Incidence, Risk Factors of Retinopathy of Prematurity Among Very Low Birth Weight Infants in Singapore

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Abstract

Introduction: To determine the incidence, risk factors and need for surgery for retinopathy of prematurity (ROP) among very-low-birth-weight (VLBW) infants. Materials and Methods: This was a retrospective study of all VLBW infants managed by the department over 14 years, from 1988 to 2001. Preterm infants were examined according to the Royal College of Ophthalmologists' guidelines, and retinopathy was graded following the International Classification of ROP. All VLBW infants examined for ROP were included and data were retrieved retrospectively and analysed for maternal, medical, obstetric and neonatal risk factors using logistic regression. Results: Of the 564 VLBW infants who fit the screening criteria, ROP was detected in 165 (29.2%) of VLBW infants; of whom 49% of infants had stage 1 disease, 24% were at stage 2, and 27% were at stage 3 or more. Among 45 infants with stage 3 disease or more, treatment was needed in 62.2% (28/45). No ROP was detected in infants greater than 33 weeks of gestation. Only 0.6 % (1/164) of infants greater than 30 weeks of gestational age (GA) needed surgery for ROP. Using birth weight (BW) criteria, stage 3 ROP was noted only in 1% (6/564) of infants with BW >1000 g. Of all ROP requiring surgery, 89% (25/28) of infants were <1000 g as compared to 11% (3/28) who were >1000 g infants. The median age of onset of ROP was 35 weeks (range, 31 to 41) corrected age. By univariate analysis for threshold ROP, preeclampsia, prenatal betamethasone exposure, gestational age, birth weight, 1-minute Apgar score, hyaline membrane disease (HMD), surfactant usage, hypotension, septicaemia, intraventricular haemorrhage duration of supplemental oxygen, ventilation and chronic lung disease were associated with ROP requiring surgery (i.e., threshold ROP, *P* <0.05). However, using multiple logistic regression analyses for ROP, maternal preeclampsia [odds ratio (OR), 2.52; confidence interval (CI), 1.32 to 4.7], birth weight (OR, 0.99; CI, 0.996 to 0.999), pulmonary haemorrhage (OR, 4.61; CI, 1.04 to 20.4), duration of ventilation (OR, 1.06; CI, 1.04 to 1.08) and duration of continuous positive airway pressure (CPAP) (OR, 1.02; CI, 1.01 to 1.04) were factors predictive of development of threshold ROP. Conclusion: The incidence of ROP among VLBW infants was 29.2%. ROP was strongly associated with smaller, more immature and sicker infants. The median age of onset of ROP was 35 weeks (range, 31 to 40 weeks) postmenstrual age. Infants <30 weeks of GA and/or infant with BW <1000 g are at considerable risk for threshold ROP. The main risk factors for development of threshold ROP by regression analysis are maternal preeclampsia, birth weight, and presence of pulmonary haemorrhage, duration of ventilation and continuous positive pressure ventilation. We suggest that both immaturity and compromised pulmonary function are both important aetiological factors in the development of ROP. Prevention of prematurity, control of preeclampsia, judicious use of ventilation and oxygen therapy are the only promising factors that may reduce the incidence and severity of ROP in this high-risk infant.

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Key words: Chronic lung disease, Follow-up, Mechanical ventilation, Pulmonary function

Introduction

Retinopathy of prematurity (ROP) is characterised by abnormal vascular development of retina in premature infants.[1] Recent advances in neonatal care have improved the survival rates for premature infants,[2] and this has been accompanied by an increase in the incidence of ROP.[3-5] ROP is a leading cause of childhood blindness[6,7] and accounts for up to 10% of childhood blindness in developed

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countries.[8-10] However, there are few studies on the incidence and risk factors of this important morbidity among very-low-birth-weight (VLBW) infants in Singapore. A high concentration of oxygen therapy was previously thought to be the major contributory factor in the development of ROP.[11,12] However, reports have found ROP in cases without oxygen therapy.[13] Even after oxygen therapy, not all premature infants develop ROP.[13] These evidence suggest that factors other than oxygen play an important role in the development of ROP. Before surfactant became available for clinical use in the neonatal intensive care unit, an incidence of 11% to 60% was reported in the VLBW population.[14,15] The last major report of the incidence of ROP was published from the cryotherapy-retinopathy of prematurity (CRYO-ROP) study completed in 1987,[16] before surfactant use was approved for treatment of hyaline membrane disease (HMD).

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 there are scarce data regarding the current incidence of ROP, particularly in Singapore. 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.[17,18] In their recent comprehensive review of ROP, Siatskowski and Flynn[19] noted that "we are as lacking in basic epidemiological data of varying rates of incidence of ROP in geographic area as we were in the 1940s and 1950s".

Materials and Methods

The objectives of this study were to determine the incidence of ROP and evaluate possible risk factors associated with the development of ROP among VLBW infants. This was a retrospective, observational analysis of VLBW infants managed from 1988 to 2001, who met established criteria for ROP screening.

The Neonatal Department of the Singapore General Hospital is a high-risk perinatal centre with 8 intensive care cots and receives an average of 50 to 60 VLBW infants per year. All VLBW infants admitted to the NICU between January 1988 and December 2001, who received eye examinations for ROP, were eligible for the study. Surfactant became available in this unit in December 1991. Bubble continuous positive airway pressure (CPAP) was made available from early 1994.

Of the 757 VLBW infants managed during the period, 634 (84%) infants were inborn and 123 (16%) infants were outborn. Five hundred and sixty-four (74.6%) infants who met the criteria for eyes examination by paediatric ophthalmologists to detect ROP were included for analysis. Excluded were VLBW infants with major congenital malformation, chromosomal anomalies and infants who died before eye examinations could be performed.

Eye Examination Schedules

Eye examinations were performed on all infants who met the criteria set by the Royal College of Ophthalmologists' guidelines published in 1995.[20,21] Eligible infants were referred by the attending neonatologist according to the Royal College Of Ophthalmologists' guidelines:

(1) Birth weight ≤1250 g. (However, we included all VLBW infants with birth weight ≥1500 g.)
(2) Maternal post-menstrual age ≤32 weeks.
(3) Neonatologists' concern over prolonged exposure to oxygen.

The infants were examined at 6 weeks chronological age or 34 weeks corrected age, whichever was earlier.

Eye Examination Methods

Cyclomydril 0.5% eye drops were instilled twice – 1 hour and 30 minutes – before examination. Indirect ophthalmoscopy was performed using a binocular indirect ophthalmoscope. Lid speculum and scleral depressors were routinely used.

Monitoring and Management of Infants at Risk for ROP

If no ROP was noted, eye examinations were continued every 2 weeks until vascularisation had reached zone 3. Those with ROP were screened at intervals indicated by the severity of the disease. The stages of ROP were classified according to the International Classification of Retinopathy of Prematurity:[22,23]

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

Stage 2. Retinal 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 threshold for treatment followed the protocol used in the CRYO-ROP trial.[16] Pre-threshold ROP was zone 1 ROP of any stage less than threshold; zone 2 stage 2 ROP or greater; zone 2 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 severity of ROP was defined as 5 or more contiguous or 8 cumulative clock hours of stage 3 plus

ROP in zone 1 or 2. The plus disease represented dilatation and tortuiousity of blood vessels in the posterior pole. All infants with threshold ROP were treated with cryo or laser therapy using indirect ophthalmoscopy. No eyeshields 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. No infants were given supplemental vitamin E as treatment for ROP.

For purposes of data analysis, the infants were divided into 3 groups:

Group 1. Infants without ROP.

Group 2. Infants with ROP not requiring any surgery.

Group 3. Infants with severe or threshold ROP requiring surgery in the form of cryotherapy or laser therapy.

Identification of Risk Factors

Data were recorded retrospectively and the presence of retinopathy was graded following the International Classification of ROP.[22,23] The perinatal variables documented included presence of fetal distress, antepartum haemorrhage, preeclampsia (PE), prolonged rupture of membrane (PROM), maternal pyrexia and maternal betamethasone and beta agonist usage. Demographic data collected included gestational age (GA), birth weight (BW), gender, maternal age and employment. Clinical data retrieved included Apgar scores at 1 minute and 5 minutes, HMD, surfactant given, pneumothorax, pulmonary haemorrhage, metabolic acidosis, hypothermia, hypotension, patent ductus arteriosus (PDA), neonatal jaundice requiring phototherapy, blood culture-positive septicaemia, intraventricular haemorrhage (IVH) and chronic lung disease (CLD). Respiratory data recorded included type of respiratory support, duration on oxygen, CPAP and synchronised intermittent mechanical ventilation (IMV). The average fractional inspiratory oxygen (FIO_2), positive inspiratory pressure, mean airway pressure and alveolar-arterial oxygen gradient in first week of life were also recorded to estimate severity of lung disease. For each infant who had ROP, age at which ROP was first detected, the maximum stage of ROP reached, site and therapy for ROP were recorded.

Definitions

VLBW was defined as infants with birth weight ≤1500 g. GA was ascertained based on maternal dates and early ultrasonographic dating in the first trimester. All infants were scored clinically using Dubowitz or Ballard scores except in vitro-fertilised infants. If there was a discrepancy of more than 2 weeks between the scored dates and maternal dates, the gestational age determined by scoring was taken. An infant was classified as small for gestational age (SGA) if the birth weight for GA was below the 10th percentile, using revised intrauterine growth curves by Kitchen et al.[24] HMD was diagnosed based on clinical and radiological evidence. Infants with severe HMD received surfactant replacement therapy. This was available to our unit from late 1991. The severity of HMD was estimated using mean alveolar-arterial oxygen gradient ($A\text{-}aDO_2 = PAO_2 - PaO_2$, where $PAO_2 = FIO_2 \times 713 - PaCO_2/0.8$) calculated using all blood gases done on first day of life. The a/A PO_2 ratio of <0.22 indicates severe HMD. Hypotension was defined as mean arterial pressure ≤35 mm Hg for infants between 1000 g and 1499 g and ≤30 mm Hg for infants <1000 g.[25] Hypotension was considered significant if inotropic support was required. The presence of a PDA was diagnosed clinically and confirmed by 2-dimensional echography. Those with significant PDA requiring treatment, either with indomethacine and/or ligation were noted. Sepsis was diagnosed based on a positive blood culture in an appropriate setting. Necrotising enterocolitis (NEC) was defined based on clinical, radiological and/or operative evidence (Bell's staging).[26] Serial cranial ultrasounds were performed from the first week of life till discharge. IVH was graded according to Papile's classification.[27] Chronic lung disease was defined as oxygen dependency beyond 36 weeks corrected age in association with chest radiographic findings of persistent hazy opacification or cyst-like pattern of density and lucency.[28] Babies were discharged when they reached a weight of 2 kg and were medically well. Prolonged rupture of membrane was taken as rupture of membrane for more than 24 hours. Adequate antenatal administration of betamethasone was defined as the completion of 2 doses of betamethasone given 12 hours apart with the second dose administered more than 24 hours prior to delivery. Maternal pyrexia was defined as maternal temperature ≥37.5^{0}C during labour. Neonatal jaundice was defined as significant jaundice requiring phototherapy.

Statistical Analysis

Statistical analysis was performed using the Statistical Package For Social Sciences (SPSS) programme. Univariate comparison of risk factors between the groups without ROP, infant with ROP not requiring surgery and ROP requiring surgery were evaluated using the Student's *t*-test and chi-square test with appropriate significance of $P < 0.05$. Stepwise multivariate logistic regression was used to evaluate factors predictive of development of ROP. The odds ratio and 95% confidence interval for each possible risk factor were also calculated.

Results

During the study period, the department managed a total of 757 VLBW infants. Of these, a hundred infants (13.2%) died during the primary hospitalisation. Thirteen infants with fatal malformations (4 anencephaly, 1 Potter's syndrome, 2 hydrops foetalis, 6 Trisomy syndromes) were excluded from the study. Of the 757 infants, 80 (10.5%) infants did not satisfy the criteria for ROP screening.

Five hundred and sixty-four infants (74.5%) met the criteria for evaluation. ROP was present in 165/564 (29.2%) of whom 45/564 (8%) infants had stage 3 ROP or greater (Fig.1). Incidence of ROP was 58/147 (39.4%) in presurfactant period (1988 to 1992) compared to 107/417 (25.6%) in surfactant period (1993 to 2001) (P <0.0001). The incidence of ROP requiring surgery was 7/147 (4.8%) in presurfactant period and 21/417 (5%) in surfactant period; that did not change significantly in 2 periods.

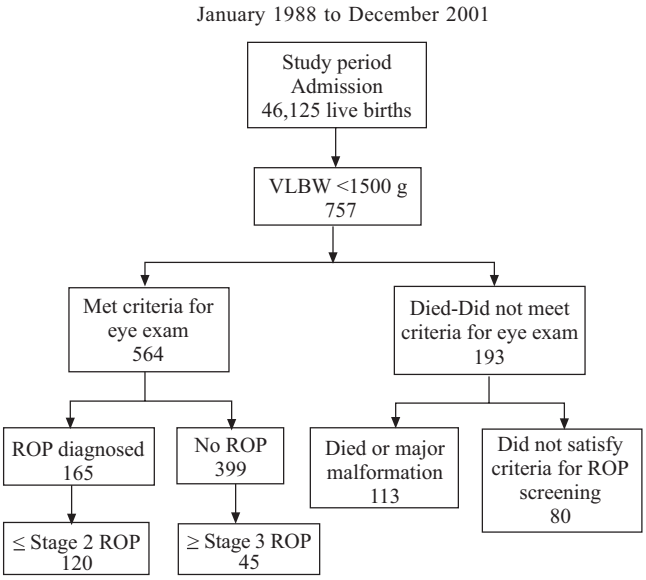

Fig. 1. Schematic diagram of the distribution of infants in the study.

Maternal Obstetric Factors

In Table 1, obstetric, perinatal and demographic factors in the infants who met the criteria for eye exams are summarised. The antenatal betamethasone usage was not significant in decreasing the severity of ROP. Only 11/28 (39%) of infants with ROP requiring surgery were given antenatal betamethasone versus 181/399 (45.5%) of the group without ROP (P = 0.564). Maternal beta agonist was used only in 114/399 (28.6%) in the group without ROP compared to 11/28 (39.3%) in ROP requiring surgery (P = 0.009). Severe ROP was seen in 21/28 (75%) of infants born to employed mothers versus 237/399 (59.4%) of unemployed mothers (P = 0.044). Normal vaginal delivery rate was higher in the group without ROP compared to the ROP group requiring surgery (P = 0.025). A lower rate of vaginal delivery in the ROP group probably reflects the high-risk perinatal status of these immature infants at the time of their delivery. One hundred and seven (26.8%) infants without ROP were born to mothers with preeclampsia, while all infants with ROP requiring surgery were born to mothers without preeclampsia (P <0.0001). Maternal age, multiple births, maternal pyrexia, antepartum haemorrhage, fetal distress, and PROM were not significantly different among infants who developed any stage of ROP and those who had not developed ROP.

Distribution of Incidence and Stages of ROP by GA

The incidence of ROP in survivors ≤24 weeks was 89%; 62% in survivors from 25 to 27 weeks GA; 28% among survivors from 28 to 30 weeks and 16% in survivors from 31 to 33 weeks. There were no infants with ROP beyond 33 weeks GA. Ninety-six per cent of threshold ROP requiring surgery occurred in infants <30 weeks GA at birth. The mean GA of infants without ROP was higher at 30.4 ± 2.2 weeks, compared with 26.7 ± 2.1 weeks in infants with ROP requiring surgery (P <0.05) (Table 2). In infants with GA ≤30 weeks, 56.6% (226/399) had no ROP versus 86.9% (173/399) in infants with GA ≥31 weeks (P = 0.0001). In VLBW infants with GA ≤30 weeks, the incidence of ROP was 84.2% (139/165) against 15.7% (26/165) in VLBW with GA ≥31 weeks (P <0.0001).

Among VLBW infants ≤30 weeks, incidences of stage 1, 2, 3 and 4 and above were 45.3% (63/139), 25.2% (35/139), 26.6% (37/139) and 2.9% (4/139), respectively. In infants with GA ≥31 weeks, incidences of stage 1, 2 and 3 were 69.2% (18/26), 23.1% (6/26) and 7.7% (2/26), respectively. There was no stage 4 ROP in infants ≥31 weeks of GA.

Distribution of Stages of ROP by Birth Weight

For infants <1000 g, the incidence of ROP of any degree was 55.4% (101/182), of whom 13.7% (25/182) had threshold ROP. The mean birth weight of infants without ROP was 1186 ± 211 g, while ROP not requiring surgery was 985 ± 224 g, compared with 797 ± 187 g in infants with ROP requiring surgery (P <0.05) (Table 2).

Distribution by Gestational Size

There were 28.7% (162/564) SGA infants. There were 30.5% (122/399) SGA infants in the group without ROP versus 25% (7/28) SGA infants in the group with ROP requiring surgery (P = 0.47). The incidence of ROP among SGA infants was not statistically significant.

Table 1. Maternal and Obstetric Factors and Comparison of Variables*

Variable	No ROP (n = 399) (%)	ROP without surgery (n = 137) (%)	ROP with surgery (n = 28) (%)	All VLBW with ROP (n = 165) (%)	*P*
Maternal age	30.9 ± 5.4	31.3 ± 4.8	31.4 ± 4.8	31.4 ± 4.7	0.791
Maternal employment	237 (59.4)	92 (67.1)	21 (75)	113 (68.5)	0.044†
Maternal PROM	82 (20.6)	31 (22.6)	8 (28.6)	39 (23.6)	0.564
Antepartum haemorrhage	53 (13.3)	26 (19)	5 (17.9)	31 (18.8)	0.232
Multiple births	79 (19.8)	31 (22.6)	18 (64.3)	42 (25.5)	0.120
Fetal distress	42 (10.5)	8 (5.8)	0	8 (4.8)	0.060
Preeclampsia	107 (26.8)	21 (15.3)	0	21 (12.7)	0.0001†
PROM	82 (20.6)	31 (22.6)	8 (28.6)	39 (23.6)	0.564
Maternal pyrexia	28 (7)	11 (8)	4 (14.3)	15 (9.1)	0.399
Antenatal beta-agonist	114 (28.6)	58 (42.3)	11 (39.3)	69 (41.8)	0.009†
LSCS	236 (59.1)	92 (69.2)	21 (75)	113 (68.5)	0.025†
Antenatal betamethasone	181 (45.4)	67 (49)	11 (39.3)	78 (47.3)	0.595

LSCS: lower segment caesarean section; PROM: prolonged rupture of membrane; ROP: retinopathy of prematurity
* Univariate comparison of maternal and obstetric factors in infants studied.
† *P* <0.05, significant

Table 2. Clinical Characteristics of VLBW Infants*

	No ROP (n = 399) (%)	ROP without surgery (n = 137) (%)	ROP with surgery (n = 28) (%)	All VLBW with ROP (n = 165) (%)	*P*
Hypothermia	5 (1.3)	2 (1.5)	2 (7.4)	4 (2.5)	0.048†
Gestational age (weeks)	30.4 ± 2.2	28.5 ± 2.3	26.7 ± 2.1	28.2 ± 2.3	0.0001†
Birth weight (g)	1186 ± 211	985 ± 224	797 ± 187	953 ± 229	0.0001†
Apgar 1 min	6 ± 2	5 ± 2.2	4 ± 2	5 ± 2	0.0001†
Apgar 5 min	7.9 ± 1.4	7.3 ± 1.5	6.5 ± 1.6	7 ± 2	0.0001†
Base excess >10 <4 days	81 (20.3)	30 (21.9)	10 (36)	41 (24.8)	0.0001†
Hyaline membrane disease	150 (37.6)	81 (59.1)	15 (53.6)	96 (58.2)	0.0001†
Surfactant given	59 (14.8)	32 (23.4)	9 (32.1)	41 (24.9)	0.037†
Hypotension	111 (27.8)	63 (46)	18 (64.3)	82 (49.7)	0.0001†
Air leak	8 (2)	10 (7.3)	7 (25)	17 (10.3)	0.0001†
Pulmonary haemorrhage	10 (2.5)	3 (2.2)	2 (7.1)	5 (3)	0.312
Patent ductus	146 (36.6)	87 (63.5)	20 (71.4)†	107 (64.8)	0.0001†
Neonatal jaundice	369 (92.5)	123 (89.8)	24 (85.7)	147 (89.1)	0.330
Necrotising enterocolites	6 (1.5)	6 (4.4)	1 (3.6)	7 (4.2)	0.135
Septicaemia	32 (8)	32 (23.4)	10 (36)†	42 (25.5)	0.0001†
Intraventricular haemorrhage	19 (4.8)	20 (14.7)	11 (39.3)†	31 (18.8)	0.0001†
Chronic lung disease	44 (11)	60 (43.8)	20 (71.4)	80 (48.5)	0.0001†

ROP: retinopathy of prematurity
* Univariate comparison of clinical factors in infants studied.
† indicates *P* <0.05, significant

Distribution by Gender

The female-to-male ratio of infants with threshold ROP was 1:1 (14/14). The ratio was 1.2:1 (200/180) in the group without ROP. It was not statistically significant (*P* = 0.3).

Apgar Scores

Infants with threshold ROP had lower 1 minute Apgar scores as compared with infants without ROP (4 ± 2 versus 6 ± 2, respectively; *P* <0.05) (Table 2).

Clinical Characteristics of Infants

These data are summarised in Table 2. Infants with ROP had higher incidence of hypothermia at birth, metabolic acidosis, hypotension requiring inotropic support, and patent ductus arteriosus requiring indomethacin or ligation (*P* <0.001). Infants who developed severe ROP also developed more septicaemia (*P* <0.0001), intraventricular haemorrhage (*P* <0.0001), neonatal seizures (*P* <0.006) and CLD (*P* <0.0001). The incidence of neonatal jaundice and NEC was not statistically different in the group without ROP and the group with ROP requiring surgery. Among infants, 18/28 (64.3%) of threshold ROP had hypotension-requiring inotrope, versus only 111/399 (27.8%) in the group without ROP (*P* <0.0001). The incidence of PDA was 71% in the group with threshold ROP versus 37% in the group without ROP (*P* <0.0001).

Table 3. Comparison of Respiratory Data of VLBW*

Variable	No ROP (n = 399) (%)	ROP without surgery (n = 137) (%)	ROP with surgery (n = 28) (%)	All VLBW with ROP (n = 165) (%)	*P*
HMD	150 (37.6)	81 (59.1)	15 (53.6)	96 (58.2)	0.0001†
Surfactant given	59 (14.8)	32 (23.4)	9 (32.1)	41 (24.9)	0.037†
Air leak	8 (2)	10 (7.3)	7 (25)	17 (10.3)	0.0001†
Pulmonary haemorrhage	10 (2.5)	3 (2.2)	2 (7.1)	5 (3)	0.312 (ns)
Duration of CPAP	6.4 ± 12.6	16.9 ± 21.2	32.2 ± 29.4	19.5 ± 23.4	0.0001†
Duration of SIMV	3.9 ± 7.3	19 ± 32.7	31.7 ± 32.7	21.1 ± 31.5	0.0001†
Duration of oxygen	10.4 ± 22.1	50.1 ± 73.3	83.3 ± 81.6	55.8 ± 75.6	0.0001†
Average FIO_2	26.3 ± 7.3	30.6 ± 9.5	35.7 ± 16.4	31.5 ± 11.2	0.0001†
Average MAP	7.5 ± 4.8	7.6 ± 2.7	7.4 ± 2.6	7.6 ± 2.7	0.54 (ns)
Average $AaDo_2$ ratio	123 ± 115	170 ± 123	174 ± 140	171 ± 126	0.0001†

$AaDo_2$: alveolar-arterial oxygen difference; CPAP: continuous positive airway pressure; FIO_2: fractional oxygen content in inspired air; HMD: hyaline membrane disease; MAP: mean airway pressure; ns: not significant; ROP: retinopathy of prematurity; SIMV: synchronised intermittent mechanical ventilation; VLBW: very low birth weight

* Univariate comparison of respiratory data of infants studied.

† *P* <0.05, significant

Respiratory Data of Infants

These data are summarised in Table 3. Severity of respiratory disease, reflected by infants with HMD (*P* <0.0001), need for surfactant, incidence of air-leak, pulmonary haemorrhage, need for prolonged oxygen requirement and respiratory support in the form of synchronised intermittent mandatory ventilation (SIMV) or CPAP, were significantly greater in those who developed ROP requiring surgery (*P* <0.001).

The incidence of HMD was 15/28 (53.6%) in the group with threshold ROP, compared to 150/399 (37.6%) in the group without ROP (*P* <0.0001). Similarly, 9/28 (32.1%) of the group with threshold ROP needed surfactant as compared to only 59/399 (14.8%) in the group without ROP (*P* <0.037).

Age of Onset of ROP

The median age at which ROP was detected was 35 weeks post-conception (range, 31 to 41 weeks). The median post-conceptional age of ROP was 36 weeks (range, 31 to 41) in infants <1000 g, compared to 34.5 weeks (range, 32 to 41) in infants ≥1001 g (*P* = 0.004).

Distribution of Severity of ROP

The incidence of stage 1 ROP was 49% (81/165), followed by 24% (39/165) of stage 2 and 27% (45/165) of stage 3 and greater. Surgery was needed in 28/45 (62.2%) of stage 3 disease and above, due to progression to threshold ROP. There was bilateral involvement of eyes in 110/137 (80.3%) of infants not requiring surgery and 28/28 (100%) of infants with ROP requiring surgery.

Multiple Logistic Regression Analysis

As most of the risk factors were functions of immaturity, a multiple logistic regression model was designed with maternal obstetric factors and perinatal events inclusive of preeclampsia, pyrexia, premature rupture of membranes, maternal betamethasone, birth weight, gestational age, Apgar at 1 minute and 5 minutes, clinical variables like HMD, hypotension, pneumothorax, pulmonary haemorrhage, CLD, PDA, NNJ requiring phototherapy, septicaemia, NEC, IVH, days on CPAP and mechanical ventilation and days on oxygen. Preeclampsia (OR, 2.51; CI, 1.32 to 4.7), pulmonary haemorrhage (OR, 4.61; CI, 1.04 to 20.4), duration of CPAP (OR, 1.02; CI, 1.01 to 1.04), duration of mechanical ventilation (OR, 1.06; CI, 1.04 to 1.08), and birth weight (OR, 0.99; CI, 0.996 to 0.999) were identified to be factors predictive of ROP (Table 4).

Table 4. Showing Stepwise Multiple Logistic Regression of Factors Related to ROP

	Odds ratio	95% confidence interval	*P*
Pulmonary haemorrhage	4.61	1.04-20.4	<0.001
Maternal preeclampsia	2.51	1.32-4.7	<0.001
Duration of mechanical ventilation	1.06	1.04-1.08	<0.001
Duration of CPAP	1.02	1.01-1.04	<0.0001
Birth weight	0.99	0.996-0.999	<0.001

CPAP: continuous positive airway pressure

Discussion

ROP continues to be an important cause of potentially preventable blindness worldwide.[29] Our study represents a comprehensive study evaluating the incidence, risk factors and severity of ROP in Singapore.

The impact of ROP on vision in the premature infant has been well appreciated since the early report by Terry.[30] There have been reports of improved survival rates for

premature infants resulting in claims of an "epidemic" of ROP. The incidence of ROP was 58/147 (39.4%) in the presurfactant period compared to 107/417 (25.6%) in surfactant period. The incidence of ROP requiring surgery was 7/147 (4.8%) in presurfactant period and 21/417 (5%) in surfactant period, which has not changed significantly in 2 periods. Recent reports from Europe and Australia suggest a decreasing incidence of severe ROP.[15,18] The CRYO-ROP[16] multi-centre study showed that among infants with BW <1251 g, 65.8% developed ROP to some degree, and an incidence of 81.6% in infants <1000 g. Darlow et al[31] from New Zealand reported an incidence of 21.5%, Maheshwari et al[32] from India had 27%, Haugen et al[33] from Norway reported an incidence of 10%, Bassiouny et al[34] from Oman reported an incidence of 34%, Lappi et al[35] of Finland had 27.3% and Smith et al[36] of Australia had an incidence of 16%. The study by Hussain et al[37] showed a significant decrease in the incidence and severity of ROP compared to previous reports. The overall incidence among infants with BW <1251 g was 34% and the incidence among extremely-low-birth-weight was 46%, which was approximately half of the incidence reported in CRYO-ROP study.

In our study, 165/564 (29.3%) among all VLBW screened had ROP with incidence of 76.5% (39/51) among infants <750 g and 55.4% (98/177) among all infants ≤1000 g. The incidence of ROP was only 67/387 (17.3%) among VLBW of birth weight between 1001 g and 1500 g. The incidence of ROP varies considerably in different populations and races in a pattern not easily explained by differences in neonatal intensive care practices. A recent study reported a missense mutation in the *ND* gene located on the short arm of the X chromosome in preterm infants with ROP. This raised the possibility of genetic predisposition to ROP in at least some cases. Norrie's disease, a rare hereditary exudative vitreopathy, which is phenotypically similar to ROP, has also been associated with mutation in the *ND* gene.[38]

Our unit screened 564 infants over a 14-year period at an average rate of 50 to 60 infants per year. This is similar to published data from other centres. Goble et al[21] reviewed data from 6 neonatal units in Birmingham (UK) over a 6-year period and screened a total of 1611 babies at a rate of 44.7 babies per neonatal unit per year. Severe ROP was seen predominantly in infants weighing <1000 g,[39-41] and the average birth weight of the screened population in the study by Goble et al was 1199 g, similar to the average birth weights in Rowland's study (1229 g).[41]

A decrease in the incidence of ROP has been reported from other centres. A Danish study found a decrease in the incidence of ROP for infants with birth weights between 1251 g and 1750 g, although there was no decrease in incidence for the infants weighing <1251 g.[42,43] A multi-centre UK study looking at neonates <1251 g found an increase in ROP in only 1 of 5 centres studied, suggesting that although there is increased survival of high-risk neonates, this is not associated with a universal increase in severe ROP.[44] In our study, the mean BW of infants screened for ROP was 1118 g (range, 520 to 1495). The mean BW of infants with severe ROP was 797 ± 187 g versus 1186 ± 211 g for infants without ROP.

Gestational Age

The mean GA of the screened population in Goble's study was 29.1 weeks[21] which, again, was similar to the mean GA of 29.7 weeks in our study. It is well recognised that the incidence and severity of ROP varies inversely to GA and BW.

Small at Gestational Age

It has been reported that infants who are born SGA may be more likely to develop ROP.[45] This was not confirmed in our study population. In our study, there was no significant difference in incidence of ROP among SGA and AGA.

Age of Onset of ROP

The importance of the clinical screening of high-risk premature infants has been confirmed because of the improved clinical outcome in infants with acute active ROP after either cryotherapy or transpupillary laser therapy.[46,47] However, optimal timing of initial screening examination is still controversial. Earlier screening would result in many unnecessary fundal examinations, while later screening might fail to diagnose the threshold ROP and miss the window period for therapy. According to Palmer's report, 7 to 9 weeks after birth is the best time for diagnosing the largest number of ROP cases.[48] The American Academy of Pediatrics, the American Association of Pediatric Ophthalmologist and Strabismus and American Academy of Ophthalmology released a joint statement recommending that the initial screening examination be performed between 4 and 6 weeks of chronological age or 31 to 33 weeks post-conception.[49] In our study, screening was performed between 4 and 6 weeks after birth. The timing of retinal vascular events of ROP correlated more closely with the post-conceptional age than the chronological age.[50] Palmer et al[48] observed that 95% of infants with stage 2 ROP had an onset at 32 weeks or later. In our study, maximum yield of diagnosis of ROP was at a median of 35 weeks corrected age (range, 31 to 41). Maheshwari et al[32] reported an age of onset of ROP at 32 to 35 weeks post-conception. Higgins et al[51] reported that the most severe stage was reached at an average of 35.3 ± 2.7 weeks post-conceptional age (range, 31 to 41).

Distribution of Severity of ROP

A study from the United States found a decreased rate of progression from pre-threshold to threshold ROP in infants studied between the years 1990 to 1993 (7%) compared to 1985 to 1999 (37%).[52] Bullard et al[53] found a decrease in the incidence of all levels of ROP across all birth weights at the Vanderbilt University Medical Center in Tennessee. Their study compared infants born over a 12-month period between 1 July 1995 and 30 June 1996 with those born over a 23-month period between 1 January 1986 and 30 November 1987. They suggested that the decrease in both the incidence and severity of ROP may be attributed to the use of surfactant, continuous pulse oximetry, improved neonatal nutritional support and the use of maternal antenatal steroids. However, Reynolds rejected the conclusions of Bullard et al, stating that the single-centre findings from the Vanderbilt University represented regression towards the mean and that this centre now resembled the national mean.[54] Furthermore, Reynolds went on to state that controlled trials have shown no benefit from surfactant and that the multi-centre LIGHT-ROP study showed no reduction in the incidence of ROP.[55]

In our study, threshold ROP was present in 28/165 (16.9%) of ROP group. Stage 1 ROP was present in 49%, followed by 24.8%, 23.6% and 2.4%, respectively, of stage 2, 3 and 4 ROP. Only 26/41 (63%) of stage 3 progressed to threshold ROP, while 17/41 (41.4%) of stage 3 regressed on follow-up, hence surgery was not required.

Maternal Obstetric Factors

Antenatal betamethasone has been reported to reduce the incidence of ROP. Blair et al[56] reported a decrease in the incidence of 36.1% of ROP compared to the international incidence of 57.2% for the Vermont-Oxford Network Database (VOND) in 1997 (P <0.001). Antenatal betamethasone was given to 62.6% of infants in Blair et al's[56] study as compared to 48.6% in the VOND (P <0.005). In addition, 48.5% of VLBW infants in Blair et al's study had CLD versus 29.5% of the VOND's infants (P <0.001). In our study group, 182/399 (45.5%) had CLD as compared with 29.5% of the infants in the VOND's study. In our study group, 181/399 (45.4%) of infants without ROP had received antenatal betamethasone versus 11/28 (39.3%) of infants with threshold ROP (P = 0.564).

The pathogenesis of ROP is still uncertain. Patz et al[57] in a prospective controlled trial clearly demonstrated the casual effects of high oxygen administration on the development of ROP. However, oxygen therapy is no longer the only and most important factor for the development for ROP. The cause of ROP is multifactorial; of which oxygen therapy is only one of the factors. The influence of various clinical factors remains unclear.

Clinical Factors

Bassiouny et al[34] reported that lower BW, GA, apnoea, blood transfusion, mechanical ventilation, metabolic acidosis, TPN, IVH and sepsis were associated with development of ROP. Smith et al[36] reported days of ventilation, multiple birth and female gender to be significantly associated with ROP. Shohat et al[58] reported apnoea requiring bag and mask ventilation, prolonged TPN, blood transfusion and episodes of hypoxaemia and hypercarbia as risk factors for the development of ROP.

Hussain et al[37] found only GA and days on oxygen as factor predictive of ROP. Higgins et al[51] reported that infants with ROP of stage 2 or more were more likely to be lighter birth weight, more premature and have RDS, BPD, PDA and receive no antenatal betamethasone. In their study, antenatal betamethasone played a major role in reducing the severity of ROP (OR, 0.14; CI, 0.02 to 0.93). Smith et al[59] reported decreased incidences of ROP, HMD, BPD, grade 3-4 IVH, NEC, sepsis and mortality when antenatal betamethasone was given. In contrast, Cuculich et al[60] reported an incidence of 26% with severe ROP (stage ≥2) among 72 infants who received no postnatal betamethasone as compared with incidence of 61% among 23 infants who received a low cumulative betamethasone dose (<1.8 mg/kg) and an incidence of 85% among 20 infants who received a high cumulative betamethasone therapy (1.8 mg/kg). Mizoguchi[61] showed that dopamine usage for hypotension and GA were factors predictive of ROP. Chye et al[62] reported a 15% incidence of ROP, with 4% of threshold ROP. Univariate analysis showed low BW, GA, higher rate of PDA, sepsis, duration of oxygen, ventilation, xanthine, antibiotic usage and intralipid to be associated with ROP. Despite these studies, the effect of antenatal and postnatal betamethasone on ROP is unclear. Usage of steroids in these high-risk infants has to be individualised.

In our study, the ROP group had statistically significant lower birth weight, younger GA, higher rate of HMD, surfactant usage, air-leak, hypotension, PDA, culture positive septicaemia, IVH, neonatal seizures and CLD and longer duration of oxygen, mechanical ventilation and CPAP.

Using stepwise logistic regression analysis, pulmonary haemorrhage (OR, 4.61; 95% CI, 1.04 to 20.4; P = 0.001), preeclampsia (OR, 2.51; 95% CI, 1.32 to 4.7; P <0.001), duration of SIMV, duration of CPAP and birth weight were identified as factors predictive of ROP. Withagen et al[63] reported a similar association between preeclampsia and the incidence of ROP. However, the effects of maternal raised blood pressure on fetal and later infant retinal vascularisation needs further evaluation. The duration of oxygen therapy and concentration of oxygen delivered is

directly related to the duration of ventilation. All these factors are related to the presence of HMD and development of CLD.

Conclusion

The incidence of ROP among VLBW infants was 29.2%. The analysis of the risk factors for ROP will help us to understand and predict its development in high-risk neonates. ROP is strongly associated with smaller, more immature and sicker infants. The median age of onset of ROP was 35 weeks (range, 31 to 40) postmenstrual age. Infants <30 weeks GA and/or infant with BW <1000 g are at considerable risk for severe ROP. The main risk factors for development of ROP are extremely low birth weight (BW <1000 g), extreme prematurity (GA <30 weeks), severe HMD with longer duration of mechanical ventilation and supplemental oxygen therapy. The presence of PDA, pulmonary haemorrhage, air-leak and hypotension often parallel severe ROP. Other risk factors are septicaemia, IVH, seizures and the development of CLD. We suggest that both immaturity and compromised pulmonary function are important aetiological factors in the development of ROP. Prevention of prematurity, control of preeclampsia, judicious use of ventilation and oxygen therapy are the only promising factors that may reduce the incidence and severity of ROP in the high-risk infant. The incidence of ROP has decreased from 39.4% in presurfactant period (1988 to 1992) to 25.6% in surfactant period (1993 to 2001), but the incidence of ROP requiring surgery has not changed significantly in 2 periods. The follow-up of VLBW infants with ROP requiring surgical intervention is essential and recommended, to minimise blindness and long-term visual morbidity in these infants.

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