing rate of ROP with longer duration of oxygen therapy is statistically significant (χ^2 13.9, df 5, P = 0.016).

TABLE VI: DIFFERENCES BETWEEN THE INFANTS WITH AND WITHOUT EYE EXAMINATIONS

	Study infants* (n = 100)	Non study infants* (n = 51)	P values
Birth weight (g)	1177 (21)	1351 (15)	<0.001
Gestational age (weeks)	29.8 (0.2)	32.5 (0.3)	<0.001
Supplemental oxygen (days)	18.5 (3.1)	0.65 (0.1)	<0.001
IPPV (days)	7.00 (1.3)	0.06 (0.0)	co.00 1
Theophylline therapy (days)	23 (2)	2 (1)	co.00 1
Antibiotics therapy (days)	17.6 (1.7)	3.0 (0.5)	<0.001
Apgar score at 1 minute	6.0 (0.2)	7.1 (0.3)	0.003
Apgar score at 5 minutes	8.5 (0.2)	9.1 (0.2)	0.015
First oral feed started (days)	3.5 (0.3)	1.2 (0.2)	co.00 1
Full oral feed established (days)	14.6 (1.3)	4.2 (0.5)	co.00 1
Intralipids (days)	17.2 (1.9)	0.4 (0.2)	<0.001
Total parenteral nutrition (days)	9.5 (1.8)	0.5 (0.3)	<0.001
Number of X-rays	3.8 (0.4)	0.5 (0.1)	co.00 1
Number of blood transfusions	2.9 (0.4)	0.1 (0.1)	co.00 1
Phototherapy (days)	5.3 (0.4)	3.2 (0.4)	co.00 1

IPPV: intermittent positive pressure ventilation

* Values are expressed as mean (standard error of mean).

Discussion

The survival rates, prevalence of ROP and rates of severe ROP for the VLBW (82%, 15% and 5%, respectively) and ELBW infants (52%, 37% and 19%, respectively) in our study are similar to recent published studies from some Western countries (Table VII), which had used the same International Classification of ROP.[11] Even though the number of surviving infants without eye examinations in our study was large [51 (28%)], most of them were at low risk for ROP, especially severe ROP, which tend to afflict the smaller (≤1000 g) and more immature (≤28 weeks) infants. If we assumed that all the 21 who had brief exposure to supplemental oxygen postnatally (4 infants received ventilatory support and 17 infants needed low inspired concentration of oxygen) were to develop variable degrees of ROP, the overall rate of ROP would be 36 (24%) of 151 VLBW infants. Severe ROP, if any, would be unlikely to be higher than the 5% found in the study infants.

With improving survival rates, particularly the ELBW infants, the absolute number of infants with ROP has increased, but the rate of ROP has not.[2] Instead, the reverse occurred in one centre, and recent advances in the care of these ELBW infants have been postulated as contributing factors.[19] Similarly, in a large population-based study, over a period from 1965 to 1986, the trends for ROP-induced blindness had been shown to respectively lessen, stabilise and decrease for the less than 750 g, 750 g to 999 g and 1000 g to 1499 g categories of

TABLEVII: PREVALENCE OF ROP IN VLBW AND ELBW INFANTS

Reference (Country)	Cohort	No. of survivors (%)	No. of infants examined	All stages of ROP (%)	Severe ROP (%)
VLBW infants					
Darlow (NZ)"	1986	337 (82)	313	67 (21)	12 (4)
Rapisardi (Italy)[15]	1987-92	204 (75)	204	39 (19)	1 (0.5)
Teoh (Malaysia)'"	1989-92	175 (53)	113	36 (32)	14 (12)
Smith (Australia)'	1990-92	103 (91)	94	15 (16)	4 (4)
Nodgaard (Denmark)"	1990-93	141 (80)	141	25 (18)	10 (7)
Present study	1994-96	151 (82)	100	15 (15)	5 (5)
Total			965	197 (20)	46 (5)
ELBW infants					
Keith (Australia)'	1985-92	312 (54)	293	105 (36)	52 (18)
Palmer (USA)'	1986-87	2237"	2237	1825 (82)	591 (26)
Darlow (NZ)[6]	1986	87 (66)	84	41 (49)	11 (13)
Rapisardi (Italy)"	1987-92	58 (60)	58	21 (36)	1 (2)
Fleck (UK)[18]	1990-94	147"	147	78 (53)	46 (31)
Carse (Australia)"	1989-95	193"	193	60 (31)	9 (5)
Present study	1994-96	27 (52)	27	10 (37)	5 (19)
Total			3039	2140 (70)	715 (24)

ROP: retinopathy of prematurity; VLBW: very low birth weight infants; ELBW: extremely low birth weight infants
* Percentages of survival not available, due to the nature of the studies

infants, after adjusting for birth weight-specific survival to the first year of life.*"

Despite extensive research work, the pathogenesis of ROP remains elusive. Whilst oxygen has been strongly incriminated,[8,16,17] its role has not been fully understood. Infants with chronic lung disease are at high risk for this disease,[5,21] but not all infants in this category develop ROP. In our study, the rates of ROP increase with increasing duration of oxygen therapy, but the majority of our infants [14 (64%)] needing prolonged periods of supplemental oxygen (>28 days) did not have ROP (Table V). In contrast, a healthy ELBW infant, who was briefly exposed to oxygen concentration in excess of air in the delivery suite, subsequently developed ROP.

Intensive monitoring of this oxygen factor, such as continuous transcutaneous oxygen ($TcPO_2$) monitoring, which allows frequent and judicious adjustments of the inspired oxygen concentration to maintain a "safe" oxygen level, has not eliminated this disease.[22,23] Neither has its use resulted in a reduction of ROP among the group of high-risk infants, the ELBW infants,[23] which is also a strong predictor for ROP development in our study. In another study, the variability in the $TcPO_2$ in the first 2 weeks of life was found to be more predictive of severe ROP than the degree or duration of hyperoxia.[24]

In view of the relatively poor nursing staff to patient ratio and shortage of equipment in our neonatal unit, monitoring of oxygenation status by pulse oximetry, albeit a less reliable form of PaO_2 monitoring than $TcPO_2$, is easier to use and less labour intensive. It has also been shown to be highly sensitive in detecting hyperoxaemic episodes.[12] Our results suggest that its use in our unit, when accompanied by frequent arterial blood gas measurement, had produced similar rates of ROP as some larger centres which have been using the $TcPO_2$ monitoring.[1,2,19]

Low birth weight and young gestational age are two consistent risk factors associated with ROP in most studies.[1-8,15-19] Similarly, ventilatory support.[7,8,25] xanthine use,[25] sepsis" and patent ductus arteriosus[8] have been described as risk factors in other studies. The high rate of late-onset clinical sepsis (suspected or confirmed with blood-cultures) in our infants with ROP is consistent with the greater duration of antibiotics usage. None of the study infants had culture positive sepsis within the first 48 hours of life. The delays in starting feeds and achieving full enteral feeds are also a reflection of the general unstable conditions of the infants with ROP. Intralipid support, unlike total parenteral nutrition, is usually continued for a week or two past the achievement of full enteral feeds, especially for the ELBW infants. The support period is significantly longer in our infants with ROP. Whether this could be linked to the potential adverse effects of lipid peroxidation on the retina[26] remains to be clarified. In short, the numerous risk factors identified in this study are indicators of the stormy neonatal course infants with ROP go through. It is the smaller and more immature infants who are more likely to undergo such a turbulent period, and therefore exposed to the multiple factors associated with this

complication.

Although cryotherapy has made an impact on the reduction of unfavourable outcomes of ROP, in terms of blindness and abnormal fundus structure, the preliminary evidence for reduced visual acuity in such treated children at 5.5 years follow-up is of some concern.[27] Due to lack of facilities, accurate visual acuity of our 5 infants with severe ROP could not be determined at this stage. It remains to be seen if newer modalities of therapy, such as the diode laser,[28] have better long-term outcome than cryotherapy. An interesting adjunct to cryotherapy to reduce the severity and sequelae of threshold ROP has been the reported use of the antioxidant Vitamin E.[29] Similarly, postnatal dexamethasone therapy, another controversial therapy,[30] has been reported to reduce the need for cryotherapy in ELBW infants with chronic lung disease.[31] Both of these drugs are not being used in our neonatal unit.

In conclusion, a reduction in the incidence of ROP may occur with improved care of the immature, small and sick neonates, but ROP will remain an inherent complication amongst these survivors. Unless new insights into its pathogenesis becomes clearer and better preventative measures are available, prevention of prematurity (which remains the strongest risk factor for ROP[32]) is the most effective way of reducing the incidence and sequelae of this disease.

REFERENCES

1. Yu V Y H, Lim C T, Downe L M. A 12-year experience of retinopathy of prematurity in infants <28 weeks gestation or ≤1000 g birthweight. J Paediatr Child Health 1990; 26:205-8.
2. Keith C G, Doyle L W. Retinopathy of prematurity in extremely low birth weight infants. Pediatrics 1995; 95:42-5.
3. Palmer E A, Flynn J T, Hardy R J, Phelps D L, Phillips C L, Schaffer D B, et al. Incidence and early course of retinopathy of prematurity. Ophthalmology 1991; 98:1628-40.
4. Ng Y K, Fielder A R, Shaw D E, Levene M I. Epidemiology of retinopathy of prematurity. Lancet 1988; 2:1235-8.
5. Purohit D M, Ellison R C, Zierler S, Miettinen 0 S, Nadas A S. Risk factors for retrolental fibroplasia: experience with 3,025 premature infants. Pediatrics 1985; 76:339-44.
6. Darlow B A. Incidence of retinopathy of prematurity in New Zealand. Arch Dis Child 1988; 63:1083-6.
7. Smith J, Spurrier N, Goggin M. Retinopathy of prematurity in a South Australian neonatal intensive care unit. Aust NZ J Ophthalmol 1995; 23:49-54.
8. Todd D A, Kennedy J, Roberts S, Watts J, Psaila K, John E. Retinopathy of prematurity in infants less than 29 weeks' gestation at birth. Aust NZ J Ophthalmol 1994; 22:19-23.
9. Lucey J F, Dangnian B. A reexamination of the role of oxygen in retrolental fibroplasia. Pediatrics 1984; 73:82-96.
10. Cryotherapyfor Retinopathyof Prematurity CooperativeGroup. Multicenter trial of cryotherapy for retinopathy of prematurity: preliminary results. Arch Ophthalmol 1988; 106:471-9.
11. Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity. Arch Ophthalmol 1984; 102:1130-4.
12. Bucher H U, Fanconi S, Baeckert I', Duc G. Hyperoxemia in newborn infants: detection by pulse oximetry. Pediatrics 1989; 84:226-30.
13. Ballard J L, Novak K K, Denver M. A simplified score for assessment of fetal maturation in newborn infants. J Pediatr 1979; 95:769-74.
14. Norusis M J. Statistical Package for the Social Sciences: SPSS User's Guide and Advanced Statistics. New York: Mcgraw Hill, 1994.
15. Rapisardi G, Donzelli G I', Frosini R, Campa L. Arterial catheters and retinopathy of prematurity risk: need for a multicenter controlled trial. Pediatrics 1993; 92:740-l.
16. Teoh S L, Boo N Y, Ong L C, Nyein M K, Lye M S, Au M K. Duration of oxygen therapy and exchange transfusion as risk factors associated with retinopathy of prematurity in very low birthweight infants. Eye 1995; 9:733-7.
17. Nodgaard H, Andreasen H, Hansen H, Sorensen H T. Risk factors associated with retinopathy of prematurity (ROP) in Northern Jutland, Denmark 1990-1993. Acta Ophthalmol Scand 1996; 74:306-10.
18. Fleck B W, Wright E, Dhillon B, Millar G T, Laing I A. An audit of the 1995 Royal College of Ophthalmologists Guidelines for screening of retinopathy of prematurity applied retrospectively in one regional neonatal intensive care unit. Eye 1995; 9(Suppl):31-5.
19. Carse E A, Lee C H, Flavilla I, Burrows E, Hayes M M, Yu V Y H. Decreasing incidence of retinopathy of prematurity in babies <28 weeks gestation [abstract A23]. Proceedings of the First Annual Congress of the Perinatal Society of Australia and New Zealand; 1997 Mar 16-20; Perth. Perth: Perinatal Society of Australia and New Zealand, 1997.
20. Gibson D L, Sheps S B, Uh S H, Schechter MT, McCormick A Q. Retinopathy of prematurity-induced blindness: birth weight-specific survival and the new epidemic. Pediatrics 1990; 86:405-12.
21. Biglan A W, Brown D R, Reynolds J D, Milley J R. Risk factors associated with retrolental fibroplasia. Ophthalmology 1984; 91:1504-11.
22. Bancalari E, Flynn J, Goldberg R N, Bawol R, Cassady J, Schiffman J, et al. Influence of transcutaneous oxygen monitoring on the incidence of retinopathy of prematurity. Pediatrics 1987; 79:663-9.
23. Flynn J T, Bancalari E, Synder E S, Goldberg R N, Feuer W, Cassady J, et al. A cohort study of transcutaneous oxygen tension and the incidence and severity of retinopathy of prematurity. N Engl J Med 1992; 326:1050-4.
24. Cunningham S, Fleck B W, Elton R A, McIntosh N. Transcutaneous oxygen levels in retinopathy of prematurity. Lancet 1995; 346:1464-5.
25. Hammer M E, Mullen P W, Ferguson J G, Pai S, Cosby C, Jackson K L. Logistic analysis of risk factors in acute retinopathy of prematurity. Am J Ophthalmol 1986; 102:1-6.
26. Inder T E, Darlow B A, Sluis K B, Winterbourn C C, Graham P, Sanderson K J, et al. The correlation of elevated levels of an index of lipid peroxidation (MDA-TBA) with adverse outcome in the very low birthweight infant. Acta Paediatr 1996; 85:116-22.
27. Cryotherapy for Retinopathyof Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity: Snellen visual acuity and structural outcome at 5 ½years after randomization. Arch Ophthalmol 1996; 114:417-24.
28. Ling C S, Fleck B W, Wright E, Anderson C, Laing I. Diode laser treatment for retinopathy of prematurity: structural and functional outcome. Br J Ophthalmol 1995; 79:637-41.
29. Johnson L, Quinn G E, Abbasi S, Gerdes J, Bowen F W, Bhutani V. Severe retinopathy of prematurity in infants with birth weights less than 1250 grams: incidence and outcome of treatment with pharmacologic serum levels of Vitamin E in addition to cryotherapy from 1985 to 1991. J Pediatr 1995; 127:632-9.
30. Ehrenkranz R A. Steroids, chronic lung disease, and retinopathy of prematurity. Pediatrics 1992; 90:646-7.
31. Sobel D B, Phillip A G S. Prolonged dexamethasone therapy reduces the incidence of cryotherapy for retinopathy of prematurity in infants of less than 1 kilogram birth weight with bronchopulmonary dysplasia. Pediatrics 1992; 90:529-33.
32. Holmstrom G, Thomassen I', Broberger U. Maternal risk factors for retinopathy of prematurity-a population-based study. Acta Obstet Gynecol Scand 1996; 75:628-35.