# INCIDENCE OF RETINOPATHY OF PREMATURITY IN VERY-LOW-BIRTH-WEIGHT INFANTS BORN AT KALAFONG HOSPITAL, PRETORIA

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*Introduction.* Retinopathy of prematurity (ROP) is a complication of prematurity, is diagnosed by ophthalmological screening of infants at risk (birth weight ≤ 1 500 g), and may lead to blindness. The incidence of ROP is under-reported in developing countries, including South Africa. Published data from the USA (CRYO-ROP) show that black infants have a lower incidence of threshold ROP than their white counterparts (3.2% v. 7.4%). Preliminary results of a screening programme initiated at Kalafong Hospital in 1999 are reported.

*Aim.* To determine the incidence of ROP in infants with a birth weight of ≤ 1 500 g born at Kalafong Hospital.

*Patients and methods.* Consecutive infants were enrolled at birth and screened for ROP 4 - 6 weeks later by indirect ophthalmoscopy. Repeat examinations were performed until vascularisation was complete or until the infant reached a postconceptional age of 40 weeks. Infants with stage 3 ROP who developed threshold disease were treated with cryotherapy or laser therapy.

*Results.* One hundred and forty-five infants were enrolled over 10 months (15 February 1999 - 25 December 1999); of these 94 were screened. Of the remaining 51 infants, 24 died before screening and 27 were discharged before screening and were lost to follow-up. ROP was diagnosed in 23 of the 94 infants screened (24.5%). Stage 1 and 2 ROP occurred in 17 of the infants screened (18.1%) and stage 3 ROP in 6 (6.4%), of whom 4 (median birth weight 995 g, range 900 - 1 450 g) developed threshold ROP and were treated.

*Conclusions.* The incidence of ROP in black very-low-birth-weight infants born at Kalafong Hospital is 24.5%. The incidence of threshold ROP is 4.3% (3.2% in infants ≤ 1 250 g) and correlates with published data from the USA. Infants with a birth weight ≤ 1 500 g should receive ophthalmological screening to diagnose stage 3 ROP timeously.

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The advent of neonatal intensive care has resulted in survival of more very-low-birth-weight (VLBW) (≤ 1 500 g) infants. Their improved survival comes at a price, because immaturity can have serious complications, such as retinopathy of prematurity (ROP).[1] This condition is a disorder of developing retinal vessels in VLBW infants which may heal spontaneously or progress to severe ROP, which is characterised by a spectrum of sequelae ranging from myopia to permanent blindness.[1] Immaturity, as determined by gestational age or birth weight, in combination with hyperoxaemia are the most important risk factors for ROP.[1] The precise causation of ROP is elusive, and because many factors may be involved,[2] it is difficult to prevent. Screening of infants at risk remains the only way to diagnose and treat ROP timeously. Screening criteria take birth weight and/or gestational age into consideration.[3,4]

The theory that premature infants may develop retinal disease, primarily as a complication of prematurity, was proposed in 1942 by Terry, an ophthalmologist from the USA, who called the condition retrolental fibroplasia.[5] More than a decade later the results of the National Cooperative Study, undertaken in the USA, showed an unequivocal link between high inspired levels of oxygen and retrolental fibroplasia.[6] Oxygen was restricted during the late 1950s, resulting in a dramatic decrease in the incidence of ROP.[1] With the development of modern neonatal intensive care during the 1970s the survival of infants of extremely low birth weight (< 1 000 g) improved and ROP made a comeback,[7] indicating that prematurity remains the most important risk factor. The role of oxygen in the form of hyperoxaemia has been proven,[6] but hypoxaemia and perhaps fluctuating levels of oxygen, even within the normal range, may also be important.[8]

The standardised interpretation of the pathognomonic signs of ROP was made possible during 1984 when the International Classification of ROP (ICROP) was published.[9] The latter was applied in the Multicenter Trial of Cryotherapy for ROP (CRYO-ROP), which reported on the incidence of ROP in 4 099 infants with a birth weight < 1 251 g.[10] This study showed that some degree of ROP occurred in 47% of infants weighing < 1 251 g, in 78% of infants weighing 750 - 999 g, and in 90% weighing < 750 g.[10] The results also showed that black infants had a lower incidence of severe (threshold) ROP than their white counterparts (3.2% v. 7.4%), even though the overall incidence of ROP was similar.[10] Multiple logistic regressional analysis substantiated black infants' lower susceptibility.[11]

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Little is known about the incidence of ROP in South Africa,[12,13] as is the case in many other developing countries. Without the availability of data, the extent of the problem may be underestimated. VLBW infants often receive unmonitored oxygen therapy in developing countries, because equipment such as blood gas machines and pulse oximeters may not be available. Undiagnosed hyperoxaemia may place infants at risk for ROP who, in ideal circumstances, would have a low risk, such as premature infants of uncertain gestational age and with a birth weight around 1 500 g. The observation that black VLBW infants have a lower incidence of threshold ROP than white VLBW infants also begs the question whether the screening criteria developed in the USA[3] and Britain[4] are applicable to black infants elsewhere. Apart from birth weight, these criteria rely on an accurate gestational age as determined by an early ultrasound examination (< 20 weeks). In the developing world the majority of women who deliver VLBW infants are unlikely to have received an early ultrasound examination, because their antenatal care was provided by hospitals or clinics without ultrasound facilities. Clinical methods to determine the gestational age in a newborn infant may not be accurate. The Ballard score,[14] for example, has 2-week variances.[15] In the absence of an accurate gestational age, the birth weight remains the only clinical parameter indicative of prematurity. It is also not possible to determine with certainty whether a given VLBW infant is growth-retarded if an accurate gestational age, as determined by an early ultrasound examination, is not available.

Screening programmes for ROP are not in place in the majority of state hospitals because ophthalmology services are either not available, or do not have the manpower to maintain screening programmes. The result is that ROP in VLBW infants will remain undiagnosed, leading to missed opportunities for the prevention of sequelae such as permanent blindness.[13] It is of concern that hospitals without the resources to screen for ROP may also lack the necessary equipment to monitor oxygen therapy.

The need for a screening programme as an essential service to VLBW infants born at Kalafong Hospital was identified and a programme initiated. The screening criteria were compiled by the Department of Ophthalmology at the University of Pretoria, based on criteria developed in the USA[3] and UK.[4] The preliminary results are reported here.

## PATIENTS AND METHODS

Screening commenced on 15 February 1999. Kalafong Hospital serves the communities residing in townships to the west of Pretoria and has an average of 5 500 births per annum with a 20% low-birth-weight rate (≤ 2 500 g). Infants with a birth weight ≤ 1 500 g were enrolled at birth. White and Indian infants born during the period of the audit were also screened for ROP but only black inborn infants were included in the final analysis since they comprise the majority.

The following data were accessed: birth weight, gestational age as determined by an early ultrasound scan (< 20 weeks), duration of mechanical ventilation, and administration of supplemental oxygen. The gestational age as determined by the method described by Ballard *et al.*[14] was also analysed. ROP was staged according to the International Classification of ROP (ICROP),[9] which is based on the severity of disease (stages 1 to 5), the area of the retina involved (zones 1, 2 and 3) and the extent of retinal involvement, expressed in clock-hours. Pre-threshold disease was defined as any stage 3 disease or any zone 1 disease. Screening for ROP commenced between 4 and 6 weeks after birth after informed verbal consent had been obtained from the mother. Thirty minutes before an infant was examined, one drop of cyclopentolate hydrochloride 2 mg/ml and phenylephrine 10 mg/ml was instilled into each eye to obtain mydriasis. The fundi were examined by a single investigator (PJLO) using an indirect ophthalmoscope and a 30D lens. If necessary, the lids were retracted and scleral indentation was done to facilitate visualisation of the retina, after instillation of oxybuprocaine 0.4%, a topical anaesthetic agent. Examinations were continued until the retina was fully vascularised and/or until the infant reached a postconceptional age of 40 weeks as determined by an accurate gestational age. If the latter was not available, the postconceptional age was calculated using the Ballard score, which was determined after birth. The frequency of examinations ranged from twice-weekly to once in 3 weeks, depending on the stage of ROP at the initial examination, whether the disease was progressing or regressing, the postconceptional age and the stage of vascularisation. If pre-threshold disease was diagnosed, an examination was done twice weekly to determine whether the disease was progressing to threshold ROP or regressing. If threshold ROP was present the peripheral avascular retina was treated under general anaesthesia with cryotherapy or laser therapy. Examination of the retina was discontinued when regression of ROP was evident and follow-up was scheduled after 6 months.

## RESULTS

Over a period of 10 months (15 February 1999 - 25 December 1999) 145 consecutive infants (birth weight ≤ 1 500 g) were enrolled. The median birth weight was 1 200 g (range 500 - 1 500 g). An accurate gestational age as determined by ultrasound early in pregnancy (< 20 weeks) was available for 10 of the 145 infants. A Ballard score was determined for 102/145 infants and the mean gestational age was 34 weeks. For the reasons outlined above, the gestational age as determined by the Ballard score was not used as a criterion for enrolment.

Of the 145 infants enrolled, 24 died before screening was commenced and 27 were discharged before they reached the chronological age for screening (4 weeks) and did not return for follow-up. The remaining 94 infants, with a median birth weight of 1 200 g, comprised the study population. They were examined on a median number of 3 occasions (range 1 - 13), and 23 (24.4%) (confidence interval (CI) 15.8 - 33.2%) were found to have ROP. Stages 1 and 2 ROP were present in 17 infants (18.1%). Stage 3 ROP was present in 6 infants (6.4%), of whom 4 (4.3%) developed threshold ROP. These 4 infants were treated with cryotherapy.

Three of the 6 infants with stage 3 ROP were members of twin pairs, and for this reason the singletons (83) and twins (11) were analysed separately with regard to clinical characteristics and the incidence of ROP. Eleven pairs of twin were born during the study period. In 8 cases both twins were enrolled (16 infants), and in the remaining 3 cases only one of each pair was enrolled (3 infants) because the other twin weighed more than 1 500 g. A total of 19 members of twin pairs were therefore enrolled at birth. Of these 7 died before screening could take place and 1 was lost to follow-up, leaving a study sample of 11 infants (Table I).

Of 126 enrolled singletons, 17 died before screening was commenced and 26 were lost to follow-up, leaving a study sample of 83 infants (Table I). At enrolment the median birth weight of the singletons was similar to that of the twins (1 200 g v. 1 100 g).

The median birth weight of the singletons and twins who died was also similar (1 200 g v. 1 150 g). However, significantly more twins (7/19) than singletons (17/126) died before screening could take place ($P < 0.001$). Stages 1 and 2 ROP occurred in 14/83 (16.9%) singletons and 3/11 (27.3%) twins. Stage 3 ROP occurred in 3/83 (3.6%) singletons and 3/11 (27.3%) twins and 2/3 infants in each group developed threshold ROP. The incidence of threshold ROP was therefore 2.4% (2/83) in singletons and 18.2% (2/11) in twins (OR 3.0, CI 0.71 - 12.71%) ($P = 0.065$).

**Table II. Incidence of ROP according to birth weight ($N = 94$)**

| Birth weight | No ROP | Stage 1 | Stage 2 | Stage 3 |
|---|---|---|---|---|
| 500 - 1 000 g ($N = 21$) | 12 (57.1%) | 2 (9.5%) | 5 (23.8%) | 2 (9.5%) |
| 1 001 - 1 250 g ($N = 33$) | 21 (63.6%) | 7 (21.2%) | 2 (6.1%) | 3 (9.1%) |
| 1 251 - 1 500 g ($N = 40$) | 38 (95%) | 0 (0%) | 1 (2.5%) | 1 (2.5%) |

The incidence of ROP by birth weight category for the study group as a whole ($N = 94$) is shown in Table II. Of the infants with a birth weight ≤ 1 000 g, 2/21 (9.5%) developed stage 3 ROP. Of the infants with a birth weight >1 000 g and ≤ 1 250 g 3/33 (9.1%) developed stage 3 ROP and of the infants with a birth weight > 1 250 g, 1/40 (2.5%) developed stage 3 ROP.

For the study group as a whole, ROP developed in 23/94 infants (24.4%). Of these 23 infants, 21 had a birth weight of ≤ 1 250 g. The 2 remaining infants with ROP weighed 1 435 g and 1 450 g respectively, and the latter infant developed threshold ROP which necessitated cryotherapy.

Of the 4 infants who received cryotherapy, 2 were singletons and 2 members of twin pairs. Three of the 4 had a birth weight < 1 050 g, while 1 infant had a birth weight of 1 450 g.

Of the 94 infants who were screened, 92 (96.7%) received oxygen therapy; of these 37 (40.2%) were mechanically ventilated for a median period of 5 days (range 1 - 16 days) followed by supplemental oxygen and 55 (59.8%) received only supplemental oxygen. Of the 92 infants who received oxygen, 69 (75%) did not develop ROP.

**Table I. Characteristics of singletons and twin-members**

| | Singletons ($N = 126$) | Twin-members ($N = 19$) | $P$ |
|---|---|---|---|
| Median birth weight (range) | 1 200 g (780 - 1 500 g) | 1 100 g (500 - 1 490 g) | |
| Number of infants who died before screening | 17 | 7 | < 0.001 |
| Median birth weight (range) | 1 200 g (700 - 1 400 g) | 1 150 g (990 - 1 420 g) | |
| Number of infants not screened | 26 | 1 | 0.29 |
| Median birth weight (range) | 1 225 g (1 000 - 1 500 g) | 1 490 g | |
| Number of infants screened | 83 | 11 | |
| Median birth weight (range) | 1 200 g (780 - 1 500 g) | 1 020 g (500 - 1 480 g) | |

## DISCUSSION

The preliminary results of the screening programme show that the incidence of ROP in black VLBW infants born at Kalafong Hospital is 24.5%. The incidence of stages 1 and 2 ROP is 18.1%, of stage 3, 6.4% and of threshold ROP, 4.3% (4/94). The 6.4% incidence of stage 3 ROP in infants weighing ≤ 1 500 g is similar to the 7.0% incidence for stages 3 and 4 reported in the only other published study from South Africa.[12]

The incidence of threshold ROP in infants weighing ≤ 1 250 g born at Kalafong Hospital is 3.2% (3/94), which is similar to the incidence of threshold ROP in black infants in the USA (3.2%).[11] The incidence of threshold ROP in infants of all races with a birth weight ≤ 1 250 g in the USA is 5%,[16] having remained virtually unchanged since the beginning of the 1990s, when it was 6%.[17]

Results from our study show that the incidence of threshold ROP was higher in twins (18.2%) than in singletons (2.4%) (OR 3.0, CI 0.71 - 12.71%) ($P = 0.065$). The mortality rate for twins was 36.8% compared with 13.5% for singletons ($P = 0.001$) despite a similar median birth weight for the two groups (Table II). The surviving twins may have been more severely ill than the singletons, predisposing to the development of ROP. Published reports are conflicting with regard to the incidence of ROP in twins versus singletons.[18,19] In discordant twins the risk of ROP has been found to be higher in the larger twin than in singletons of comparable weight.[20] Until more twins from our population have been studied, it is considered advisable to screen both members of a pair of twins for ROP even if only one of them qualifies for screening by birth weight.

In our study the majority of infants with ROP (21/23) had a birth weight less than 1 250 g, corresponding to an expected gestational age of 30 weeks (50th centile). One of the remaining 2 infants, with a birth weight of 1 450 g, had stage 3 ROP and developed threshold ROP necessitating cryotherapy. This finding argues against screening only the smallest infants (e.g. ≤ 1 250 g) until more data on the outcome of infants with a birth weight > 1 250 g and ≤ 1 500 g in this population are available.

Of 145 enrolled infants, 27 were not screened. Their median birth weight was 1 335 g and they were discharged from hospital before their scheduled date for screening. Appointments were made but were not kept. All attempts to trace these infants were unsuccessful and their visual outcome is not known. It is therefore advisable that infants should not be discharged before screening, unless follow-up can be assured.

While the majority of VLBW infants receive oxygen, only a minority develop stage 3 ROP. It is, however, imperative to screen for the presence of ROP in all infants at risk in order to proceed with ophthalmological examinations (which may need to be frequent) if indicated. Timeous therapy in the form of cryotherapy or laser coagulation improves visual outcome, but unfortunately permanent blindness will not be prevented in all cases.[8]

This study has also shown that gestational age cannot be used as a screening criterion in VLBW infants born in our setting because an accurate gestational age is available in only about 10% of cases. Birth weight is therefore the only parameter indicative of prematurity that can be determined with accuracy in the population under investigation. At Kalafong Hospital we therefore screen all infants with a birth weight ≤ 1 500 g for ROP, and screen both members of twin pairs if the birth weight of one member is < 1 501 g.

As shown by our results, the vast majority of VLBW infants receive supplemental oxygen, which plays a major role in the causation of ROP. All neonatal units treating VLBW infants should therefore have: (*i*) access to pulse oximeters for the monitoring of oxygen saturation; and (*ii*) written guidelines for oxygen administration to VLBW infants. For example: (*i*) all infants receiving supplemental oxygen and at risk for ROP should be monitored by a pulse oximeter; (*ii*) the upper limit for the oxygen saturation by pulse oximetry ($SpO_2$) should be prescribed by a physician and should preferably not exceed 93%; (*iii*) daily attempts should be made to lower the fractional inspired oxygen concentration ($FiO_2$) in stable, convalescing infants; (*iv*) if arterial samples are obtained, simultaneous $FiO_2$, $SpO_2$ and partial arterial oxygen concentration ($PaO_2$) should be recorded; and (*v*) pulse oximetry should be used during short- term blow-by oxygen administration to prevent hyperoxaemia or hypoxaemia.

All surviving VLBW infants should be regarded as having ROP until proved otherwise.

The responsibility to screen these infants for ROP is as compelling as the responsibility to save their lives in the first place. Infants who are being salvaged with the help of sophisticated technology and do not receive ophthalmological surveillance to optimise their visual outcome are not receiving the accepted standard of care. The provision of technology to reduce the mortality of VLBW infants should be accompanied by access to visual screening.

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# REGULATION OF CALCIUM HOMEOSTASIS IN ACTIVATED HUMAN NEUTROPHILS — POTENTIAL TARGETS FOR ANTI-INFLAMMATORY THERAPEUTIC STRATEGIES

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*Objectives.* The objectives of the current study were to: *(i)* present an integrated model for the restoration of calcium homeostasis in activated human neutrophils based on current knowledge and recent research; and *(ii)* identify potential targets for the modulation of calcium fluxes in activated neutrophils based on this model and to investigate the effects of intracellular probes which target key processes involved in calcium homeostasis and pro-inflammatory activity in these cells.

*Design and setting.* Laboratory-based experimental research using purified human neutrophils from healthy, adult human volunteers.

*Outcome measures.* Calcium metabolism and pro-inflammatory activity of neutrophils.

*Results.* Modulation of calcium fluxes in activated human neutrophils can be achieved by cAMP-dependent upregulation of the activity of the endomembrane $Ca^{2+}$-ATPase which resequesters cytosolic $Ca^{2+}$. Formoterol, a long-acting $\beta_2$-agonist, elevates intracellular cAMP levels, accelerates $Ca^{2+}$ restoration in activated neutrophils and downregulates the pro-inflammatory responses of these cells. Alterations in the membrane potential of activated neutrophils may play a role in regulating calcium reuptake into the cells as attenuation of the membrane depolarisation response is associated with accelerated calcium influx.

*Conclusions.* Modulation of the activity of the endomembrane $Ca^{2+}$-ATPase in human neutrophils represents an important target for anti-inflammatory

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