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Development and Risk Factors of Severe Retinopathy of Prematurity (ROP) in Very Low Birth Weight Infants

by

Yingmei Ding

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled, **"Development and Risk Factors of Severe Retinopathy of Prematurity (ROP) in Very Low Birth Weight Infants"** submitted by Yingmei Ding in partial fulfilment of the requirements for the degree of Master of Science.

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Abstract

The major purposes of this study were: 1) to estimate the incidence, prevalence and timing of retinopathy of prematurity (ROP); 2) to identify the risk factors associated with the development of severe ROP. Four hundred and fifty-eight very low birth weight infants from Southern Alberta in 1985-1990 were identified as study population.

Acute ROP developed in 70.3% of infants and severe ROP attacked 19.2% of infants. The more premature the infants, the higher the incidence of severe ROP. Prevalence rate of severe ROP at near term 12.3% . The age of onset for various stages of ROP was detected.

Thirty six variables were identified as risk factors for the development of severe ROP. Stratification analysis showed that maternal race, hospital stay, follow-up criteria, days in oxygen and bronchopulmonary dysplasia were significantly associated with severe ROP after controlling for prematurity.

A discussion on strengths and limitations of this study was provided.

Acknowledgements

This thesis project could not have been completed without the assistance of many persons.

I would first like to thank my supervisor, Dr. Reg Sauve, for his excellent guidance, advice and support. My thanks go as well to the members of my supervisory committee, Dr. Rollin Brant and Dr. Carolyn Skov for their inputs and their enthusiasm for the project. I thank Dr. Ursula Dawe, the external examiner, for her encouragement as well as new perspectives.

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Much appreciation to Dr. N. W. Hindle for ophthalmologic consultation, constructive feedbacks to the questions as well as providing additional access to the data source.

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Finally, I am deeply grateful to my family and friends for their understanding, inspiration and sacrifices during my studies.

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Abbreviations

AA:	Adjusted age of the child at the time of assessment; AA=age days at assessment-days of premature delivery
AGA:	Average for gestational age
APA:	Antepartum Hemorrhage
BPD:	Bronchopulmonary dysplasia
BW:	Birth weight
CA:	Chronological age
CI:	Confidence interval
EFP:	Extraretinal fibrovascular proliferation
ET:	Endotracheal tube
CPAP:	Continuing positive air pressure
COPD:	Chronic obstructive pulmonary disease
ICROP:	International Classification of Retinopathy of Prematurity
LBW:	Low birth weight; According to World Health Organization, low birth weight infant is defined as any newborn with birth weight less than 2500 grams
IHV:	Intraventricular hemorrhage
IUGR:	Intrauterine Growth Retardation
NICU:	Neonatal intensive care unit
PDA:	Patent ductus arteriosus
PFC:	Persistent fetal circulation
PID:	Pulmonary or respiratory insufficiency of prematurity
PPV:	Positive pressure ventilator
RDS:	Respiratory distress syndrome
RLF:	Retrolental fibroplasia
ROP:	Retinopathy of prematurity
RR:	Relative risk
SA-PNFU:	Southern Alberta Perinatal Follow-up Program
SGA:	Small for gestational age
SPSS:	Statistical package for social science

TTN: Transient tachypnea of the newborn

VSD: Ventricular septal defect

VLBW: Very low birth weight; According to the World Health Organization, the VLBW infant is defined as any newborn with birth weight less than 1500 grams.

CHAPTER 1 INTRODUCTION

Retinopathy of prematurity, previously called retrolental fibroplasia (RLF) is a vasoproliferative retinopathy which occurs principally, but not exclusively, in prematurely born infants (Flynn, 1990).

ROP is a very common eye disease, affecting as high as 65.8% of less than 1250g birthweight infants (Palmer et al, 1991). The disease process may be progressive and the prognosis of ROP parallels its severity. The majority of ROP can go on to spontaneous regression, healing with minimal scarring and little or no visual loss. But some of those severe cases will bring a significant adverse visual outcome to affected infants (Ben Sira et al, 1988).

The previous reported frequencies of ROP were ranging widely from 11.4% to 70% (Bossi et al; Palmer et al, 1991). Most of these reported rates were prevalence, and incidence of various stages of ROP were not well documented. It was recognized that the estimate and comparison of incidence or prevalence of ROP was complicated by the ROP classification used, the study population selected as well as the methodology of eye examination adopted (Ng et al, 1988; Palmer et al, 1991).

Despite 50 years of medical progress since its first recognition, the causes of ROP remain poorly understood but are likely multifactorial (Ben Sira et al, 1988). It is generally believed that the primary risk factor for ROP is prematurity and the most critical factor of the postnatal environment is oxygen exposure. This combination of factors can lead to an irregular growth of vasoformative tissue in the eye which results in the disease (Ben Sira, 1988; Bossi et al,

1984).

ROP continues to be a cause of significant morbidity among very low birth weight survivors of Neonatal Intensive Care Unit (NICU) and represents one of the leading cause of childhood blindness. The need to better understand the nature of the disease process as well as the risk factors, especially the risk factors of severe ROP, to predict and prevent the disease is well recognized by health professionals (White et al, 1991).

I Study Rationale

The population based cohort study is very important in estimating the incidence of ROP as well as the risk factor analysis. Although many studies have reported the frequency of ROP as well as risk factors associated with its occurrence, most of them are hospital or center based (Flynn et al., 1987; Shohat et al., 1983; Valentine et al., 1989); few reports are population based (Darlow, 1988, Ng et al., 1988). Reports of earlier studies can not be directly compared with recent findings due to different ROP classifications and variation in preterm populations as well as the methodology of eye examination.

Also, most of the previous ROP risk factor studies are basically aimed at studying the factors associated with the occurrence of ROP rather than severe ROP. No Severe ROP risk factor study has been reported in Canada. As the survival rate of very low birthweight (VLBW) infants, who are most likely to develop the severe forms of ROP (great than stage 2 ROP) has increased, the frequency of ROP has increased. It is therefore very important to have a current population based

study to explore the risk factors which relate to the occurrence of severe ROP in order to most effectively predict, manage and prevent it.

Development of the international classification of ROP and the availability of comprehensive perinatal, neonatal and outcome data on the infants weighing 500-1250g at birth from Southern Alberta have created an excellent opportunity to study some poorly understood aspects of ROP on a geographically defined population basis. Hence "the Development and Risk Factors of Severe Retinopathy of Prematurity in VLBW Infants of Southern Alberta" was initiated.

II Research Questions

This thesis project is based on the epidemiology of ROP and two research questions will be answered.

1. What are the incidence, prevalence and timing of ROP among preterm infants born in Southern Alberta between 1985-1990 with birth weight 500-1250 grams ?

2. What factors are associated with development of acute severe ROP ?

The cicatricial and visual outcomes of ROP, as well as their relation to severe ROP will be also described and discussed.

CHAPTER 2 LITERATURE REVIEW

I First and Second Epidemics

Retinopathy of prematurity (ROP), was first recognized as a condition particular to preterm births by Terry in 1942 (Terry, 1942). He noted that some infants who were born preterm, were found , between two and six months of age, to have developed fibroplastic tissues behind the lens, referred to as retrolental fibroplasia (RLF). Over the next 10 years, cases were reported in many areas and countries. Then it was referred to as an epidemic (called the first epidemic) and regarded as the leading cause of infant blindness (Zacharias, 1952). Silverman (1980) estimated that in the decade 1942-1953, 7,000 children in U.S and 10,000 worldwide were blinded by ROP.

Because of the technological advances, it was routine during that decade to administrate high concentrations of oxygen to essentially every premature infant. It was not until 1954, that a large multicenter cooperative study indicated oxygen as the culprit for the epidemic of ROP (Kinsey, 1955; Kinsey et al., 1956). The incrimination of oxygen in the etiology of ROP led to a general routine restriction of oxygen in preterm infants to a concentration of 40%-50% in 1950s and the incidence of ROP decreased dramatically (Campbell, 1951; Kinsey et al., 1956; Lanman et al., 1954).

By the 1960s paediatricians recognized increased mortality and morbidity due to restricting the use of oxygen in the premature infants, which resulted in severe oxygen deprivation in infants with respiratory distress syndrome (Avery & Oppenheimer, 1960; McDonald, 1963). Consequently, in

the late 1960s and early 1970s, there was a gradual trend toward the liberalization of oxygen and with the development of modern means of continuous oxygen monitoring in the 1970s and 1980s, oxygen was supplied more safely (Bancalari et al., 1985). Guidelines and standards for oxygen delivery and monitoring by the American Academy of Paediatrics and the American College of Obstetricians and Gynaecologists (1988) became widely distributed and followed, and the frequency of ROP was expected to decline.

But in the past 18 years, there has been again an increase in the incidence of ROP as well as an increase in ROP induced blindness (some have called it a second epidemic). The primary basis of this is an increased number of severe cases of ROP occurring in the lowest birth weight infants, now surviving in great number than ever before due to the introduction of modern technology to the Neonatal intensive Care Unit (NICU; Bossi et al., 1984; Gibson et al., 1989, 1990; Gunn et al., 1980; Hammer et al., 1986; Kalina et al., 1982; Lucey & Dangman, 1984; Shohat et al., 1983; Valentine et al., 1989).

II Incidence and Prevalence

The accurate reporting of incidence and prevalence of ROP were complicated by some factors.

Firstly, reported frequency of ROP was influenced by the classification used. Before 1984, the efforts to describe and to compare the incidence and prevalence of ROP were thwarted by the lack of a uniform, widely accepted classification system. It was not until 1984 that the international classification of retinopathy of prematurity (ICROP I, 1984)

was first introduced. The ICROP I was soon accepted and well followed by different research centers and institutions (Ng et al., 1988; Palmar et al., 1991; Hammer et al., 1986; Flynn et al, 1992).

Secondly, the incidence and prevalence of ROP are determined partially by the strategies of eye examination because of the uniqueness of the process of the disease. ROP is a progressive disease, but many cases reach only stage 1 and resolve, while others progress to stage 2 or 3 and resolve and still others progress to subdivisions of stage 3 at which cryotherapy is indicated. In the worst case scenario, some may progress to stages 4 or 5 and to cicatricial disease, resulting in blindness. So, the timing and frequency of eye examination was a very important component in determining the occurrence of various stages of ROP (Flynn, 1983; Tan & Cats, 1988).

The other influence on incidence and prevalence rates of ROP is the type of population on which the measurements are being described (Ng et a, 1988). Some study populations were center-based rather than geographically-based and hence their interpretation and generalizability were restricted. The variation in nature of preterm populations selected could also lead to the difference in the frequency of ROP, because it was well documented that there was an inverse relationship between degree of prematurity and the incidence of ROP (Bossi et al, 1984; Gunn et al, 1980; Hammer et al, 1986; Patz, 1969; Shoat et al, 1983).

Accurate estimates of incidence or prevalence rates will require population-based statistics in a specific preterm infant population, as well as the strong strategy of the eye examination. The reported frequencies of ROP ranged widely from 11.4% to 70% (Bossi et al, 1984; Darlow, 1988; Ng et al,

1988; Palmer et al, 1991) and were difficult to compare with each other because of the difference in determination of the rates. Also, the reported frequencies of ROP were mostly prevalence estimates. The exact incidence rate of ROP in very low birth weight (VLBW) infants was not well documented.

III Classification

The early classification of ROP by Reese, King, & Qwens (1953) divided the disease into acute and cicatricial stages, and before July 1984 there was no standard classification system in use . This caused difficulties in the study and management of ROP. Progress in examination techniques with careful attention to the peripheral retina has enabled the ophthalmologist to better identify and follow the stages of acute ROP. The International Classification of ROP 1984 (ICROP I, 1984), is now generally accepted and has further helped to scientifically record the different retinal vascular changes. This classification embodies three major concepts for the description of the early phase of the disease: specifying its location by zones of retinal involvement; recording the extent of retinal involvement by clock hours; and, finally, staging the disease according to the degree of abnormality observed. Four stages of ROP are recognized and described as:

Stage 1= demarcation line, lying within the plane of the retina at the junction of the vascularized and avascular retina.

Stage 2= ridge, the demarcation line extends out of the plane of the retina.

Stage 3= ridge with extraretinal fibrovascular proliferation (EFP). This stage is divided into three grades:

mild, moderate and severe, according the amount of fibrovascular proliferation and disease.

Stage 4= retinal detachment.

Additionally, "plus disease", a term used to describe progressive vascular dilation and tortuosity of the posterially retinal vessels, may be added to any of the stage 1-4.

The ICROP (ICROPI, 1984) committee recommended the retention and use of Reese classification of cicatricial disease (Reese, King & Owens, 1953) to describe the disease changes beyond those described in ICROP I. The cicatricial disease of ROP is divided into five grades in Reese classification:

Grade I = small mass of opaque tissue in the periphery of the fundus without visible retinal detachment.

Grade II = large mass of opaque tissue in periphery of the fundus with localized retinal detachment. Some retinal traction may be present.

Grade III = large mass incorporating a traction retinal fold to the optic disc.

Grade IV = retrolental tissue covering part of the pupillary area.

Grade V = retrolental tissue covering the entire pupillary area.

In 1987, the international committee for the classification of the late stages of retinopathy of prematurity (ICROP II, 1987) subclassified stage 4 of ROP or retinal detachment into stage 4a, 4b and stage 5 was added. The ICROP II committee also recognized that regression is the most common outcome of ROP. Regression has a broad spectrum of peripheral and posterior retinal and vascular changes,

which are described in the ICROP II original paper. Although the ICROP II was considered to completely describe all stages of ROP, it has not generally replaced all other classifications. Reported studies still use ICROP I for the classification of acute stages of ROP and Reese classification for the cicatricial disease (Ng, et al., 1988; Valentine et al., 1989; Hindle, 1990; Cryo-ROP 1988, 1990).

In addition, Hindle in 1983 (Hindle, 1990) proposed a qualitative subdivision of stage 3 ROP that is somewhat parallel to the quantitative mild, moderate, and severe stage 3 of ICROP, but is distinct and identifiable qualitatively by its appearance:

Stage 3a= tiny accumulations of extraretinal fibrovascular proliferation (EFP) are found in the interstices of these vessels at the posterior aspect of the ridge.
Stage 3b= the isolated pieces of EFP join into a continuous mass which expends and obscures the ridge.
Stage 3c= the EFP organises into more well differentiated blood vessels -- actually a sheet of them that grows out into the retrolental space.

Hindle (1986) has used this qualitative subdivision of stage 3 ROP in his cryotherapy studies and recommended that optimal timing for treatment intervention is during progression of stage 3b+ ROP.

IV Factors Associated with ROP and Outcomes of ROP

ROP remains a poorly understood disease process. The causes of ROP are not clear but they are likely multifactorial, with oxygen being but one critical factor

(Bossi, et al., 1984; Hammer et al., 1986; Zierler, 1988). Brown et al (1990) studied the relationship between ventilatory support duration and severe ROP. He found that the premature babies receiving ventilatory support longer than 28 days will be 13 times more likely to develop severe ROP compared to the premature babies receiving ventilatory support shorter than 29 days. Other risk factors suspected of playing a role in the etiology of ROP are summarized in Table 1-1 (For neonatal factors, all factors are grouped into physiological, complication, therapeutic categories as well as the probable, likely and controversial categories based on the review of the published literatures).

The primary risk factor for ROP is prematurity. The only eyes at risk for development of ROP are those in which the peripheral retina is incompletely vascularized. Immature retinae are only found in premature infants and perhaps some infants with Intrauterine Growth Retardation (IUGR). The more premature the infant, the more immature the retinal blood vessels, and consequently the greater risk that ROP will develop (White, et al., 1991). Brown et al (1990) reported that for neonates with birthweight of 500-750 gm, 24.3% of survivors had stage 3 or 4 ROP in at least one eye. Comparable prevalence rates for larger babies were 15.3 if birth weight was 750-1000 gm and 3.4% if birthweight was 1001-1250 g. It is believed that a combination of disturbances can lead to irregular growth of vasoformative tissue. Very low birthweight (VLBW) premature infants suffer from a number of risk conditions that can disturb regular vasoformation. Cases of ROP occur despite the most careful attention to oxygen therapy and monitoring.

Table 2-1 Suspected risk factors of ROP*

Maternal Factors	Neonatal Factors
Alcohol(Zierler,1988)	**PHYSIOLOGICAL FACTORS:**
Anemia (Zierler,1988)	Birthweight[p] (Lucey, 1984; Yu,1990)
Diabetes(Zierler,1988)	Apgar Score[p](Hammer,1986;Zierler,1988)
Drugs (Zierler,1988)	Intrauterine Growth Retardation[p] (Zierler, 1988)
Duration of ruptured membranes (Zierler, 1988)	Gestational age[p] (Yu,1990; Ng, 1988; Valenline, 1989)
Maternal bleeding (Hammer, 1986)	**COMPLICATIONS:**
Multiple birth (Bossi, 1984)	Acidosis[l] (Bossi,1984; Ben-sera, 1988)
Smoking(Zierler,1988)	Alkalosis[c] (Zierler, 1988)
Threatened abortion (Zierler, 1988)	Hypercarbia[l](Shohat,1983; Baucer,1981)
Toxemia(Zierler,1988)	Hypocarbia[c] (Shohat, 1983)
Race (Ng, 1988; Palmer, 1991)	Hyperoxia[p] (Lucey,1984; Zierler, 1988)
	Hypoxia[c] (Lucey, 1984; Shohat, 1983)
	Anemia[l] (Hammer, 1986; Zierler, 1988)
	Sepsis[l] (Charles, 1991; Hammer, 1986)
	Apnea[p] (Lucey, 1984; Shohat, 1983)
	Bronchopulmonary dysplasia[p] (Brown, 1990; Zierler, 1988)
	Respiratory distress syndrome[p] (Charles, 1991; Hammer, 1986)
	Intraventricular hemorrhage[l] (Brown, 1990; Charles, 1991)
	Patent ductus arteriosus[l] (Hammer, 1986; Purohit, 1985)
	Vitamin E deficiency[c] (Zierler, 1988)
	THERAPEUTIC FACTORS
	Blood transfusion[l] (Lucey, 1984; Clark, 1985)
	Edotracheal intubation[l](Zierler, 1988)
	Indomethacin[l] (Zierler, 1988)
	Light[c] (Glass, 1985; Fielder, 1988)
	Prolonged parenteral nutrition[l] (Gunn, 1980, Shohat, 1983)
	Ventilatory support[p] (Hammer, 1986; Bossi, 1984)
	XanthineAdministration[c](Hammer, 1986)
	Days of O_2 administration (Bassi, 1984; Charles, 1991)

* -- Mostly based on the univariate analysis .
p -- Probable risk factors for ROP.
l -- Likely risk factors for ROP.
c -- Controversial factors for ROP.

The risk of cicatricial disease of ROP and visual impairment parallels the severity of acute ROP. Stage 1 or 2 ROP regress spontaneously without any significant visual sequelae. Severe ROP, stage 3 or worse, has a poorer prognosis for spontaneous regression without cicatricial disease. Using the qualitative subdivision, it is found that only stage 3b+ or worse progress to cicatricial disease (Hindle, 1990). Some eyes with extensive peripheral EFP, usually in a more posterior location, with vascular tortuosity and engorgement, and most with retinal detachment are likely to have visual sequelae, as the visually functioning retina in the posterior pole of the eye is affected during involution and cicatrization of the acute ROP. The most commonly reported types of ocular impairment from mild ROP are amblyopia, myopia, astigmatism, and strabismus (Kushner, 1985).

Of course, the most threatening outcome is blindness. In a 1981 review of the literature estimated that among infants weighing between 1000-1500 grams at birth, 0.3 to 1.1 percent are eventually blinded; for the infants under 1000 grams, approximately 5 to 11 percent are blinded (Phelps, 1981). Most recent studies report lower blindness rates which may be the results of advanced NICU care, such as continuous oxygen monitoring, and advances in respiratory management, or advances in ophthalmologic care such as improved ROP monitoring and the use of cryotherapy(Ng et al, 1988).

V Intervention : Prevention and Treatment

Many efforts have been made in the past 35 years to decrease the incidence and the severity of ROP and to optimize

visual outcomes. The most recent or promising methods are listed in Table 2-2 (DeVoe, 1988).

Table 2-2 Possible means to prevent/treat ROP

Prevention of prematurity
Continuous oxygen monitoring
Decrease pulmonary disease (Artificial Surfactant)
Vitamin E ?
Cryotherapy

The most effective means of preventing significant ROP would be to decrease the numbers of infants at risk for the disease, or to prevent prematurity, because the risk of developing ROP is directly correlated to the degree of prematurity. This can most efficiently and economically be done through improved prenatal care (DeVoe, 1988).

Continuous oxygen monitoring, such as the transcutaneous PO_2 monitor was first made available in the 1970s, allowed more accurate adjustment of patients's respiratory support and oxygen dosage, and decreased the amount of time that patients were exposed to either hypoxia or hyperoxia which are suspected risk factors for developing ROP (DeVoe, 1988; Ben Sira, 1988).

Currently, there are ongoing trials of surfactant replacement for RDS. Since surfactant replacement has been demonstrated to reduce mortality due to RDS and to reduce oxygen exposure, the use of surfactant replacement is now showing an impact on the frequency or severity of ROP among preterm infants (Hindle, N.W. personal communication, 1991).

Vitamin E was suggested in some studies to be helpful in

preventing the severe stages of the disease. Its efficacy has yet to be proved since the overall data from the prospective studies were conflicting and the routine use of Vitamin E in premature babies is not recommended at present time (Phelps, 1985).

Transscleral cryotherapy has been used since 1972 at various centres, but universal acceptance of the procedure has only occurred since the results of a large multicenter study were reported in 1988 (Cryo-ROP, 1988). That study evaluated infants of birth weight less than 1250 g for ROP. Once an infant's eye or eyes attained "threshold ROP", the eye was randomized to either control or cryotherapy. The short term (3 months) outcome showed the cryotherapy group benefited with an approximate 50% reduction in unfavourable outcome, defined as the presence of a retinal fold, retinal detachment or retrolental membrane. Recently, the multicenter study reported one-year follow-up outcomes (Cryo-ROP, 1990) which indicated that cryotherapy reduced the risk of unfavourable retinal and functional outcome from threshold ROP.

Since effective intervention is possible, routine ophthalmologic examination to detect severe ROP is essential.

CHAPTER 3 METHOD

I Study Design

1 Study Design

This study was a retrospective population-based cohort study which had an ongoing prospective cohort component. Prematurely born infants were routinely identified and followed through a high risk infant surveillance program for Southern Alberta region, the Southern Alberta Perinatal follow-up Program (SA-PNFU Program). The retrospective component consisted of analysis of data which had already been collected in a SA-PNFU program database or could be transcribed from existing ophthalmologic or perinatal follow-up charts of the program. The prospective component involved ongoing routine data collection on infants who were followed in the Follow-up Program.

2 Study Population and Sample Size

The target study population was all infants with birth weight 500-1250 g, whose mothers were residents of Southern Alberta, born between Jan. 1, 1985 and Dec. 31, 1990. From this population the cohort studied consisted of all infants who were born alive and discharged from the Neonatal Intensive Care Unit (NICU) alive. This comprised 458 infants. The unit of analysis was basically the individual premature infant, with the exception in some special situations in which the individual eye was the unit of analysis.

The sample was one of convenience, including all neonates under the birthweight 500-1250g definition. Although no sampling procedure was involved in this study design, sample

size estimation was done using the technique described by Qian (1989) to examine if the included study population was large enough to detect a statistical significant effect of a given magnitude if one truly existed (Rothman, 1986). The second research question for this study was to analyze the relationship between the risk factors and development of severe ROP. Theoretically, the sample size should be estimated for every suspected risk factor. The example given here was the sample size estimation for the probable risk factor, birth weight. According to Qian (1989), the sample size for a cohort study can be obtained by formula:

$$N=\frac{(Z_\alpha \sqrt{2\bar{P}\bar{Q}} + Z_\beta\sqrt{P_eQ_e+P_cQ_c})^2}{(P_e-P_c)^2}$$

The value of the variables in formula were assumed and defined as follows:

1. α =level of statistical significance; choose α=0.05 Z=1.96.
2. β =chance of missing a real effect; choose β=0.10 Z=1.282.
3. P_e=severe ROP rate in exposure (birthweight 500-1000 gm); suppose P_e=0.183 (according to the study of Brown, 1990).
4. P_c=severe ROP rate in control (birthweight 1001-1250 gm); suppose P_c=0.034 (according to the study of Brown, 1990).
5. Magnitude of effect; P_e-P_c=0.183-0.034=0.149.
6. $\bar{P}=(P_e+P_c)/2$; $\bar{P}=(0.183+0.034)/2=0.1085$.
   $\bar{Q}=1-\bar{P}$; $\bar{Q}=1-0.1085=0.8915$.

Placing the values into the formula would result in following:

$$\frac{[1.96 \sqrt{2*0.9815*0.1085}+1.282\sqrt{0.0183(1-0.10813)+0.034(10.034)}]^2}{0.149^2}$$

=90

The estimation revealed that an optimal size to provide power for the portion of the studies exploring correlates of severe ROP, would be 90 infants in each of three birthweight groups, 500-749, 750-999, 1000-1250g.

3 ROP Classification

International classification of ROP I (ICROP I, 1984) as described in Chapter 2 was used for acute ROP classification. Instead of subdivision of stage 3 of ICROP I, Hindle's qualitative subdivision of stage 3 ROP, 3a, 3b, 3c was adopted (Hindle, 1990).

Reese Classification (Reese & King & Owens, 1953) was used for cicatricial disease of ROP for this study and described in chapter 2.

4 Ethical Approval

Access to the health information needed for this study received ethics approval from the Conjoint Medical Ethics Committee of University of Calgary (Appendix 1).

II Data Preparation and Collection

1 Data Preparation:

In this retrospective cohort study, the variables were divided into two categories, the independent variables and outcome variables. The followings were operational definitions for the variables used in the study.

1) Independent variables

Based on the review of previous studies, the following basic socio-demographic data, perinatal and neonatal variables for study subjects (see Appendix 3b) were considered as potential risk factors for developing severe ROP and were

taken as independent variables in this retrospective cohort study. The operational definition for each of them was given and was followed throughout data collection and analysis (Appendix 3b).

2) Outcome variables I - acute ROP

To estimate the incidence of various stages of ROP, prevalence rate of ROP as well as the age of onset for various acute stages of ROP was the first research objective of this study. A set of almost 100 variables was needed and collected in Ophthalmologic Examination Data Collection Form (Appendix 2a) for each followed infant. The operational definitions for variables collected in Ophthalmologic Examination Data Collection Form (Appendix 2a), were given in corresponding Coding Menu (Appendix 2b).

The prevalence rate of ROP quantifies the proportion of individuals in a population who have ROP at a specific instant. It provides the estimate of the probability or risk that an individual will develop ROP at a point in time (Hennekers & Buring, 1997). Prevalence of ROP can be expressed as:

$$\text{Prevalence of ROP} = \frac{\text{Total cases with maximum stage in worst eye at a given point in time}}{\text{Total 500-1250g birthweight infants}}$$

The reference time points were: a) first eye examination; b) near term; c) four months adjusted age; d) 12 months adjusted age.

The incidence rate of ROP quantifies number of new cases of ROP that developed in a population of individuals at risk

during a specific time interval and it provides an estimate of the probability or risk that an individual will develop during a specified period of time (Hennekers & Buring, 1987). The incidence of ROP can be expressed as:

$$\text{Incidence rate of stage 1 ROP} = \frac{\text{Number of the new cases of ROP arising during a given time period}}{\text{Total 500-1250g birth weight infants}}$$

The observation time for incidence of ROP was basically under four month adjusted age.

3) Outcome Variables II - Cicatricial ROP and Visual Outcome

Although the two major research objectives of this study did not cover this part of outcome variables, the description of cicatricial stages of ROP as well as the visual outcome will definitely benefit in understanding the whole picture of ROP development and what the outcomes of acute ROP will bring to the affected children. Further more, the availability of the data form SA-PNFU Program database make the description and exploratory analysis on those variables possible.

Cicatricial ROP:

The operational definition for Cicatricial ROP used the Reese 5 grades classification (1953) described in chapter 2.

Visual outcome:

The following variables were available to assess the visual outcome: visual acuity, refraction, strabismus. For each of them, one of three categories, normal, abnormal or

suspect would be assigned to every followed infant at 4 and 12 months adjusted age follow-up assessments.

2 Data Collection Process

Prematurely born infants were routinely identified and followed through the SA-PNFU program, and generally received their acute care in the NICU, Foothills Provincial General Hospital.

1) Independent variables

All independent variables for the study, the basic socio-demographic, perinatal and neonatal information were collected in 'NICU Discharge Summary' (Appendix 3a) when infant was discharged from NICU. This part of the data collection was undertaken by ongoing SA-PNFU program, prospectively for the infants under the definition of study subjects.

2) Outcome variable I - acute ROP

Routinely ophthalmologic examination were performed in a standard manner for every study subject by one of two ophthalmologists (NWH or CMBS) and were started when infants were 4-5 weeks of chronological age. The ICROP I classification (1984) and the qualitative subdivision of stage 3 (Hindle, 1990) were used for acute ROP and Reese Classification (1953) was used for cicatricial ROP. If no ROP developed, the examination was repeated every two weeks until the retinal vascularization was completed. If ROP had developed, the examination was repeated weekly or more frequently and at discretionary intervals until it had resolved. Infants transferred back to referring centres had their ophthalmological examination performed at those centres or at Alberta Children's Hospital PNFU clinic.

The findings of each ophthalmologic examination were recorded in ophthalmologic consult sheets and included in the files or charts maintained at the SA-PNFU Program office or Ophthalmology office in Alberta Children' Hospital. Some infants' ophthalmologic consult sheets could be found through reviewing the charts from other hospitals where the infants used to be cared for or in two ophthalmologists clinics (NWH or CMBS).

The major outcome variables for this study, the prevalence and incidence as well as the age of onset of various stages of ROP should be transcribed from the information collected in these existing ophthalmologic examination consult sheets of study subject. A data collection form (Appendix 2a) was developed to extract the information in ophthalmologic consults sheets for every study subject. This part of data collection was done by the writer.

3) Outcome variables II - cicatricial ROP and visual outcome

The outcome variables II, cicatricial ROP and visual outcome for study subjects were assessed in SA-PNFU program clinic in Alberta Children' Hospital at 4 and 12 months adjusted age follow up and recorded in "Follow up outcome form' (Appendix 4). Like the data collection for all independent variables, this part of data collection was also undertaken by the ongoing SA-PNFU program prospectively for the infants under definition of study subjects.

In addition, the following information was needed for study data verification: total infants under the definition of the study population, through the review of the South Alberta birth notification summaries to ensure the accuracy of information; and detailed information about the deaths and infants lost to follow-up during the observation period (12

months adjusted age for included infants).

3 Computer Database Setup and Combination

The data collected by ongoing SA-PNFU program: independent variables collected in "NICU Discharge Summary and Outcome variables II: cicatricial ROP and visual outcome at 4 and 12 adjusted age collected in "Follow up Outcome Form' were entered into SA-PNFU program database by the program research assistants.

The ophthalmologic examination collected by the writer were carefully coded and verified following the Coding Menu (Appendix 2b) and entered onto a computer data base by SPSS Data Entry II.

Combination of two data systems was made according to different data analysis task and help was always offered from SA-PNFU office in reporting the data from SA-PNFU program Database.

III Analysis

All data processing and analysis were performed using either SPSS/PC+ program (Norusis, 1986) or Epi-Info (Dean et al, 1990).

1 Data Examination

Before going for formal data analysis, a necessary step was to make sure the information entered was correct. This part of the work was limited to the ophthalmologic examination data collected and entered onto the computer by the writer.

The procedures for this step were: 1) Data checking, including the range checking as well as logical checking for some variables. 2) Data screening for quantitative data, to get first idea of average value, the variability, the shape of distribution, and outliers and missing values. This procedure generated the guidance in terms of the data grouping and suitable statistic method selection.

2 Descriptive Analysis

The descriptive analysis was performed on all independent variables of the study population. Depending on the nature of data, percentages, median with upper and lower quartile or means with standard deviation were provided for each variable. Analysis will then focus on the prevalence at 4 different cross-section time points and incidence of ROP of each stage as well as highest stage. Incidence and prevalence were also determined in birth year specific, birth weight specific and gestational age specific. The median age of onset for various stage of ROP was calculated in total and in birth weight specific. The cicatricial ROP and visual outcomes for followed infants was briefly described.

3 Risk Factor Analysis

All basic socio-demographic, prenatal and neonatal data factors investigated by the study were considered as potential risk factors for developing severe acute ROP and served as independent variables in risk factors analysis. The outcome or dependent variables was the development of severe ROP based on the highest stages of ROP for either eye. The severe ROP was taken as a binary variable here:

-- severe acute ROP (stage 3 and 4 of ICROP)

-- no severe acute ROP (stage 0, 1 or 2 of ICROP)

The initial analysis was the univariate analysis exploring relation between potential risk factors and severe ROP.

Relative risk would be determined (with 95% confidence intervals) to describe strength of the relationship observed (Rothman, 1986). Suitable significance tests (eg. X^2 test, X^2 linear trend test or Fisher exact test) were performed to determine if there were significant relationships between the potential risk factors and the outcome, acute severe stages of ROP.

Based on the findings of univariate analysis, the subsequent bivariate analysis on selected variables was also performed to further look at the association between risk factors and severe ROP after controlling the degree of prematurity measured by birth weight and gestational age. The Mantel-Haenzel weighted estimate of the relative risk was used to estimate the overall estimate of relative risk without the interference of third variable, the degree of prematurity (Rothman, 1986).

The final analysis was to examine the association between severe ROP and development of cicatricial ROP as well as the visual outcomes.

In a multifactorial process such as the development of ROP, the results of risk factor analysis based on univariate or bivariate statistical test may be conflicting. Significance obtained with "isolated" variables could be artifacts caused by dependence among different variables tested. Such artifacts can be avoided by using multivariate statistical method (Rothman, 1986). But this thesis project could not cover this section and it will be left for the further data analysis.

CHAPTER 4 RESULTS

I Study Population

1 Data Availability

According to the definition of the study population, 458 infants were identified as the study cohort. Figure 4-1 shows the study population tree. Among these 458 infants, 10 were lost to follow up from the Southern Alberta Perinatal Follow-up Program and had no information in the computer database. Sixteen infants born in 1989 and 1990 were followed by the program but their information had not been inputted onto the computer database. Thus data collection regarding ophthalmologic examination findings was started with 432 subjects. There were 58 infants identified as lost to follow up for the ophthalmologic examinations, all of them discharged from the Foothills Hospital NICU to out of the Calgary area before routine eye examination started or shortly after the first eye examination was done. Since only two ophthalmologists perform ROP screening examinations in the Calgary area, it was impossible to obtain more information about standard eye examinations in these 58 infants. The remaining 374 infants were the subjects on whom ophthalmologic information was available. Data completion rate at this point was 81.7%. The estimates of ROP incidence rate, ROP prevalence rate at first neonatal eye examination and near term examination, and risk factor analysis, are all based on this 374 infants.

Infants recruited for four months adjusted age and 12 months adjusted age follow up ophthalmologic assessment numbered 298 and 218 respectively. Estimates of prevalence rate of ROP, cicatricial ROP and visual outcome evaluation

are based on the followed infants at separate two time points.

2 Comparison of the Lost and Followed Infants

In total, 84 infants were lost to follow up for the study under four months adjusted age, but on 58 infants, some information was available on a computer database. A comparison of selected basic characteristics between these 58 lost and 374 followed infants was made.

Table 4-1 illustrates differences between lost and followed infants for selected quantitative variables. Since all data listed in the table were not normally distributed except for the total NICU days of stay in lost group, median was used to measure the central tendency and lower quartile and upper quartile were used to describe the spread or the variation of data. Comparing the medians of variables between groups, the lost babies were less premature than who were followed. Followed babies had longer
total NICU stay, total hospital stay and longer duration of supplemental O_2.

Table 4-2 gives the results of comparisons between two groups for selected qualitative categorical variables. Except for gestational week, the differences between lost and followed infants for all variables in the table were all significantly different. Larger proportion of lost infants was in the heavier birth weight categories compared with that in followed ones. In contrast, more followed babies were in the multi follow up risk criteria group compared to those in lost group. Also, compared to those who were lost, the followed infants had longer total NICU stay (>60 days), longer total hospital stay (>91 days) as well as longer duration of O_2 supplementation (>60 days).

Overall, the lost babies were a "positively" biased group. They had heavier birth weight, were healthier, and had less chance to develop ROP. So, as the followed cohort of 374 infants was used to estimate ROP prevalence rate, and incidence rate, and to evaluate the strength of associations between exposure and outcome, the results could have overestimated the true rates and strength of association. This is a very important point what should be borne in mind for the rest of this thesis.

3 Survival Rate of Infants Over Study Period

Survival rate of very premature babies has been reported to be related to the incidence rate of Retinopathy of Prematurity (Bossi et al., 1984; Hammer et al., 1986; Valentine et al, 1989). Therefore, it is necessary to examine whether the survival or death rate of infants varies over the six year study period. Table 4-3 gives death rates over the six years for all 632 infants followed by SA-PNFU program (X^2=20.55, P=0.001). The death rate was continuously decreasing from 1985 to 1988; there was a slight increase in 1989, and a greater increase in 1990. The linear decreasing trend of death rate over years is highly statistically significant (X^2_{LT}=10.54, P=0.0012).

It is obvious that the data displayed here (Table 4-3) do not coincide with the data shown in the Study Population Tree (Figure 4-1). The differences reflect dilemmas faced by this project: one is the dependency on the SA-PNFU program database, a common disadvantage of secondary data analysis; another is that this study is restricted ti the infants from Southern Alberta who were followed by SA-PNFU program, not all infants followed by SA-PNFU program. For the 632 infants in table 4-3 (10 losses from SA-PNFU program not included), there were 39 infants (among them, 23 died before NICU discharge and

16 survived the NICU stay) on whom information was not available in the database. Of all 593 infants with information in database, 132 died before discharge from NICU. Among the 461 who survived, 27 were from outside of Southern Alberta and two died before age five weeks without any eye examination done but survived the NICU stay. According to study population definition, these 29 cases were excluded from study although they met the criteria for the SA-PNFU program. Since this study was restricted to the survivors of NICU, it is not sure how many of those who died were from outside of Southern Alberta. The death rate analysis included all infants followed by Southern Alberta Follow up Program. Incomplete information about 155 deaths and 39 infants whose data were not available in database made the death analysis difficult in the study population.

Efforts have been made on 374 followed infants to determine if there was any difference in birthweight distribution over the six years and any difference of gestational week distribution over the 6 years. No significant differences were found (data not shown).

4 General Descriptive Variables in Study Population

1) Parents socio-demographic characteristics (Table 4-4)

For this very low birth weight infant population, the average age of mothers at delivery was 27 years. Only 3.7% mothers were under the age of 18, and 9.6% mothers were over the age of 35. The majority of mothers were Caucasian (85.6%). Ten mothers (2.8%) were black and 11 (3.1%) were native.

Eleven percent of infants were from single parent families. Average years of education was 13 for both mothers

and fathers. 20% of mothers and 23% of fathers had less than 12 years education.

Nineteen fathers were either unemployed or studying full-time at the time the baby was delivered. Of 296 families for whom the father's occupational information was available, 21.6% had a Blishen's socioeconomic index less than 30. The median Blishen'index for this study population was 41, which is about the average for Canadians (Blishen, et al, 1987).

2) Maternal factors (Table 4-5)

Some related maternal information about obstetrical history, labour and delivery were collected and presented in Table 4-5.

Fifty percent of mothers were primiparous and 31.5% were primigravida. Among 186 multiparous mothers, 34.4% had a history of preterm birth. Fifty-two percent of mothers had at least one other child living at home.

For the total seven categories of drugs investigated (refer to Chapter 3-3), 42.7% mothers received at least three kinds drugs during their labour and delivery, 82.7% mothers received at least one drug. Fetal Heart Monitoring was done in 84.9% of mothers.

Among all 374 VLBW infants, 51% were delivered by C-section. Of 191 C-section deliveries, 70% were indicated by more than one clinical condition which could be fetal distress, antepartum hemorrhage (APH), breech presentation, abnormal lie, failure to progress, or others. Among all indications for C-section observed, fetal distress and APH were most frequent. Ninety-two (24.6%) of mothers' C-sections were indicated by fetal distress, and 55 mothers' C-section

were indicated by APH.

Foul smelling amniotic liquor which indicated chorioamionitis were found in 44% of mothers. Fever (>38^{0}c) was observed in 12.2% of mothers and positive cultures, increased WBC or foul smelling discharge in 18.4%.

Among these VLBW mothers, 94.4% had an increased Coopland Risk Score .

3) Neonatal characteristics (Table 4-6)

Gender was evenly distributed in this study population. Twenty-two percent of infants were either twins or triplets.

The average birth weight was 960 gram, and average gestational weeks was 27. Both of these two measures were given as medians since they were not normally distributed. The birthweight and gestational weeks for newborn populations are usually normal distributed, but the study arbitrarily selected the birth weight range from 500 to 1250 grams from the whole birth weight spectrum, so it was not normally distributed.

One-third (33.4%) of infants were small for gestational age (SGA) and majority (66.6%) were average for gestational age (AGA). There were only 5.1% of infants with a 1 minute Apgar score of 8 or more, which range was considered normal. Thirty-eight percent of infants had 5 minute Apgar scores 8 or more. Almost all of these VLBW infants required resuscitation after birth.

There were 320 infants (85.6%) born in Foothills Hospital and 98.7% infants were cared for in the NICU, Foothills Hospital. 36.9% of infants were discharged directly to home

and the remainder were discharged to other hospitals.

4) Neonatal follow-up criteria and duration of hospital stay (Table 4-7)

All of the study population met one of the SA-PNFU program follow up criteria, birth weight 500-1250 grams. Seventy percent of the infants followed by the program also had other reasons; 60.2% met the 'on ventilatory assistance' risk criteria; 1.9% met 'congenital infection' and 9.1% met 'neurological disorder'.

The average acute NICU stay for the infants was 37.5 days. For total NICU stay, what is the sum of acute NICU stay and other NICU stay, 64 days was the average. Eighty-four days was the average total hospital stay.

5) Neonatal ventilatory assistance and O_2 supplementation (Table 4-8)

Ninety percent of infants received ventilatory assistance and 94% (312/336) of the ventilatory assistance started within 1 hour after birth. 89.6% of infants received positive pressure ventilatory assistance for an average of 9.5 days. The average maximum inspiratory ventilator pressure of all infants was 21.5 cmH_2O, and the average maximum expiratory pressure was 4.0 cmH_2O. 89.3% of infants experienced at least one arterial PO_2 >100, and 69.5 of infants experienced at least one capillary PO_2 >50.

For all 374 VLBW infants, 97.6% received O_2 for some time, with an average of 43 days. 35% of infants received ventilatory support more than once.

Different complications of ventilatory assistance were

observed and listed in Table 4-8(continued).

6) Neonatal respiratory problems (Table 4-9)

Apnea was observed in 75% of the population and 45% needed ventilatory treatment. The average onset of apnea was 6 days after birth and the average duration of apnea was 18 days.

There were 68.7% of infants who developed RDS in NICU. Meconium aspiration happened in three infants. Sixty five infants were found to have a pneumothorax and transient tachypnea were observed in 83 infants.

Forty eight infants were diagnosed as having PIP and 60% of infants were diagnosed as having BPD. Sixty-six infants were diagnosed as having emphysema and 189 had atelectasis.

Eight two infants were found to have other neonatal respiratory problems rather than the problems listed above.

7) Neonatal drug utilization (Table 4-10)

Drug utilization was frequently used in the study population with an average of 12 kinds of drugs for each infant during the hospital stay. Adverse drug reactions were found in 67.6% infants. 63.5% of infants experienced BPD or/and ROP as the adverse drug effect.

8) Other neonatal factors (Table 4-11)

Table 4-11 listed the other neonatal problems investigated. PDA was diagnosed in 57.7% infants, and 18.9% of infants received surgery for PDA.

Parenteral feeding was needed for 84% infants and the

average for parenteral feeding was 13 days for all followed infants. These VLBW infants took all food orally at an average of age 15 days.

The study population received blood or blood products at an average of six times and 29% of them received blood or blood products 10 or more times. The average maximum haematocrit observed was 530 SI units and average minimum haematocrit observed was 299 SI units.

IVH was found in 27% of study population and 83 infants were conformed to have sepsis.

Figure 4-1 Study Population Tree

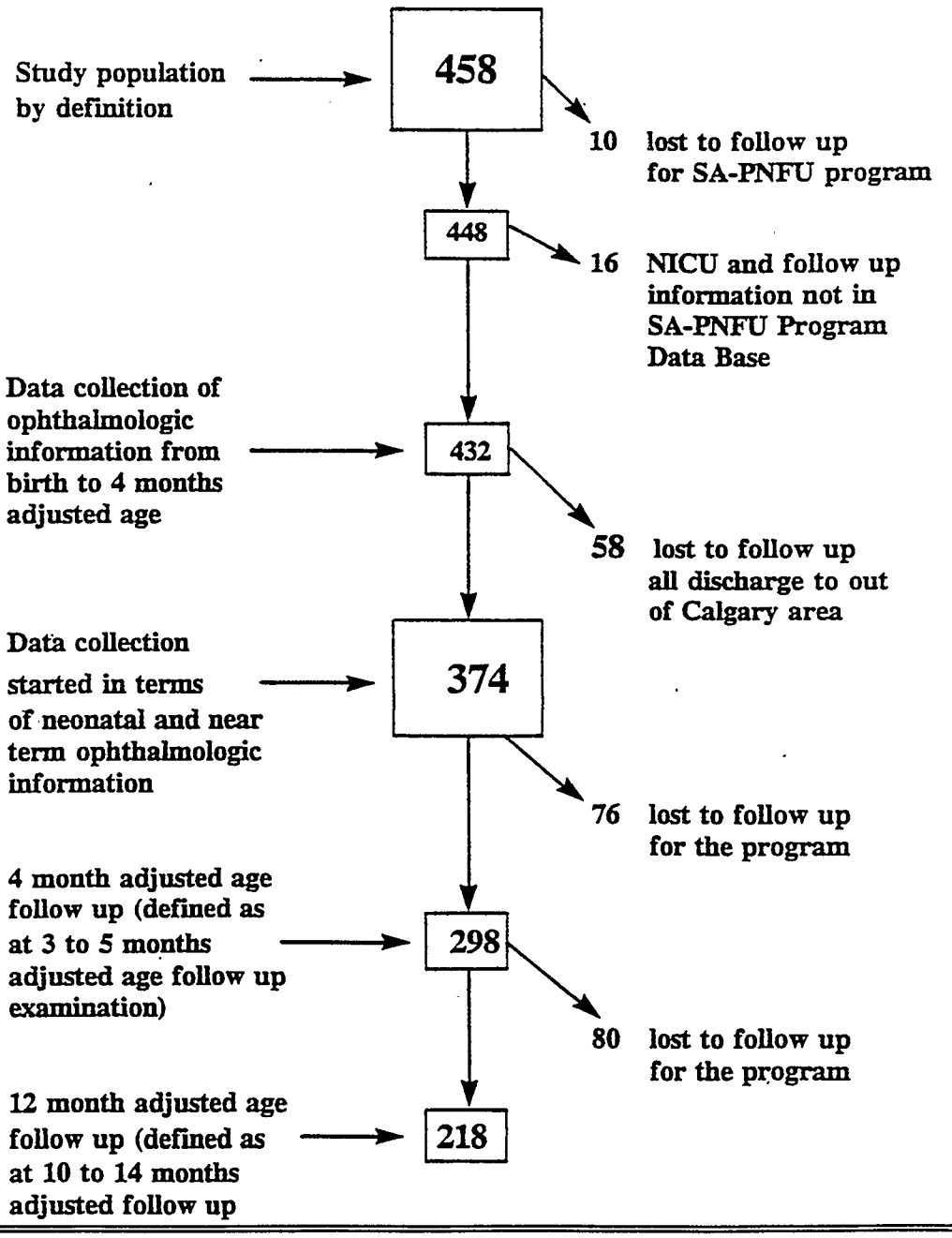

Table 4-1 Differences between lost and followed infants for selected variables (quantitative data)

Variables	Lost (58)			Followed (374)		
	Median	Quartile		Median	Quartile	
		Lower	Upper		Lower	Upper
Birth Weight	1090.0	925.0	1152.5	960.0	807.5	1110.0
Gestational Week	28.0	27.0	29.0	27.0	26.0	29.0
Total NICU Days	36.0	24.8	46.8	64.0	40.0	90.0
Total Hospital Days*	72.5	62.3	87.0	84.0	65.0	108.0
Total O_2 Days	27.0	5.0	42.3	43.0	10.0	82.0

* There were 18 infants with missing values in the Lost group and 29 infants with missing values in the Followed group.

Table 4-2 Differences between lost and followed infants for selected variables (qualitative data)

Variable	Lost (58)		Followed(374)		X^2-test (P-value)
	n	%	n	%	
Birth weight					
500- 749	8	13.8	66	17.6	10.56
750- 999	11	19.0	140	37.4	(0.005**)
1000-1250	39	67.2	168	45.0	
Gestational week					
22-26	12	20.7	119	31.8	2.96
27-28	26	44.8	142	38.0	(0.228)
29-36	20	34.5	113	30.2	
# of risk criteria for follow up					
1	26	44.8	110	29.4	11.14
2	18	31.0	87	23.3	(0.011*)
3	12	20.7	151	40.4	
4	2	3.4	26	7.0	
Total NICU Days					
<61	51	88.0	176	47.1	33.64
≥61	7	12.0	198	52.9	(0.000**)
Total Hospital Days[a]					
<61	8	20.0	62	18.0	7.66
61-90	24	60.0	139	40.3	(0.022*)
≥91	8	20.0	144	41.7	
Total O_2 Days					
<60	52	89.7	232	62.0	17.0
≥60	6	10.3	142	38.0	(0.000**)

@ There were 18 infants with missing value in the lost group and 29 infants with missing value in the followed group.
* statistically significant
** highly statistically significant

Table 4-3 Death rates for infants followed by the Southern Alberta Perinatal Follow up Program with birth weight 500-1250g during 1985 - 1990

Birth Year	Total Newborns	Died before NICU Discharge	Death Rate %
1985	122	46	37.7
1986	91	25	27.5
1987	101	24	23.8
1988	87	13	14.9
1989	98+(14)=112	9+(9)= 18	16.1
1990	94+(25)=119	15+(14)= 29	24.4
Total	593+(39)=632	132+(23)=155	24.5

Note:
1 the infants include 26 from British Columbia, 1 from Edmonton, and 2 who died after discharge from NICU but under the age the eye examination could be applied.
2 the cases numbered in "()" for 1989 and 1990 have not been entered into database; among them, 16 survived.
3 X^2=20.55 P=0.0010 X^2_{LT}=10.54 P=0.0012; both of the X^2 statistics were calculated by the number of death and survival newborns before NICU discharge in each year.

Table 4-4 Parents socio-demographic characteristics (374 infants)

Variable	Frequency	%	Others*	
Maternal age (years)				
<18	14	3.7	Mean	27.0
18-34	324	86.7	SD	5.3
≥35	36	9.6		
Maternal race				
Caucasian	303	85.6	-	
black	10	2.8		
Native	11	3.1		
Others	30	8.5		
(missing=20)				
Marital status				
single parents	42	11.3	-	
two parents	331	88.7		
(missing=1)				
Maternal Schooling Years				
<12	63	20.1	Median	13.0
≥12	251	79.1	lower	12.0
(missing=60)			upper	14.3
Paternal schooling years				
<12	68	22.7	Median	13.0
≥12	231	77.3	lower	12.0
(missing=75)			upper	16.0
Blishen's Index				
<30	64	21.6	Median	41.0
≥30	232	78.4	lower	30.0
(missing=59, excluded 19 fathers who were unemployed or students)			upper	60.0

* Based on the distribution of raw data, measures of central tendency and dispersion are provided where applicable. SD means standard deviation, lower means lower quartile, upper means upper quartile.

Table 4-5 Maternal factors (374 infants)

Variables		Frequency	%
OBSTETRICAL HISTORY			
Parity	0	185	49.9
(missing=3)	≥1	186	50.1
Gravidity	0	117	31.5
(missing=3)	1	106	28.6
	≥2	148	39.9
# of previous preterm birth			
(missing=0)	yes	64	34.4
	no	122	65.6
# of living children			
(missing=4)	0	177	47.5
	1	118	31.9
	≥2	75	20.3
LABOUR AND DELIVERY			
# of total drugs used			
(missing=9)	0	63	17.3
	1-2	146	40.0
	3-4	156	42.7
Fetal heart monitor			
(missing=4)	yes	314	84.9
	no	56	15.1
Cesarean-section			
(missing=0)	yes	191	51.1
	no	183	48.9
# of indictions for C-section			
(missing=0)	0	183	48.9
	1	57	15.2
	2	102	27.3
	3	32	8.6
Fetal distress as C-section indicator			
(missing=0)	yes	92	24.6
	no	282	75.4
APH as C-section indicator			
(missing=0)	yes	55	14.7
	no	319	85.3
Infection: foul smelling liquid			
(missing=13)	yes	159	44.0
	no	202	56.0
Infection: maternal fever			
(missing=12)	yes	44	12.2
	no	318	87.7
Infection: others			
(missing=20)	yes	65	18.4
	no	289	81.6
Coopland's Risk Score			
(missing=1)	increased	352	94.4
	average	21	5.6

Table 4-6 Neonatal characteristics (374 infants)

Variables		Frequency	%	Others*	
Sex	male	183	48.9	-	
	female	191	51.1		
Multi-birth	yes	82	21.9	-	
	no	292	78.1		
Birth weight (gram)					
	500- 749	66	17.6	Median	960.0
	750- 999	140	37.4	lower	807.0
	1000-1250	168	44.9	upper	1100.0
Gestational week					
	23-26	119	31.8	Median	27.0
	27-28	142	38.0	lower	26.0
	29-35	113	30.2	upper	29.0
Intrauterine Growth Status					
	SGA	125	33.4	-	
	AGA	249	66.6		
1 minute Apgar Score					
(missing=1)	0- 2	119	31.9	-	
	3- 7	235	63.0		
	8-10	19	5.1		
5 minute Apgar score					
(missing=1)	0- 4	30	80.0	-	
	5- 7	201	53.9		
	8-10	142	38.1		
Resuscitation required					
yes, cardiac massage		12	3.2	-	
yes, intubation		285	76.2		
yes, O_2, bag/mask		73	19.5		
no		4	1.1		
Birth Place					
Foothills Hospital		320	85.6	-	
other hospital		54	14.4		
Place of hospitalization					
Foothills Hospital		369	98.7	-	
other hospital		5	1.3		
Disposition					
other hospital		236	63.1	-	
home		138	36.9		

* Measures of central tendency and dispersion are given where applicable. Lower means lower quartile, upper means upper quartile.

Table 4-7 Neonatal follow-up criteria and duration of hospitalization (374 infants)

Variable	Frequency	%	Others*	
FOLLOW UP CRITERIA				
# of risk criteria				
1	110	29.4	-	
2	87	23.3		
3	151	40.4		
4	26	7.0		
On ventilator				
yes	225	60.2	-	
no	149	39.8		
Congenital infection				
yes	7	1.9	-	
no	167	98.1		
Neurological disorder				
yes	34	9.1	-	
no	340	90.9		
HOSPITALIZATION				
Acute NICU days				
<31	147	39.3	Median	37.5
31-60	131	35.0	lower	16.8
≥61	96	25.7	upper	62.0
Total NICU days				
<31	66	17.6	Median	64.0
31-60	110	29.4	lower	40.0
61-90	106	28.3	upper	90.0
≥91	92	24.6		
Total hospital days				
<61	62	18.0	Median	84.0
61-90	139	40.3	lower	65.0
91-120	88	25.5	upper	108.0
≥121	56	16.2		
(missing=29)				

* Measures for central tendency and dispersion are given where applicable. Lower means lower quartile, upper means upper quartile.

Table 4-8 Neonatal ventilatory assistance and O_2 supplementation (374 infants)

Variables		Frequency	%	Others*	
Ventilatory assistance					
	Yes	336	89.8	-	
	no	38	10.2		
Age in hours of onset					
	<1	312	83.4	-	
	≥1	24	6.4		
	NA	38	10.2		
Days of PPV					
	0	39	10.4	Median	9.5
	1- 7	137	36.6	lower	2.0
	8-27	69	18.4	upper	39.3
	≥28	129	34.5		
Days of other ventilatory assistance	0	164	43.9	Median	1.0
	1-2	115	30.7	lower	0.0
	≥3	95	25.4	upper	4.0
Maximum inspiratory pressure cmH_2O	0	39	10.4	Median	21.5
	1-19	83	22.2	lower	18.0
	20-29	191	51.1	upper	26.0
	≥30	61	16.3		
Maximum expiratory pressure cmH_2O (missing=1)	0	38	10.7	Median	4.0
	1-4	242	64.7	lower	4.0
	≥5	93	24.9	upper	5.5
# of arterial PO_2>100					
	0	53	14.2	Median	4.0
	1-4	197	52.7	lower	2.0
	≥5	124	33.2	upper	7.0
# of capillary PO_2>50					
	0	114	30.5	Median	3.0
	1-4	151	40.4	lower	0.0
	≥5	109	29.1	upper	6.3
Total days in O_2					
	0	9	2.4	Median	43.0
	1-29	141	37.7	lower	10.0
	30-59	82	21.9	upper	82.0
	60-89	68	18.2		
	≥90	74	19.8		
Episodes of ventilatory support >1	yes	132	35.3	-	
	no	242	64.7		

* Measures of central tendency and dispersion are given where applicable. Lower means lower quartile, upper means upper quartile.

Table 4-8 Neonatal ventilatory assistance and O_2 supplementation (continued)

Complications during ventilatory assistance	Frequency	N	%
atelectasis	190	363	52.3
prolonged hypoxia	71	373	19.0
prolonged acidosis	37	373	9.9
post extubation airway obstruction	101	374	27.0
emphysema	64	359	17.8
other extrapleural air	9	371	2.4
others	12	373	3.2

Table 4-9 Neonatal respiratory problems (374 infants)

Variables		Frequency	%
Apnea			
yes, vent. treat.		168	44.9
yes, no vent. treat.		113	30.2
no		93	24.9
Apnea age of onset (days)			
	NA	93	24.9
	1-9	152	40.6
	≥10	129	34.5
Apnea duration (days)*			
(missing=10)	0	103	28.3
	1-29	134	36.8
	≥30	127	34.9
RDS			
(suspect=23)	yes	241	68.7
	no	110	31.3
Meconium aspiration			
(missing=1)	yes	3	0.8
	no	370	99.2
Pneumothorax			
	yes	65	17.4
	no	309	82.6
Transient tachypnea			
(suspect=7)	yes	83	22.6
	no	284	77.4
PIP			
(suspect=3)	yes	48	12.9
	no	323	87.1
BPD			
(suspect=9)	yes	219	60.0
	no	146	40.0
Emphysema@			
(suspect=15)	yes	66	18.4
	no	293	81.6
Atelectasis@			
(suspect=11)	yes	189	52.1
	no	174	47.9
Others			
(missing=3)	yes	82	22.1
	no	289	77.9

* "0" includes no apnea cases and cases with apnea only lasted 1 days.

@ The majority of cases overlapped with the atelectasis and emphysema as complications of ventilatory assistance.

Table 4-10 Neonatal drug utilization (374 infants)

Variable	Frequency	%	Others*
# of total drugs used			
1- 9	138	36.9	Median 12.0
10-14	106	28.3	lower 8.0
15-37	130	34.8	upper 18.0
Adverse drug reaction			
yes, BPD or/and ROP+others	43	11.5	-
yes, BPD or/and ROP only	194	52.0	
yes, others	15	4.0	
no	121	32.4	

* Measures of central tendency and dispersion were provided where applicable. Lower means lower quartile, upper means upper quartile.

Table 4-11 Other neonatal factors (374 infants)

Variables		Frequency	%	Others*	
CARDIOVASCULAR PROBLEMS					
Patus ductus arteriosus					
	yes, surgery	70	18.9		-
	yes, drug treat.	143	38.8		
	no	156	42.3		
	(suspect=5)				
NUTRITION AND FEEDING					
Parenteral days					
	0	60	16.0	Median	13.0
	1-14	160	42.8	lower	6.0
	15-90	154	41.2	upper	22.0
Age days of all food taken orally					
	1-14	189	53.2	Median	15.0
	15-85	167	46.9	lower	10.0
	(missing=18)			upper	23.0
HAEMATOLOGY					
# of blood products given					
	0	55	14.7	Median	6.0
	1- 4	110	29.4	lower	2.0
	5- 9	101	27.0	upper	11.0
	10-36	108	28.9		
Maximum haematocrit (SI unit)					
	<500	97	25.9	Median	530.0
	500-549	142	38.0	lower	498.8
	550-780	135	36.1	upper	571.3
Minimum haematocrit (SI unit)					
	<280	121	32.4	Median	299.0
	280-319	136	36.4	lower	270.0
	320-642	117	31.3	upper	333.3
HEMORRHAGE					
Intraventricular(IVH)					
	yes	104	27.8		-
	no	270	72.2		
OTHERS					
Sepsis	yes	83	37.6		-
	no	138	62.4		
	(missing 1 suspect 152)				

* Measures of central tendency and dispersion are provided where applicable. Lower means lower quartile, upper means upper quartile.

II The Development of Acute Retinopathy of Prematurity

Prevalence Rate

The information collected in this study was able to provide the estimates of ROP prevalence rates at four time points. These are the prevalence rates of ROP at the first neonatal ophthalmologic examination, at near term, at four months adjusted age and at 12 months adjusted age.

1 Time Point One: First Neonatal Ophthalmologic Examination

The criteria for valid cases included as first neonatal ophthalmologic examination was infants who had their first eye examination at chronological age (CA) 20 to 40 days. Exceptions were the infants who had their first eye examination later than CA 40 days because they were extremely premature or the infants who had their first eye examination before CA 20 because they were less premature (with relatively higher birth weight and larger gestational age). Thirty-two cases did not meet these criteria, so 342 infants were selected for prevalence rate investigation at this time point.

1) Average age and estimate of ROP prevalence rate

The average ages at first neonatal eye examination are presented in Table 4-12. The average CA was 33 days and AA was -54 days.

The point estimates and 95% confidence intervals of prevalence rates of ROP at first neonatal examination are given in Table 4-13. Overall, 17% of infants were found to have ROP in at least one eye, with 13.2% stage 1 ROP and 3.8% stage 2 at this time point. No severe ROP was observed.

2) Prevalence rate of ROP by birth year, birth weight and gestational week

Table 4-14 exhibits the ROP prevalence rate distribution according to birth year, birth weight categories and gestational week categories. There is no significant difference in ROP prevalence rate according to birth year. The differences are found between birth weight and ROP prevalence rate, and gestational week and ROP prevalence rate. Heavier birth weight, and later gestational week correlate with higher prevalence rate of ROP.

2 Time Point Two: Near Term

The time criteria for near term valid case inclusion was set as the infants whose eye examination were done at AA -20 to +20. Exception was given to the cases whose routine ophthalmologic examinations were stopped before AA -20 if the opthalmologist judged that no further examination was required. Twenty-nine cases were excluded according to this criteria. The remaining number of infants was 345.

1) Average age and estimate of ROP prevalence rate

The average age (days) at near term eye examination as presented in Table 4-15 was -6.53 for AA and 81.55 for CA. There were some missing values for CA and AA.

Ophthalmologic examination findings for the worse eye affection were shown in the left of Table 4-16. One hundred and sixty-seven infants were found to have ROP with different stages, 62 infants who were previously found to have ROP, were resolved by the time of the near term eye examination. Fourteen infants had received cryotherapy treatment and were difficult to be grouped into standard ROP stages, but they

should have stage 3a at least at near term if the cryotherapy treatment did not be applied. There were also three infants with type II ROP which was not of interest to this study and one case with ROP information missing.

Table 4-16 also provided the estimate and 95% confidence interval for ROP prevalence rate at near term after taking resolved cases as no ROP and cases under cryotherapy as stage 3 ROP, excluding three cases of type II ROP and one missing case. The prevalence rate of severe ROP (stage 3 or more) was 12.3%. Mild ROP was found in 40.8% and overall 53.6 % of 341 infants had ROP at near term.

2) Prevalence rate of ROP by birth year, birth weight and gestational week

Severe ROP (stage 3 or more) prevalence rate in different birth year, in different birth weight categories and gestational week categories were examined and results were given in Table 4-17.

There is no significant difference for changes for prevalence rate of severe ROP as the birth year varies. Prevalence rate of severe ROP was significantly increased as birth weight decreased and gestational week decreased.

3 Time Point Three and Four: Four and 12 Months Adjusted Age

For four months adjusted age follow up, case inclusion criteria was defined as the infants who had follow up ophthalmologic assessment at three to five months adjusted age. For 12 months adjusted age, time criteria was defined as the infants who had follow up ophthalmologic assessment at 10 to 14 month adjusted age. Table 4-18 gives adjusted age month

distribution of included infants for these two time points.

The prevalence rates of ROP and 95% confidence intervals for worse eye at four months adjusted age and 12 months adjusted age are summarized in Table 4-19. At four months adjusted age, only 2.7 % of the infants had mild ROP and 5.4 % had severe ROP. At 12 months adjusted age, severe ROP was observed in 5.2% of total 153 infants. Among them, only one had stage 4 ROP, which was defined as retina detachment. There were large number of cases with missing information for these two time points.

The special interests and clinical importance of ophthalmologic assessment at these two time points were to assess cicatricial ROP and visual outcome rather than the acute ROP. Both of them will be discussed at Part IV of the results section. Further look at the prevalence by birth year, birth weight and gestational week as done at first two time points is not necessary.

4 Comparison of Prevalence Rate of ROP at Four Different Time Points

Figure 4-2 provides a comparison of prevalence rate of ROP at four different time points. Only first time (first neonatal ophthalmologic examination) was cut-off at chronological age, the other three time points were all cut-off at adjusted age. In summary, the compositions of prevalence rate of ROP stages for four crossectional time points are different. At the earliest age time point, only mild ROP with lower rate was observed. At near term, half of infants were observed as having ROP with mild stages as a major composition, but the highest rate of severe ROP among 4 time points was found at this time point. At four months adjusted age, the acute ROP in total was very small, but

severe ROP overweighed the mild one. At 12 months adjusted age, only a small portion of severe ones were left.

Incidence Rate

1 Incidence Rate of Various Stages of ROP, ROP Plus Disease in Different Eye Affection.

The cumulative incidence rate of different ROP stages for right eye affection, left eye affection, bilateral eye affection (defined as both eye affected at some stage of ROP on at least one occasion during observation) as well as unilateral eye affection (defined as either of both eye developed some stage of ROP at least one occasion during observation) are presented in Table 4-20. To present the results of right eye affection, left eye affection and bilateral affection of different ROP stages is mainly for the fulfilment of the profile of ROP development, and possible clinical importance. The focus here is placed on unilateral eye affection.

There were 66.8% of infants who had developed stage 1 ROP in at least one eye on at least one examination. For stage 2, the rate was 51.6%, stage 3a was 13.7% and stage 3b was 14.5. Overall, 70.2% (240 infants) of the infants were found to have some stage of ROP in at least one eye on at least one examination. 6.4 % of infants were found to have ROP plus disease in at least one eye on at least one occasion.

2 Incidence Rate of Highest Stage of ROP, Birth Year, Birth Weight and Gestational Week Specific.

The major epidemiological interest in inquiring about the

frequency of ROP is to estimate the highest stages of ROP for the infants presented in Table 4-21. Thirty infants were not included, three of them were type II ROP and 27 did not have complete information for the highest stage of ROP.

In 18.6% of all infants, stage 1 was the highest active stage of ROP observed and in 32.6%, stage 2 was the highest stage of ROP. Stage 3a b c, or in other words, severe ROP, was the highest stage observed in 19.2% of infants. The 95% confidence intervals of these were also provided in the table. For the rest of the paper, this rate will just be considered as incidence rate of ROP and will be taken as most important outcome or dependent variable in risk factor analysis.

Table 4-22 shows the comparison of severe ROP by birth year, birth weight and gestational week. Not like the prevalence rate at near term and first time examination, the incidence rate of ROP significant varied by birth year($P<0.01$). At the same time, the incidence rate of ROP has significant negative relationship with the birth weight and the gestational week.

Age of Onset for Various Stages of ROP

1 Age of Onset for Various Stages of ROP

The age of first time of finding each ROP stage was recorded for individual affected eyes and a control variable was created for each first time finding age to make sure the eye examination which first found new stage ROP development was performed within the normal ophthalmological examination interval.

The calculation for median age of onset for various stages of ROP in both chronological and adjusted age was first made for right and left eye separately. No major difference was found between right and left eye (data not shown). Table 4-23 presents the median age of onset for various stages of ROP for either affected eye. All calculation excluded the infants who did not develop that specific stage of ROP under consideration.

The median age of onset was 47 CA days for stage 1 ROP, 56 days for stage 2 ROP, 70 days for stage 3a ROP, 73 days for stage 3b, and 69 days for ROP plus disease. For adjusted age, median age of onset for ROP was -44 for stage 1, -40 for stage 2, -25 for stage 3a, -24 for stage 3b and -26.5 for ROP plus disease (Table 4-23). Mild ROP (stage 1 and 2) was found to have close median age of onset (CA 47 to 57, AA -44 to -40); severe ROP (stage 3a 3b) and ROP plus disease were found to have close age of onset as well (CA 69 to 73, AA -26.5 to -24).

2 Age of Onset for Mild and Severe Stages of ROP by Birth Weight

Further calculation of median age of onset for mild and severe ROP in different birth weight groups was made and presented in Table 4-24 and Table 4-25. Calculation uses the age of onset for stage 1 ROP as the age of onset for mild ROP, uses the age of onset for stage 3a as the age of onset for severe ROP.

For mild ROP, less birth weight infants took longer CA to occur, but took almost same adjusted age to occur. Similar results was found in the age of onset of severe ROP, but the AA had a fluctuation.

Table 4-12
Average age at first neonatal ophthalmologic examination*

Age (days)	Mean	SD	Range	N
Chronological	33.11	4.35	13 to 65	342
Adjusted	-54.19	14.64	-91 to 7	342

* Valid cases were defined as the infants who had their first Ophthalmologic Examination at CA 20 to 40 days. 32 among 374 infants were excluded because of this restriction

Table 4-13 Prevalence rate at first neonatal ophthalmologic examination (for worse eye, 342 infants)

ROP	Frequency	%	95% CI
None	284	83.0	79.1 - 87.0
Stage 1	45	13.2	9.6 - 16.7
Stage 2	13	3.8	1.8 - 5.8

Table 4-14 Prevalence rate of acute ROP at first neonatal ophthalmologic examination by birth Year, birth weight, gestational week (342 cases)

Birth Year	ROP			BW(g)	ROP			GW	ROP		
	Yes	(%)	No		Yes	(%)	No		Yes	(%)	No
1985	8	(15.7)	43	500- 749	2	(3.2)	60	23-26	4	(3.5)	111
1986	7	(14.6)	41	750- 999	20	(15.3)	111	27-30	44	(22.4)	152
1987	13	(21.7)	47	1000-1250	36	(24.2)	113	31-35	10	(32.3)	21
1988	10	(16.9)	49	Total	58	(17.0)	284	Total	58	(17.0)	284
1989	11	(16.7)	55								
1990	9	(15.5)	49								
Total	58	(17.0)	284								

X^2=1.29 P=0.9365
X^2_{LT}=0.002 P=0.9638

X^2=14.06 P=0.0009
X^2_{LT}=13.89 P=0.0002

X^2=24.19 P=0.0000
X^2_{LT}=25.44 P=0.0000

Table 4-15 Average age at near term ophthalmologic examination[1] (345 infants)

Age (days)	Mean	SD	Range	N
Chronological	81.55	18.58	43 to 130	339[2]
Adjusted	-6.53	10.98	-35 to 24	331[3]

1 Valid cases were defined as the infants who had their near term Ophthalmologic Examination at AA -20 to 20 days, 29 among 374 infants were excluded because of this restriction.
2 Missing value for CA was 6
3 Missing value for AA was 14

Table 4-16 Ophthalmologic examination findings and prevalence rate of ROP at near term (for worse eye, 345 infants)

Examination Findings		ROP Prevalence Rate and 95% CI			
Item	Frequency	Stage[a]	Frequency	%	95% CI
No	98	No	160	46.9	41.6-52.2
ROP stage 1	47	stage 1	47	13.8	10.1-17.4
ROP stage 2	92	stage 2	92	27.0	23.3-31.7
ROP stage 3a	3	stage 3	42	12.3	8.8-15.8
ROP stage 3b	24				
ROP stage 3c	1				
Cryotherapy Tx	14				
Resolved ROP	62	no	160	46.9	41.6-52.2
Type II ROP	3	mild	139	40.8	35.5-46.0
Missing	1	severe	42	12.3	8.8-15.8
Total	345	Total	341	100.0	

@ Taking resolved ROP cases as no ROP and cases under cryothepy treatment as stage 3 ROP;
Excluding 3 type II ROP and 1 Missing case.

Table 4-17 Prevalence rate of severe ROP at near term by birth year, birth weight, gestational week (341 cases)

Birth Year	Severe ROP		BW(g)	Severe ROP		GW	Severe ROP	
	Yes	(%) No		Yes	(%) No		Yes	(%) No
1985	6	(8.6) 44	500- 749	14	(22.2) 49	23-26	27	(23.9) 86
1986	5	(9.6) 47	750- 999	20	(15.6) 113	27-28	11	(8.3) 121
1987	8	(13.8) 50	1000-1250	8	(5.5) 137	29-35	4	(4.2) 92
1988	11	(21.2) 41	Total	42	(12.3) 299	Total	42	(12.3) 299
1989	6	(8.5) 65						
1990	6	(10.3) 52	X^2=12.84	P=0.0016		X^2=21.87	P=0.0000	
Total	42	(12.3) 299	X^2_{LT}=12.71	P=0.0004		X^2_{LT}=19.39	P=0.0001	
X^2=5.42	P=0.3662							
X^2_{LT}=0.064	P=0.7998							

Table 4-18 Age distribution at four and twelve months adjusted age follow-up

Adjusted month age		N	%
Four (298)	3	14	4.5
	4	205	68.8
	5	79	26.5
Twelve (218)	10	13	6.0
	11	22	10.1
	12	104	47.7
	13	62	28.4
	14	17	7.8

Table 4-19 Prevalence rates of ROP at four and twelve months adjusted age follow-up

ROP	4 months adjusted age			12 months adjusted age		
	Frequency	%	95% CI	Frequency	%	95%CI
No	239	91.9	88.6-95.2	147	94.8	93.0-99.2
Mild	7	2.7	0.7- 4.7	0	0.0	NA
Severe	14	5.4	2.6- 8.1	8	5.2	1.7- 8.8
Total	260	100.0		153	100.0	
Missing	38			63		

Figure 4-2 Comparison of prevalence rate of ROP stages at 4 different time points

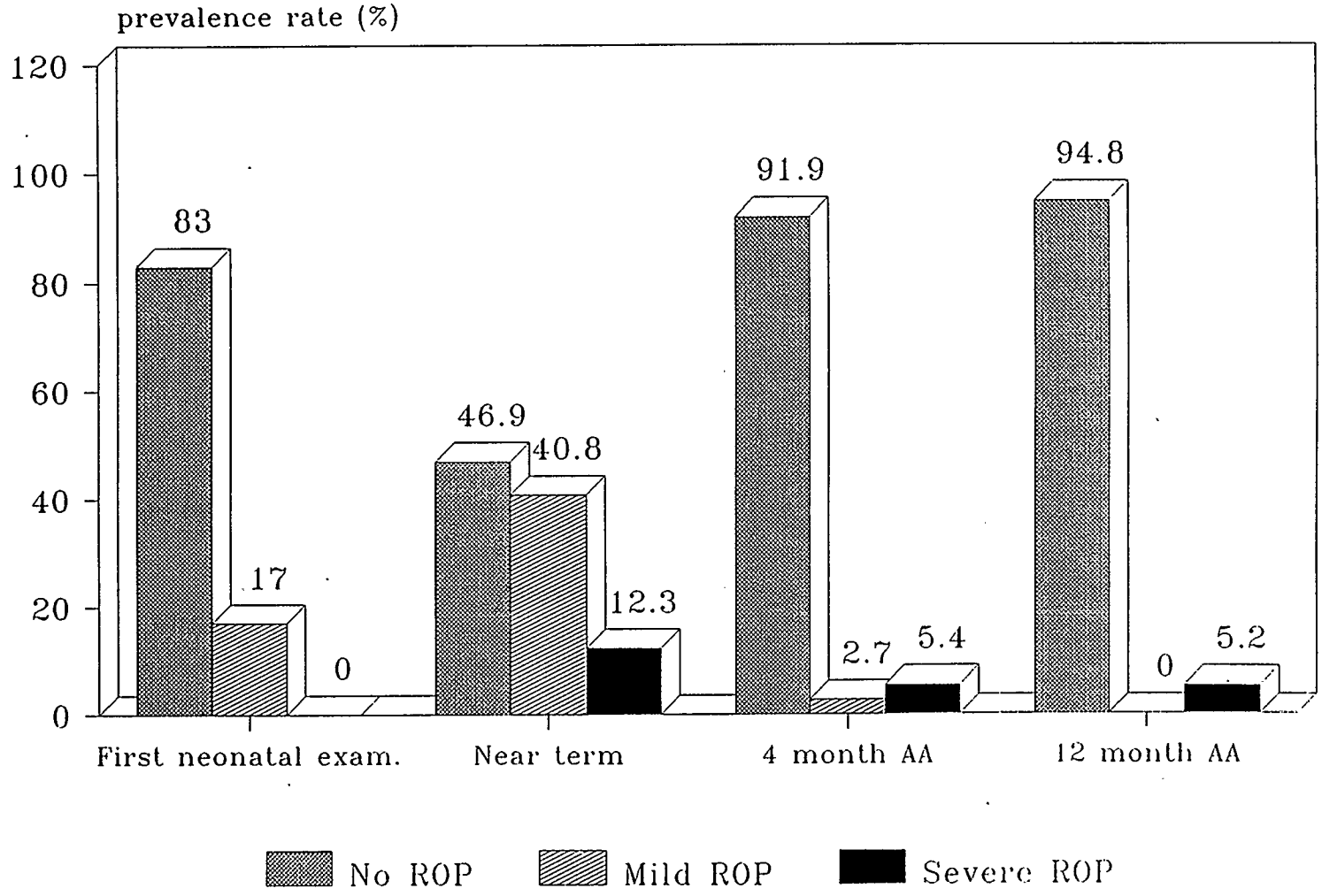

Table 4-20 Incidence rates of ROP stages , ROP plus disease by different eye affections

ROP Stages	Right Eye			Left Eye			Bilateral[1]			Unilateral[2]		
	N	+	%	N	+	%	N	+	%	N	+	%
stage 1	351	216	61.5	348	209	60.1	346	187	54.0	346	231	66.8
stage 2	347	172	49.6	345	158	45.8	345	150	43.5	345	178	51.6
stage 3a	344	37	10.8	345	37	10.7	344	27	7.8	344	47	13.7
stage 3b	345	44	12.8	344	40	11.6	344	33	9.6	344	50	14.5
Mild	346	237	68.5	345	228	66.1	345	221	64.1	345	243	70.4
Severe	344	58	16.9	344	57	16.6	343	49	14.3	343	65	19.0
ROP	344	235	68.3	343	226	65.9	342	218	63.7	342	240	70.2
Plus disease	344	22	6.4	344	18	5.2	344	18	5.2	344	22	6.4

1 Bilateral eye affection was defined as both eye affected specific stage of ROP at least one occasion during observation.
2 Unilateral eye affection was defined as either eye affected specific stage of ROP at least one occasion during observation.

Table 4-21 Cumulative incidence Rate of ROP (highest stages observed for worst eye)

ROP		frequency	%	95% CI
Stages	no	102	29.7	24.8 - 34.4
	1	64	18.6	14.5 - 22.7
	2	112	32.6	27.6 - 37.5
	3a	13	3.8	1.8 - 5.8
	3b	52	15.1	11.3 - 18.9
	3c	1	0.3	-
Severity	no	102	29.7	24.8 - 34.4
	mild	176	51.2	45.9 - 56.4
	Severe	66	19.2	15.0 - 23.3
ROP	no	102	29.7	24.8 - 34.4
	yes	242	70.3	65.5 - 75.1
Total*		344	100.0	

* Excluding 3 cases of type II disease and 27 cases without complete ROP information.

Table 4-22 Cumulative incidence rate of severe ROP by birth year, birth weight and gestational week (344 cases)

Birth Year	Severe ROP		BW (g)	Severe ROP		GW	Severe ROP	
	Yes (%)	No		Yes (%)	No		Yes (%)	No
1985	8 (16.0)	42	500- 749	26 (41.3)	37	23-26	42 (36.8)	72
1986	7 (13.2)	46	750- 999	30 (22.7)	102	27-28	19 (14.3)	114
1987	11 (18.6)	48	1000-1250	10 (6.7)	139	29-35	5 (5.2)	92
1988	17 (30.4)	39	Total	66 (19.2)	278	Total	66 (19.2)	278
1989	10 (14.3)	60						
1990	13 (23.2)	43	X^2=59.92	P=0.0000		X^2=24.19	P=0.000	
Total	66 (19.2)	278	X^2_{LT}=35.66	P=0.0000		X^2_{LT}=32.58	P=0.0000	

X^2=24.560 P=0.0062
X^2_{LT}=0.822 P=0.3647

Table 4-23 Age of onset for various stages of ROP

ROP stage	Chronological age (days)			Adjusted age (days)			N
	Median	quartile		Median	quartile		
		lower	upper		lower	upper	
Stage 1	47.0	40.0	58.0	-44.0	-51.0	-36.0	223
Stage 2	56.0	47.0	64.0	-40.0	-47.0	-29.0	173
Stage 3a	70.0	58.0	86.0	-25.0	-36.0	-15.0	47
Stage 3b	73.0	60.0	84.0	-24.0	-36.0	-16.0	49
plus disease	69.0	61.8	84.5	-26.5	-37.5	-17.5	22

Table 4-24 Age of onset for mild ROP by birth weight

Birthweight (grams)	Chronological age (days)			Adjusted age (days)			N
	Median	quartile		Median	quartile		
		lower	upper		lower	upper	
500- 749	60.0	49.5	66.0	-44.5	-53.5	-39.3	53
750- 999	47.0	43.0	55.0	-43.5	-53.0	-36.0	98
1000-1250	42.0	33.0	47.5	-43.0	-48.0	-33.0	73
Total	47.0	40.0	58.0	-44.0	-51.0	-36.0	223

Table 4-25 Age of onset for severe ROP by birth weight

Birthweight (grams)	Chronological age (days)			Adjusted age (days)			N
	Median	quartile		Median	quartile		
		lower	upper		lower	upper	
500- 749	85.0	73.8	93.8	-22.5	-31.8	-21.5	16
750- 999	65.0	58.5	75.5	-33.0	-39.5	-20.5	25
1000-1250	53.5	51.5	73.5	-18.5	-23.5	-5.25	6
Total	70.0	58.0	86.0	-25.0	-36.0	-15.0	47

III Risk Factors for the Development of Severe ROP

Risk factor analyses consisted of two parts: firstly, univariate analysis was done to screen all risk factors, and secondly, bivariate analysis was done to evaluate adjusted relative risks for risk factors determined to be highly significant in the first step. Outcome or dependent variable was severe ROP (stage 3 or more), and independent or exposure variables were all variables described in part II of chapter 3.

The maximum number of cases available for the risk factor analysis was 344 out of 374 followed infants; 30 cases were excluded from the assessment severe ROP because there was inadequate information (27 cases) or because the infants has type II disease (3 cases).

Univariate Analysis

Univariate analysis was conducted firstly to assess the associations with all potential risk factors of severe ROP. The way the exposure level categorized was for each factor is the same as that done in the variable descriptions (part II, chapter 3).

Statistical significance was determined for those categorical data using either the chi-square test, chi-square test with Yates correction, chi-square linear trend test, or Fisher exact test (refer part III, chapter 3 for detailed explanation).

As part of the analysis, relative risks and corresponding 95% confidence intervals were calculated to evaluate strength

of association and interval estimator of the association. Since 85 associations between risk factors and severe ROP were examined, the significant P-value was adjusted to 0.01, but all significant associations at P=0.05 would be presented in the tables in this section. When the statistical test of the differences of severe ROP rates among different level of exposures was significant at 0.01 (such as X^2 test significant at 0.01), the corresponding RR would also be significant at 0.01, theoretically, RR 99% CI would not include a value of one. RR CIs provided in this section were 95% CIs.

1 Parents Social Demographic Factors and Severe ROP

Six social demographic factors of parents were taken into account. The associations between these factors and severe ROP were examined. Apart from maternal race, no significant differences were observed in severe ROP incidence rates with respect to maternal age, marital status, maternal school years, paternal school years, and Blishen Index. Having a Native mother was associated with a significant (7-fold) increase in risk in development of severe ROP when it was compared to Black mothers (shown in Table 4-26), although the number of both were low.

2 Maternal Factors and Severe ROP

Of all 14 factors (refer to chapter 4 part II) of mothers' previous obstetrical history, labour and delivery history of current delivery that were investigated, no significant associations were observed between these factors and development of severe ROP at α level 0.01. Only fetal heart monitor and maternal fever during delivery were significantly related to the development of severe ROP at α level 0.05 (Table 4-27).

3 Neonatal Characteristics and Severe ROP (Table 4-28)

No significant associations were found between severe ROP and infants sex, multiple birth, intrauterine growth status, Apgar score at 1 and 5 minutes, birth place, place of hospitalization, and the disposition. Only three factors among the neonatal basic characteristics investigated conferred at least a five-fold increase in risk to development of severe ROP. These are gestational weeks at birth, birth weight and the resuscitation procedures required.

Infants with gestational weeks 23-26 had 7.2 times the risk of developing severe ROP, and infants with gestational weeks 27-28 had 3.1 times the risk when they were compared with infants with gestational weeks 29-35.

To compare with infants with heavier birth weight (1000-1250), infants with birth weight 500-749 g had a 9.8 times increase in the risk to develop ROP and infants with birth weight 750-999 g had 3.4 times increase in risk.

Resuscitation with cardiac massage was associated with 5.8-fold increase in risk to develop severe ROP, compared with no resuscitation or resuscitation with oxygen only. Resuscitation with intubation was associated a 3.5 times in risk of developing severe ROP. This comparison was made among different procedures of resuscitation rather than "yes" or "no" to expose to resuscitation since only 4 infants did not required any resuscitation among 374 cohort.

4 Neonatal Follow-up Criteria, Hospital Stay and Severe ROP (Table 4-29)

Examining the follow up risk criteria separately, there is no significant association between severe ROP and congenital

infection, nor between severe ROP and neurological disorder. A strong association was observed between "on ventilator" as a risk criteria and the development of severe ROP (RR=6.9).

Compared with one risk criteria (birth weight 500-1250 g) describing why infants were follow-up by SA-PNFU Program, meeting four risk criteria was associated with a highly significant 15.6 fold increase in risk of developing severe ROP. Three risk criteria were associated with a 9.1 increase in risk in development of severe ROP.

Longer length of hospital stay measured in acute NICU days, total NICU days and total hospital days separately, were identified as strong risk factors to development of severe ROP. Acute NICU stay two months or longer was associated 7.4 times risk in development of severe ROP, compared with acute NICU stay of less than one month. Total NICU stay three months or longer was associated with 13.3 times risk in development of severe ROP, compared with total NICU stay of a month. Total hospital stay 4 months or longer was associated with a 13.3 times risk in development of severe ROP, compared with total hospital stay within two months.

5 Neonatal Ventilatory Assistance, O_2 supplementation and Severe ROP (Table 4-30)

Of 344 infants under analysis, only 27 infants never received any ventilatory assistance during their stay in NICU and none of them developed severe ROP. Comparison of incidence rates of severe ROP was made between two groups: a) infants who received ventilatory assistance and beginning within one hour after birth; b) infants who never received ventilatory assistance or received ventilatory assistance but starting at one hour or later after birth. The results show that infants who received ventilatory assistance within one

hour after birth had 5.3 times the risk of developing severe ROP.

Of 317 infants who received ventilatory assistance, 99.7% (316 infants) were supplied with positive pressure ventilation (PPV). Twenty eight infants never received PPV and none of them developed severe ROP. Compared to the infants who received PPV under eight days or zero days, infants who received PPV 28 days or longer had 5.0 times the risk of developing severe ROP. No significant association was found between duration of other ventilatory assistance and severe ROP.

Highest inspiration ventilator pressure of 30 cmH_2O or more was significantly associated with a 3.8 increase in risk in development of severe ROP, compared with that under 20 cmH_2O. Highest inspiratory ventilator pressure of 20-29 cmH_2O was associated with a 2.3-fold increase in risk of developing severe ROP, compared with that under 20 cmH_2O.

Highest expiratory pressure 5 cmH_2O or more was also found to be significantly associated with development of severe ROP when it was compared with cmH_2O under 5 (RR=2.0).

Five or more arterial O_2 measurements above 100 during ventilatory assistance was associated with a highly significant, 12.9-fold increase in risk in developing severe ROP, and 1-4 arterial O_2 measurements more than 100 was associated with a 6.4- fold increase in risk of developing severe ROP, compared to zone times. If infants who were experienced 5 times or more capillary O_2 pressure more than 50 during ventilatory assistance, the chance of them developing severe ROP was increased to 4.6 times, compared with the infants who were never received ventilator assistance or experienced no capillary PO_2>50.

Highly significant association between the duration of oxygen administration and development of severe ROP was observed. Compared to the infants whose O_2 supplementation were within a month or zero (never received O_2), infants who received O_2 90 days or longer have 12.1 times the risk of developing severe ROP, and infants who received O_2 between 60 and 89 days had 6.4 times the risk of developing severe ROP. Infants who received O_2 between 30 and 59 days had 2.9 times the risk of developing severe ROP.

If infants were ventilated more than once during their NICU stay, their chance to develop ROP was 2.1 times increased, compared with infants who received ventilatory assistance once or not at all.

The associations between different complications of ventilatory assistance and severe ROP were examined and results were given in Table 4-30(continued). All of these complications were significantly associated with the development of severe ROP. The RRs ranged from 2.5 to 3.5.

6 Neonatal Respiratory Problems and Severe ROP (Table 4-31)

The association between apnea and severe ROP was examined in different ways: treatment procedures for apnea affected infants, age of apnea onset, and duration of apnea. No significant associations were found.

Several respiratory risk factors conferring at least a 1.9-fold in increase in risk of developing severe ROP were identified: respiratory distress syndrome (RDS, RR=3.2), pneumothorax (RR=1.9), bronchopulmonary dysplasia (BPD, RR=4.8), emphysema (RR=2.6), atelectasis (RR=3.7), other pulmonary problems (RR=2.3). Transient tachypnea of newborn (TTN) was found as a protective factor for development of

severe ROP (RR=0.3).

The majority of atelectasis and emphysema cases identified here were also diagnosed as the complications of ventilatory assistance.

7 Neonatal Drug Utilization and Severe ROP (Table 4-32)

The total number of drugs used during in hospital was identified as a risk factor for the development of severe ROP. Compared to the infants who received less than 10 drugs, infants who were received 15 drugs or more had a 11.4-fold increase in risk of developing severe ROP. Infants who received 10 to 14 drugs had a 3.7-fold increase in risk in development of severe ROP.

8 Other Neonatal Factors and Severe ROP (Table 4-33)

Among three cardiovascular factors examined (PDA, VSD, PFC), only patus ductus arteriosus (PDA) was found to a have significant association with the development of severe ROP. Compared to the infants with no PDA, Infants diagnosed as having PDA and undertaking surgical treatment had 4.3 times the risk of developing severe ROP. Infants diagnosed as having treated with drugs only had 3.3 times the risk of development of severe ROP.

Among 344 infants studied, only 43 did not need parenteral feeding, and there 43 were not observed as having severe ROP. Parenteral feeding for 15 days or longer, was associated with a 2.2-fold increase in risk of development of severe ROP, compared with parenteral nutrition days under 15 days (including zero days). Infants who took all foods orally not before the age of 15 days or beyond had 3.5 times risk of developing severe ROP, compared with infants who took all food

orally under the age of 15 days.

For the three hematology factors examined, only the total number of blood or blood products transfusions was significantly associated with the development of severe ROP. Infants who were given the blood or blood products 10 times or more has a 8.8-fold increase in risk to develop severe ROP.

Intraventricular hemorrhage (IVH) was found significantly associated with the development of severe ROP (RR=2.2). The other types of intracranial hemorrhage (subarachnoid hemorrhage, cerebral hemorrhage) were not found to have that relationship.

Sepsis was associated with an 3.0 time increase in the risk of developing severe ROP. Hypoxic ischemic encephalopathy was not found to have relation to severe ROP.

Bivariate Analysis

1 Bivariate Analysis for selected variables

In univariate analysis, 36 risk factors were identified as significantly associated with severe ROP. The risk factors with RR great than four are listed in Table 4-34 according to the descending order of the magnitude of associations.

Seven variables among 36 were selected for further bivariate analysis according to the strength of the association, the biological plausibility or the clinical importance, and the comparable value with other related publications. They are maternal race, infants' birth weight, gestational age, # of follow up criteria, total hospital

days, total days of O_2 supply, and BPD.

Infants' birth weight and gestational age might be confounders or effect modifiers when the associations between the other 5 risk factors and severe ROP as assessed, since birth weight and gestational week are known risk factors for severe ROP, at the same time, they may be related to the level of exposure (such as total hospital days).

Stratified by birth weight (three strata 500-749, 750-999, 1000-1250) and gestational week (three strata 23-26, 27-28, 29-35) respectively, the association between severe ROP and maternal race, # of follow up risk criteria, total hospital days, total days of O_2 supply and BPD were evaluated and presented in Table 4-35. The Mantel-Haenszel weighted RR (RR_{MH}) was calculated as a pooled estimate of the association over three strata. The confidence interval for each RR_{MH} is provided. Statistical significance for each stratification analysis were determined by Mantel-Haenszel summary chi-square value (refer to chapter 3 part III for detailed methodology issue). Unadjusted (unstratified) analysis for those factors was also performed since the categories for risk factor here was binary which is different from the categories of risk of factor in univariate analysis.

Without adjustment, native mother was associated with an 4-fold increase in risk for severe ROP, comparing to non-native mothers. After stratification or adjustment, the association was still significant but with different magnitude. Stratified by birthweight, RR_{MH} was 3.42, and stratified by gestational weeks, the RR_{MH} was 3.14.

Infants with three or more follow up risk criteria had a highly significant increase in risk (RR=7.17) to develop severe ROP, compared to the infants with follow up risk

criteria less than three. This association was still significant when it was adjusted by birth weight (RR_{MH}=5.82) or by gestational week (RR_{MH}=5.51).

Total days of hospital stay 90 or longer was identified as a highly significant risk factor for severe ROP, comparing to the total days of hospital stay less than 90 days. The relative risk was 3.38 with adjustment of birth weight, 3.46 with adjustment of gestational week, 4.83 without any adjustment.

Stratification by birth weight and gestational week respectively, total days of O_2 supply 31 days or more was associated with an 4.12-fold increase in risk, and 3.87-fold increase in risk to develop severe ROP when it was compared to the total days of O_2 supply less than 31 days. The crude RR for this association was 6.30.

Compared to infants without bronchopulmonary dysplasia (BPD), infants with BPD had 2.7 times risk to develop severe ROP after adjusted by birthweight, and had 2.8 times risk to develop severe ROP after adjusted by gestational week, and have 4.8 times risk to develop severe ROP without any adjustment.

Overall, native mother, three or more follow up risk criteria, 90 days or longer hospital stay, more than 30 days of O_2 exposure, and BPD were significant risk factors for severe ROP after adjusted by birthweight and gestational week. Birth weight and gestational week were the possible effect modifiers or confounders of the associations between those factors and the risk of severe ROP.

Table 4-26 Parents socio-demographic factors and severe ROP

Factor		Severe ROP cases	n	%	RR(RR 95% CI)	X^2	P-value
Maternal Race (325)	Native	7	10	70.0	7.0(1.0-47.0)	19.73	<0.01
	other	8	29	27.6	2.8(0.4-19.4)		
	Caucasian	46	276	16.7	1.7(0.3-10.9)		
	Black	1	10	10.0			

Table 4-27 Maternal factors and severe ROP (344 infants)

Variable		Severe ROP cases	n	%	RR(RR 95% CI)	X^2	P-value
Fetal heart monitor							
	yes	61	287	21.3	2.3(0.95-5.34)	4.00	<0.05
	no	5	53	9.4			
	(missing=4)						
Maternal fever							
	yes	12	40	30.0	1.8((1.03-3.0)	3.89	<0.05
	no	50	293	17.0			
	(missing=11)						

Table 4-28 Neonatal characteristics and severe ROP

Variable		Severe ROP cases	n	%	RR(RR 95% CI)	X^2 (P value) X^2_{LT} (P value)
Gestational weeks (344)	23-26	42	114	36.8	7.2(2.94-17.35)	5.60<0.001
	27-28	19	113	14.3	3.1(1.03- 9.79)	
	29-35	5	97	5.2		
Birth weight (344)	500- 749	26	63	41.3	9.8(4.06-24.00)	36.66<0.001
	750- 999	30	132	22.7	3.4(1.72- 6.66)	
	1000-1250	10	149	6.7		
5 minutes Apgar (343)	0- 2	7	28	25.0	2.0(0.90-4.33)	5.24 <0.05
	3- 7	43	189	22.8	1.8(1.06-3.04)	
	8-10	16	126	12.7		
Resuscitation required						
cadiac massage		4	11	36.4	5.8(1.70-19.89)	9.95 <0.01
intubation		58	269	21.6	3.5(1.30- 9.15)	
O_2 only, or none (344)		4	64	6.3		

Table 4-29
Neonatal follow-up criteria, hospital stay and severe ROP

Variable		Severe ROP cases	n	%	RR(RR 95% CI)	X^2 P-value X^2_{LT} P-value
FOLLOW-UP CRITERIA (344)						
on ventilator	yes	61	220	27.7	6.9(2.84-16.66)	28.72<0.001
	no	5	120	4.0		
congenital infection	yes	4	7	57.1	3.1 (1.57-6.13)	Fisher<0.05
	no	62	337	18.4		
neurological disorder	yes	11	32	34.4	2.0 (1.14-3.33)	5.25 <0.05
	no	55	312	17.6		
# of risk criteria	4	13	25	52.0	15.6(4.82-50.49)	47.27<0.001
	3	45	148	30.4	9.1(2.92-28.49)	
	2	5	81	6.2	1.9(0.46- 7.51)	
	1	3	99	3.3		
HOSPITAL STAY						
acute NICU days (344)	>61	38	93	26.3	7.4(3.47-15.86)	41.80<0.001
	31-60	21	124	16.9	3.1(1.35- 6.97)	
	<31	7	127	5.5		
total NICU days (344)	>91	43	89	48.3	13.3(3.35-52.67)	55.78<0.001
	61-90	16	105	15.2	4.2(1.00-17.57)	
	31-60	5	95	5.3	1.5(0.29- 7.21)	
	<31	2	55	3.6		
total hospital days (322)	>121	25	55	45.3	13.3(2.89-46.49)	42.71<0.001
	91-120	24	86	127.9	7.1(1.75-28.89)	
	61- 90	11	130	8.5	2.2(0.50- 9.40)	
	<61	2	51	3.9		

Table 4-30
Ventilatory assistance, O_2 supplementation and severe ROP

Variable		Severe ROP cases	n	%	RR(RR 95% CI)	X^2 P-value X^2_{LT} P-value
Ventilator assistance(344)	yes	66	317	20.8	NA	6.96 <0.01
	no	0	27	0.0		
age hours of onset(344)*	<1	64	295	21.7	5.3(1.34-21.01)	8.41 <0.01
	>1	2	22	9.1		
	0	0	27	0.0		
Days of PPV (344)*	>28	46	126	36.5	5.0(2.71-9.26)	37.01<0.001
	8-27	9	67	13.4	1.8(0.80-4.24)	
	1- 7	11	123	8.9		
	no	0	28	0.0		
Days of other ventilatory assistance (344)	>3	24	92	26.1	2.0(1.14-3.38)	6.18 <0.05
	1-2	23	109	21.1	1.6(0.91-2.76)	
	0	19	143	13.3		
Maximum inspiratory pressure (cmH_2O,344)*	>30	20	59	33.9	3.8(1.87-7.88)	15.31<0.001
	20-29	37	183	20.2	2.3(1.15-4.55)	
	1-19	9	74	12.2		
	0	0	28	0.0		
Maximum expiratory pressure (cmH_2O, 343)*	>5	27	89	30.3	2.0(1.29-3.03)	9.52<0.01
	1-4	39	227	17.2		
	0	0	27	0.0		
# of arterial PO_2>100 (344)	>5	37	118	31.4	12.9(1.82-90.75)	19.71<0.001
	1-4	28	179	15.1	6.4(0.90-45.79)	
	0	1	41	2.4		
# of capillary PO_2>50 (344)	>5	38	104	36.5	4.6(2.26-9.40)	27.16<0.001
	1-4	20	139	14.4	1.8(0.84-3.99)	
	0	8	101	7.9		

* For the marked variables, the "0" or "no" group did not develope severe ROP. The calculation of RR and X^2 for these variables combined last two groups together.

Table 4-30 Ventilatory assistance, O_2 supplementation and severe ROP (continued)

Variable		Severe ROP cases	n	%	RR(RR 95% CI)	X^2 P-value X^2_{LT}P-value
Total days in O2(344)	>90	35	73	48.6	12.1(4.95-29.49)	59.45<0.001
	60-89	17	67	25.4	6.4(2.47-16.57)	
	30-59	9	79	11.4	2.9(1.00- 8.26)	
	0-29	5	126	4.0		
Episode of ventilatory support>1(344)	yes	36	126	28.6	2.1(1.35-3.20)	11.30<0.001
	no	30	218	13.8		
COMPLICATION DURING VENTILATORY ASSISTANCE						
prolonged hypoxia(343)	yes	27	69	39.1	2.8(1.82-4.16)	21.99<0.001
	no	39	274	14.2		
prolonged acidosis(343)	yes	17	35	48.6	3.1(1.99-4.68)	21.58<0.001
	no	49	308	15.9		
post extubation airway obstruction(344)	yes	34	98	34.7	2.7(1.75-4.07)	21.26<0.001
	no	32	216	13.0		
other extra-pleural air(341)	yes	5	8	62.5	3.5(1.94-6.22)	Fisher<0.01
	no	60	333	18.0		

Table 4-31 Neonatal respiratory problems and severe ROP

Variable		Severe ROP cases	n	%	RR(RR 95% CI)	X^2	P-value
Apnea duration (days, 334)	≥30	35	122	28.7	1.5(0.89-2.47)	3.88	<0.05
	1-29	14	124	11.3	0.6(0.30-1.12)		
	none	17	88	19.3			
Respiratory distress syndrome(324)	yes	57	232	24.6	3.2(1.52-6.81)	11.95	<0.001
	no	7	92	7.6			
Pneumothorax (344)	yes	20	64	31.3	1.9(1.21-2.98)	7.38	<0.01
	no	46	280	16.4			
Transient tachypnea(337)	yes	5	72	6.9	0.3(0.13-0.74)	8.96	<0.01
	no	60	265	22.6			
Brochopulmonary dysplasia(335)	yes	57	211	27.0	4.8(2.25-10.16)	23.08	<0.001
	no	7	124	5.6			
Emphysema (330)	yes	24	65	36.9	2.6(1.71-4.09)	18.26	<0.001
	no	37	265	14.0			
Atelectasis (333)	yes	53	182	29.1	3.7(2.03-6.60)	23.55	<0.001
	no	12	151	7.9			
Other pulmonary problems(342)	yes	27	79	34.2	2.3(1.51-3.51)	14.60	<0.001
	no	39	263	14.8			

Table 4-32 Neonatal drug utilization and severe ROP(344 infants)

Variable		Severe ROP cases	n	%	RR (RR 95% CI)	X^2_{LT}	P-value
# of drugs used	≥15	49	125	39.2	11.4(4.24-30.51)	50.02	<0.001
	10-14	13	103	12.6	3.7(1.23-10.87)		
	0- 9	4	116	3.4			

Table 4-33 Other neonatal factors and severe ROP

Variable		Severe ROP cases	n	%	RR (RR 95% CI)	X^2 P-value X^2_{LT}P-value
CARDIOVASCULAR						
PDA	yes & surgery	22	68	32.4	4.3(2.14-8.63)	20.76<0.001
	yes & drug	34	137	24.8	3.3(1.84-9.33)	
	no	10	134	7.5		
NUTRITION AND FEEDING						
parenteral* days(344)	≥15	41	149	27.5	2.15(1.37-3.36)	11.77<0.001
	1-14	25	152	16.4		
	0	0	43	0.0		
age of all food taken orally (day, 326)	≥15	49	162	30.2	3.5(2.04-6.16)	24.64<0.001
	<15	14	164	8.5		
HAEMATOLOGY						
# of blood products given(344)	≥10	45	105	42.9	8.8(2.23-34.56)	58.26<0.001
	5-9	16	98	6.3	3.4(0.81-13.90)	
	1-4	3	100	3.0	0.6(0.11- 3.55)	
	0	2	41	4.9		
Min. hematocrit (344)	<280	27	115	23.5	2.3(1.16-4.47)	5.59 <0.05
	280-319	29	132	22.0	2.1(1.09-4.16)	
	≥320	10	97	10.3		
HEMORRHAGE						
intra-ventricular hemorrhage(344)	yes	31	98	31.6	2.2(1.46-3.91)	13.69<0.001
	no	35	246	14.2		
Sepsis (202)	yes	28	81	34.6	3.0(1.68-5.32)	15.58<0.001
	no	14	121	11.6		

* 43 infants never had parenteral feeding, none of them developed ROP. The last two groups (0, 1-) were combined together when calculated RR and X^2.

Table 4-34 Summary of the univariate analysis of risk factors to severe ROP*

Factors	RR		Explanation
# of follow up risk Criteria	15.6		4 criteria vs LBW only
		9.1	3 criteria vs LBW only
Total hospital days	13.3		>120 vs <60
		7.1	91-120 vs < 60
Total NICU days	13.3		>90 vs <30
		4.2	61-90 vs <30
# of arterial P02>100	12.9		>5 vs no
Total days of O2	12.1		>90 vs <30
		6.4	60-90 vs <30
# of drug used	11.4		>15 vs <10
Birth weight	9.6		<750 vs 1000-1250
# of blood products given	8.8		>10 vs no
Native mother	7.5		compared with black mother
Acute NICU days	7.4		>60 vs <30
Gestational week	7.2		23-26 vs 29-35
On ventilator as follow criteria	6.9		yes vs no
Adverse drug reaction	6.4		combination(BPD/ROP & others vs others or none
Resuscitation	5.8		cardiac massage vs O2 only/none
Age of ventilatory assistance onset	5.3		with 1 hour of birth vs >1 hour or none
BPD	4.8		yes vs no

* Select the RRs 4.0 or greater.

Table 4-35 Risk factors analysis for severe ROP with stratification of birth weight and gestational weeks

Risk Factor	Unstratified		Stratified by BW		Stratified by GW	
	RR	RR 95% CI (X^2 P-value)	RR_{MH}	RR_{MH} 95% CI (X^2_{MH} P-value)	RR_{MH}	RR_{MH} 95% CI (X^2_{MH} P-value)
Maternal Race Native vs non-native (325)	4.01	2.50-6.42 17.33 <0.001	3.42	2.51-4.67 12.53 <0.001	3.14	2.20-4.49 10.39 0.001
# of Follow Risk Criteria ≥3 vs <3 (344)	7.17	3.53 -14.55 46.16 <0.001	5.82	2.40-14.11 22.90 <0.001	5.51	2.35-12.90 22.35 <0.001
Total Hospital Days ≥91 vs <91 (322)	4.84	2.74- 8.56 38.75 <0.001	3.38	1.70-6.75 14.30 0.002	3.46	1.71-7.03 14.03 <0.001
Total Oxygen Days ≥31 vs <31 (344)	6.30	2.80-14.18 30.12 <0.001	4.12	1.61-10.54 11.00 <0.001	3.87	1.46-9.80 8.91 0.003
BPD yes vs no (335)	4.79	2.25-10.16 23.08 <0.001	2.66	1.22-5.80 6.49 0.011	2.80	1.19-6.60 5.88 0.015

IV Cicatricial ROP and Visual Outcome

Cicatricial ROP and visual outcome were assessed at four months as well as 12 months adjusted age for the followed infants. The relationships between acute severe ROP and cicatricial ROP, and acute severe ROP and visual outcome at these two time points were examined separately and results follow.

Four Months Adjusted Age

The case inclusion criteria for ophthalmological examination at four months adjusted age follow up was given in part II of this chapter (page 46). There were 298 infants followed for cicatricial ROP and visual outcome.

1 Prevalence Rate of Cicatricial ROP and its Relationship with Acute Severe ROP

Table 4-36 gives the prevalence rate of cicatricial ROP and correspondence 95% confidence interval for worst eye at four months adjusted age. Cicatricial ROP affected 13.8% (9.6, 18.0) of the followed infants at this time cut-off. Of 36 cicatricial ROP cases identified, 10 were grade 1, one was grade 2, but the majority of them (25) were not graded.

Acute severe ROP was associated with a significant 6.5-fold increase in risk in developing cicatricial ROP at 4 months adjusted age (Table 4-37). 47.7% of infants who had been found to have severe ROP developed cicatricial ROP by four months adjusted age. The rate in infants who were never observed as having severe ROP (no ROP or ROP under stage 3), was only 7.4%.

2 Visual Outcome

1) Visual outcome description

Abnormal visual acuity was found in 3.7% of infants, and suspect visual acuity was found in 16.4% of infants. Upon refraction, 16.9% of infants were found to be abnormal, and 34.8% of infants were considered as "suspect". Only 2.2% of infants were confirmed to have strabismus, with 8.2% of infants were suspected of having strabismus.

There were large numbers of cases with missing information and large numbers of suspect cases in terms of visual outcome assessment at this time point. Two hundred and ninety-eight (298) infants were followed by SA-PNFU program by four months adjusted age, but only 189 (63.4%) infants had visual acuity recorded and, 178 infants ((59.7%) had refraction information. "Suspect" cases outweighed the confirmed cases for all kinds of visual outcome indicators.

2) The relationship between acute severe ROP and visual outcome

Since there were such a large number of suspect cases, the relationships between acute severe ROP and visual outcomes at four months adjusted age were evaluated including then excluding suspect cases separately. The results are given in Table 4-39a and 39b.

When the suspect cases were excluded from the abnormal visual outcomes, no significant association was found between acute severe ROP and visual acuity, refraction, or strabismus. Acute severe ROP was significantly associated with abnormal visual acuity (RR=3.39), abnormal refraction (RR=1.38) and strabismus (RR=2.65) when the suspect cases were included in

abnormal group.

Twelve Months Adjusted Age

The case inclusion criteria for ophthalmologic examination at the 12 months adjusted age follow up was given in part II of this chapter (page 47). In total, 218 infants were followed at this time point and estimates and analysis of prevalence rate of cicatricial ROP and visual outcome were followed.

1 Prevalence Rate of Cicatricial ROP and its Relationship with Acute Severe ROP

The prevalence rate of cicatricial ROP at 12 months adjusted age for worst eye of followed infants was 7.7%, with confidence interval 3.5% to 12.0%. Of 12 identified cicatricial ROP cases, one was grade 1, seven were grade 2, one was grade 3, two were grade 4. Information for prevalence rate estimation was missing in 63 (28.9%) subjects. Table 4-40 gives the detailed figures.

Twenty-five percent of infants who had previous acute severe ROP were observed having cicatricial ROP at 12 months adjusted age, but no infants who had never been diagnosed as having severe ROP previously were found to have cicatricial ROP at this time point (Table 4-41). The difference in cicatricial ROP prevalence rates between these two groups was highly statistically significant, but calculation of relative risk was not feasible since a zero value was encountered in the denominator.

2 Visual Outcome

1) Visual outcome description

Higher proportions of abnormal visual outcomes were observed at this time point, compared to that at four months adjusted age. Seven percent of infants had abnormal visual acuity, and 12.9% of infants were suspected of having abnormal visual acuity. Abnormal refraction was found in 16.9% of infants and suspect refraction problem was found in 34.8% . Only 2.2% of infants were confirmed as having strabismus, while 8.2% of infants were suspected of having strabismus.

The number of cases with missing information regarding visual outcome was also large; 63(29%) for visual acuity, 85(40%) for refraction, and 59(27%) for strabismus. There was also a large proportion of suspect cases in each visual outcome indicator.

2) The relationship between acute severe ROP and visual outcome

The relationship between acute severe ROP and cicatricial ROP at 12 months adjusted age were evaluated and presented in Table 4-43a and 43b.

Excluding the suspect cases from each visual outcome indicator, acute severe ROP were significantly associated with an increased risk of developing abnormal visual acuity and abnormal refraction. The relative risks were 4.46 and 2.76 respectively.

Taking the suspect cases as abnormal, acute severe ROP was significantly associated with an increased risk in

abnormal visual acuity (RR=2.26), abnormal refraction (RR=1.80) and strabismus (RR=2.19).

Table 4-36 Prevalence rate of cicatricial ROP at four months adjusted age (worst eye, 298 infants)

Cicatricial ROP	Frequency	%	95% CI
No	225	86.2	82.0 - 90.4
Yes	36	13.8	9.6 - 18.0
grade 1	10	3.8	-
grade 2	1	0.4	-
not graded	25	9.8	-
(missing=37)			

Table 4-37 The relationship between acute severe ROP and cicatricial ROP at four months adjusted age (298 infants)

Severe ROP	Cicatricial ROP cases	N	%	RR (RR 95% CI)	X^2	P-value
Yes	21	44	47.7	6.49(3.65-11.56)	47.6	0.0000
No	15	204	7.4			
(missing=50)						

Table 4-38 Visual outcomes at four months adjusted age (worst eye, 298 infants)

Item	Frequency	%	95% CI
Visual acuity			
abnormal	7	3.7	1.0 - 6.4
suspect	31	16.4	11.1 - 21.7
normal	151	79.9	74.2 - 85.6
(missing=109)			
Refraction			
abnormal	30	16.9	11.4 - 22.4
suspect	62	34.8	27.8 - 41.8
normal	86	48.3	40.9 - 55.7
(missing=120)			
Strabismus			
abnormal	6	2.2	0.5 - 4.0
suspect	22	8.2	4.9 - 11.5
normal	240	89.6	85.9 - 93.2
(missing=30)			

Table 4-39a The relationship between severe ROP and visual outcomes at four months adjusted age (excluding suspect cases)

	Visual Acuity (146)			Refraction (112)			Strabismus (232)		
	abnormal	N	%	abnormal	N	%	abnormal	N	%
Severe ROP									
Yes	2	14	14.3	7	21	33.3	2	37	5.4
No	5	132	3.8	22	91	24.2	4	195	2.1
RR (RR 95% CI)	3.70 (0.80-17.67)			1.38 (0.68- 2.79)			2.64 (0.50-13.87)		
X^2 (P-value)	Fisher's (0.1359)			0.75 (0.3879)			Fisher's (0.2449)		

Table 4-39b The relationship between severe ROP and visual outcomes at four months adjusted age (including suspect cases)

	Visual Acuity (177)			Refraction (173)			Strabismus (251)		
	abnormal & suspect	N	%	abnormal & suspect	N	%	abnormal & suspect	N	%
Severe ROP									
Yes	14	26	53.8	27	41	65.9	9	44	20.5
No	24	151	15.9	63	132	47.7	16	207	7.7
RR (RR 95% CI)	3.39 (2.03-5.65)			1.38 (1.04-1.83)			2.65 (1.25-5.60)		
X^2 (P-value)	18.95 (0.000)			4.12 (0.042)			Fisher's(0.022)		

Table 4-40 Prevalence rate of cicatricial ROP at 12 months adjusted age (worst eye, 218 infants)

Cicatricial ROP	Frequency	%	95% CI
No	143	92.3	88.1 - 96.5
Yes	12	7.7	3.5 - 12.0
grade 1	1	0.6	-
grade 2	7	4.5	-
grade 3	1	0.6	-
grade 4	2	1.3	-
not graded	1	0.6	-
(missing=63)			

Table 4-41 The relationship between acute severe ROP and cicatricial ROP at 12 months adjusted age (218 infants)

Severe ROP	Cicatricial ROP			RR(RR 95% CI)	Fisher's exact test P-value
	cases	n	%		
Yes	10	40	25.0	NA	0.000
No	0	105	0.0		
(missing=73)					

Table 4-42 Visual outcomes at 12 months adjusted age (worst eye, 218 infants)

Item	Frequency	%	95% CI
Visual acuity			
abnormal	11	7.1	3.1 - 11.1
suspect	20	12.9	7.6 - 18.2
normal	124	80.0	73.7 - 86.3
(missing=63)			
Refraction			
abnormal	26	19.5	12.8 - 26.3
suspect	27	20.3	13.5 - 27.1
normal	80	60.2	51.8 - 68.5
(missing=85)			
Strabismus			
abnormal	16	10.1	5.4 - 14.7
suspect	15	9.4	4.9 - 14.0
normal	128	80.5	74.3 - 86.7
(missing=59)			

Table 4-43a The relationship between severe ROP and visual outcomes at 12 months adjusted age (excluding suspect cases)

	Visual Acuity (125)			Refraction (100)			Strabismus (133)		
	abnormal	N	%	abnormal	N	%	abnormal	N	%
Severe ROP									
Yes	5	34	14.7	13	30	43.3	5	34	14.7
No	3	91	3.3	11	70	15.7	8	99	8.1
RR (RR 95% CI)	4.46	(1.13-17.66)		2.76	(1.40-5.44)		1.82	(0.64-5.19)	
Fisher's exact text		0.033			0.003			0.316	

Table 4-43b The relationship between severe ROP and visual outcomes at 12 months adjusted age (including suspect cases)

	Visual Acuity (144)			Refraction (125)			Strabismus (148)		
	abnormal & suspect	N	%	abnormal & suspect	N	%	abnormal & suspect	N	%
Severe ROP									
Yes	13	42	31.0	22	39	56.4	13	42	31.0
No	14	102	13.7	27	86	31.4	15	106	14.2
RR (RR 95% CI)	2.26	(1.16-4.38)		1.80	(1.18-2.73)		2.19	(1.14-4.19)	
X^2 (P-value)	5.80	(0.016)		7.05	(0.008)		5.54	(0.019)	

CHAPTER 5 DISCUSSION

The discussion will mainly focus on two research questions to be answered: First, what are the incidence, prevalence and timing of ROP of ROP among preterm infants born in Southern Alberta between 1985-1990 with birthweight 500-1250g? Second, what factors are associated with development of acute severe ROP? In addition, the discussions on other study findings as well as the strength and limitations of this study are provided.

I The Development of Severe ROP

1 Incidence and Prevalence of ROP

The results of this study, a population based retrospective cohort study in Southern Alberta, showed that acute ROP was very common, affecting 70% (95% CI 65.5%-75.1%) of infants with birthweight 500-1250 g (Table 4-21). The incidence of ROP in infants birthweight less than 1000 g was 84.1% and in infants birth weight less than 750 g, it was 88.9% (data not show). Severe ROP affected almost one-fifth of study infants (19.2%, 95% CI 15.0%-23.3%). The rate in infants birthweight less than 1000 g was 28.7% and in infants birthweight less than 750 g it was 41.3% (Table 4-22).

There is little information available on the epidemiology of ROP since it was first recognized in the early 1940s (Terry, 1942; Ng et al, 1988; Alberman, 1985). The previous investigations of the incidence of ROP were difficult to compare with each other because of variation in the nature of preterm populations, methodology of examinations, and previous lack of a ROP classification. Furthermore, the majority of previous studies were hospital-based or center-based. The

need for population-based studies of the incidence of ROP as a preliminary to a better understanding of the aetiology , prevention, and treatment of this disorder has been highly emphasised(Phelps, 1979; Alberman,1985). There have been three population-based or multicenter based ROP incidence studies to date and comparison between these studies and this thesis project was made and presented in Table 5-1. All compared studies used ICROP I (1984) for acute ROP classification.

The multicenter trial of cryotherapy for ROP in U.S.A is the largest ROP incidence study to date (Palmer et al, 1991). The study had a sample of 4099 infants representing about 15% of the lowest birth weight infants receiving care in the United States. The results of this study were summarized in Table 5-1. The findings of this thesis project were very close to the findings of the multicenter study, but a little higher in overall ROP incidence rate and severe ROP incidence rate. The methodology of these two studies was quite similar except that the multicenter study also monitored the ROP incidence in infants with birthweight less than 500 g and the sample size was much bigger than this thesis project; data utilized in this thesis project was collected using direct ophthalmoscopy to examine the retina rather than the indirect ophthalmoscopy which was used in multicenter study. The infants who were followed for this thesis project were more premature and sicker than infants lost from the overall target population, but the multicenter study did not provide related information on lost group. The socio-demographic factors of infants differed between the two studies including a higher black race percentage (38.6%) in the multicenter study. All of these differences could contribute to the possible explanations for the slight difference in the incidence of ROP for these two studies. Of course, "by chance" should be taken into account as a possible explanation for the slight rate difference of ROP.

Darlow (1988) reported a New Zealand nationwide ROP incidence study and the incidence of ROP and severe ROP were much lower than the findings of this thesis project findings (Table 5-1). These differences could be explained largely by the differences in methodology of examination for these two studies. The first eye examination for New Zealand study was at 6-9 weeks and the frequency of examination was low, only 28% had more than two examinations. For this thesis project, the first eye examination was at 4-6 weeks and 91.1% of the study subjects had more than two examinations. The frequency of eye examinations averaged 5.6 times for every followed infant.

Previous investigations had shown that the mild stages of ROP could be detected before 6 weeks chronological age and could be completely resolved within a few weeks; the age of onset for various stages of ROP could be different (White et al, 1991; Palmer et al, 1991; Flynn et al, 1987). So early start of first eye examination followed by sufficient frequency of eye examinations at reasonable intervals are very important in detecting the age of onset as well as the incidence of various stages of ROP. Since the first eye examination in New Zealand Study was later than the time that ROP could be detected and the frequency of eye examination was very low, some cases of various stages of ROP might be missed and the reported incidence of ROP was probably under-estimated.

Another possible explanation in the difference of ROP incidence is the study population selected. Compared to this thesis project which studied infants of birth weight 500-1250 g, the New Zealand study selected the infants birth weight 500-1499 which involved the heavier birthweight range 1251-1499 g. So, the New Zealand study would have a lower ROP incidence rate even if the methodology of eye examination were

the same as this thesis project because less premature infants were selected.

The incidence of ROP found in England (Ng et al, 1988) was also lower than that found in this thesis project. Less premature infant selection (BW 490-1500 g) is one possible explanation. Another explanation was the heavier composition of infants weighing <750 g at birth who have the highest risk to develop ROP among all three birth weight groups in this thesis project. The Ng's study had a much smaller proportion of infants in the birth weight category 490-750 g (2.1% of 331) than this thesis project in which 41.3% study subjects weighed 500-749 g at birth.

Other possible reasons for the variations of incidence of ROP among the four studies listed in Table 5-1 include: differences in the survival rate for the most immature newborn infants, variations of neonatal management, the experience of the eye examiners and environmental influences.

In summary, the incidence rate of ROP and severe ROP for this study is comparable to the findings of Multicenter study in United states which is the largest ROP study in the world to date, and higher than the other two reported population-based study. The incidence rate of ROP is reliable and valid in terms of the study design, the large sample size as well as the strategies of eye examination which reduce the probability of missing case for various stages of ROP.

Cumulative incidence was used to estimate the probability that individual very low birth weight infants (BW 500-1250 g) would develop ROP during the specified observation time (under four months adjusted age in general). If any stage of ROP was developed, the termination of observation was either the resolution or progression to a more advanced stage. If ROP

Table 5-1 Comparison of the previous population-based studies and this study

	Multicenter Trial of Cryotherapy for ROP (Palmer, et al, 1991)	New Zealand (Darlow, 1988)	East Midlands, England (NG, et al, 1988)	Southern Alberta Canada (This Study)
Study subjects	4099	313	331*	344
Birth weight(BW)	<1251 g	500-1499 g	490-1500 g	500-1250 g
ROP incidence	Overall 65.8%	Overall 21.0%	Overall 49.1%	Overall 70.3%
	BW	BW	BW	BW
	<750 90.0%	500- 999 49.0%	490- 750 100.0%	500- 749 88.9%
	750- 999 78.2%	1000-1499 11.0%	751-1000 87.3%	750- 999 81.8%
	1000-1250 46.9%		1001-1500 52.5%	1000-1250 53.3%
	BW <1000 81.6%		BW ≤1000 88.6%	BW <1000 84.1%
Severe ROP incidence	Overall 18.3%	Overall 3.8%	Overall 6.3%	Overall 19.2%
	BW <750 37.4%	BW	BW	BW
	750- 999 21.9%	500- 999 13.1%	490- 750 28.6%	500- 749 41.3%
	1000-1250 8.5%	1000-1499 0.4%	751-1000 19.1%	750- 999 22.7%
	BW <1000 26.4%		1001-1500 2.7%	1000-1250 6.7%
			BW ≤1000 20.0%	BW <1000 28.7%
Type of ophthalmoscope	Indirect	Indirect	Indirect	Direct
First eye Examination	4-6 weeks	6-9 weeks	3 weeks	4-6 weeks

* The original study subjects are 505 infants with birth weight 490-1700 g. For comparison reason, the writer summarized published ROP information of this study for infants with birth weight 490-1500 g.

did not develop at all, the termination of observation was the time of complete vascularization of the retina. Obviously, the length of follow-up, or the time in which the different stages of ROP could be observed was not uniform for the study subjects. Theoretically, a more precise estimate of the incidence rate , the incidence density, would be used to account for these varying time period of follow-up (Hennekens & Buring, 1987).

Unfortunately, there is no definite termination of observation recorded for each followed infant regarding exactly when vascularization was completed and ROP was resolved. For routine ophthalmologic examinations, the way the observation was conducted, was that it was usually stopped at a time close to complete vascularization, or when the judgement that ROP would not progress, but regress, has been reached. This brings difficulty in obtaining an accurate incidence density since the time of observation for each infant for each specific stage of ROP is the key element of the denominator when one calculates the incidence density of that specific stage of ROP, but has little influence on the accurate cumulative incidence. So in this thesis project, cumulative incidence was used as an estimate of incidence rate.

The study design is a retrospective cohort study and this made the estimate of incidence rate possible. The comprehensive database of the SA-PNFU program, detailed data collection for ophthalmologic examination which is the first hand data collection for this thesis project by the writer, made estimation of ROP prevalence rates in four time points possible. The prevalence rate quantifies the proportion of the existing cases of ROP in followed infant populations at a reference point in time. It does not estimate the probability or risk of ROP in the study population and it is a proportion

in nature, but it is very important in giving a snapshot of the ROP status at a given point in time and providing the useful information for health professionals in care planning.

Among the four time point estimates of ROP prevalence (first neonatal eye examination, near term, 4 month adjusted age and 12 months adjusted) made in this study, the near term was most important in terms of identifying severe ROP which was related to unfavourable retinal and functional outcome.

2 Age of Onset of Various Stages of ROP

ROP is a condition that develops some weeks after birth and resolves or deteriorates in the weeks following, and effective intervention is possible. Thus, detection of ROP is important from a therapeutic point of view as well as for monitoring the incidence of ROP in relation to other clinical factors (Tan & Cats, 1989). In addition, detection the timing of onset along with detecting incidence of various stages of ROP will benefit better understanding of the natural course of the disease as well as guiding practice for ophthalmologic examinations. In this study, the age of onset for various stages of ROP were recorded in both post-conceptional age (or adjusted age) and postnatal age (or chronological age) on the basis of the scheduled ophthalmologic examinations for the high risk population for ROP.

The ophthalmologic data obtained in this study indicated that both mild stages had very close timing of onset postnatally (chronological age, CA) as well as post-conceptionally (adjusted age, AA) (Table 4-23), the same was found for severe stages of ROP as well as plus disease. The mild stages of ROP were first observed at CA 47 to 56 days and AA -44 to -40 days; the severe stages of ROP and ROP plus

disease were first detected at CA 69 to 73 days and AA -26.5 to -24 days.

The age of onset for mild and severe stages of ROP was further examined in different birthweight and gestational week groups (Table 4-24, 25). The events of mild stages of ROP arose at different times for different birthweight categories when the time was that from birth to the event (CA) as measured by CA. Smaller infants had a higher incidence of mild ROP (data not shown), but took relatively longer for it to appear. Once again, the event of mild stages of ROP arose at almost the same point in time for different birthweight categories when the event was timed from conception to the event as measured by AA (Table 4-24). For severe stages of ROP, smaller babies took a longer postnatal time (CA) for the event to appear. But post-conceptional age (AA) of onset of severe ROP fluctuated in different birthweight groups ranging -33 days to -18.5 days (Table 4-25).

There have been several publications regarding the timing of ROP (Palmar et al, 1991; Flynn, 1983; Tan & Cats, 1988). Palmer et al (1991) found that the postnatal age of onset for threshold ROP was different in different birthweight categories, but AA for threshold ROP is almost same across birth weight categories. This thesis project found that AA for severe ROP was fluctuated across birthweight categories but within 14 days. It is probably because of the small case number (N=47) of severe stages of ROP found in this study.

The analysis of the age of onset for mild and severe ROP in different birthweight categories demonstrated that timing of various stages of ROP correlated more closely with post-conceptional age (AA) than postnatal age (CA) since the post-conceptional age is related to the maturity of the infants. This implied that the level of maturity was more important

than postnatal environmental influences in governing the timing of the vascular events.

Therefore, it will be more profitable to discuss the timing of ROP events in terms of post-conceptional age (Flynn, 1983; 1988) because this essentially corrected for the differences in birthweight. Implicating these research findings to ophthalmologic practice in detection the ROP, it was suggested that ophthalmologists take birthweight into account as an index of the infants' maturity when postnatal age (CA) is used for examination schedule purposes (Palmer et al, 1991). The practice of simultaneously considering both postnatal age and birthweight appears merely to be a surrogate for the post-conceptional age whenever dealing with time issues. Of course, when considering only the incidence of ROP, not the timing of its occurrence, birthweight is an important variable.

With the findings of timing of various stages of ROP in different birthweight categories (Table 4-24, 25), the reverse relationship between prevalence rate of ROP at first neonatal ophthalmologic examination and birthweight (Table 4-14) could be explained. The crucial point here is that time point cut-off was set at chronological age 4-5 weeks with median CA 33 for all birthweight categories (Table 4-12), but infants in different birthweight categories, took different CA but almost the same AA to develop ROP (Table 4-24, 25). Since the median age of onset for mild ROP was at CA 47-56 and AA -44 to -40 days (table 4-23) for all infants, more than 50 % of mild ROP had not developed yet at this time point. The smallest babies (birth weight 500-749) at this time needed the longest extra chronological time to develop mild stages of ROP (on average of 60-33=27 days) and of course, the smallest proportion of all mild cases in this birthweight category had developed at this time. The heaviest infants with birthweight

1000-1250 needed the shortest chronological time to develop mild stages of ROP (on average of 43-33=10 days), so a relatively large proportion of mild ROP cases in total in this category had developed. This is why the reverse relationship was found when the time of observation was set at CA 4-5 weeks. This example also reflected the limitation of the prevalence' implication that it cannot be used for etiology research. Based on this reverse finding we can not generalize the hypothesis that heavier infants had a higher chance to develop mild stages of ROP. The prevalence rate merely tells the ROP status at a given time point (Rothman, 1987).

II Risk factors

1 Methodology Issue

The first part of the risk analysis, univariate analysis, was proposed to screen out the risk factor from all independent variables considered, the potential risk factors. Since almost 85 associations between potential risk factors and severe ROP were studied, caution should be paid in interpretation of P-values or "significance" tests.

Supposing "significance" testing is performed using the P=0.05 level as "significant" for these 85 associations, there would be about 4 to 5 "significant" relationships even though there was no real association in the data. These "false" positive associations represent type I or alpha error. That is, "statistically significant" associations that occur only by chance. The point here is that chance "guarantees" a certain proportion of such associations, and when many associations are studied, many "false" positive associations are possible and the credibility of a given significant result

is diminished (Rothman, 1986; Thompson, 1987).

There are different ways to deal with type I error in multi-comparisons including p-value adjustment and reporting the total number of comparisons made, but none is perfect (Rothman, 1986). Thompson's opinion (1987) was that large numbers of comparisons did greatly increase the likelihood of inappropriately excluding the null value for at least one of total set of associations examined, but the result for a particular association depended in no way on what else had been examined. What made a particular positive finding suspect was its low biological plausibility and the paucity of prior data in support of it.

In this thesis project, with the recognition of "false" positive errors at the time of multi-comparisons, the screening criteria for statistical "significance" for the 85 associations was set more stringently, at 0.01, to reduce the chance of "false" positive errors. Clearly, when a smaller type I errors is feasible, the chance of "false" negative, or type II errors is increased. Meanwhile, the number of negative associations reported along with the number of positive associations, although only those associations significant at 0.05 would be listed on the tables in the univariate risk factor analysis section.

The Confidence intervals (CIs) are relatively wide for several suggestive RRs. This is largely because of the small number of affected children, and small sample size for the subgroup infants.

2 Risk Factors Analysis

The etiology of ROP is not yet conclusively defined. Overwhelming evidence from epidemiologic studies for the

assumption that a principal role of both immaturity of retinal vascularization and oxygen administration has repeatedly been described. The previous reports also covered some other risk factors like infant ethnic origin, the prenatal factors, although it is controversial. All of those risk factors for the development of ROP previously reported are summarized in Table 1-1. As mentioned before, the previous researchers were mainly hospital-based or center based studies with major study interest on the associations of risk factors and the ROP development. So, generalizability and comparability for the findings generated from some reported studies were limited.

In this geographical population-based study, we were able to provide the estimate of incidence rate for various stages of ROP, and so the relative risk could be calculated. Also, this study moves the emphasis on examining the associations between the risk factors and development of severe ROP, what was the second research question to be answered.

Firstly, the univariate analysis was performed for the all potential risk factors under investigation and to examine whether they were associated with the development of severe ROP. Of all 85 associations tested, 36 factors were found significantly associated with the development of severe ROP. The risk factors which demonstrated a very strong relation (defined as RR more than 4.0 defined in this study) to severe ROP were summarized in Table 4-34. The mechanism of most of these risk factors to development of severe ROP could be explained by the assumption of a principal role of either prematurity or oxygen exposure. The majority of identified risk factors to severe ROP were reliable and valid in terms of the strength of association, biological plausibility, and the comparability to the previous publications. Most of them were identified as risk factors to ROP previously (Table 1-1).

Some of potential risk factors were first identified or examined in this study. Among them are the follow-up risk criteria, transient tachypnea of newborn (TTN), total number of drugs used in hospital, and total hospital stay. Except for the TTN, the other three variables could be taken as complex variables which represent some covariates. One factor, the total number of drugs used, is a newly defined variable in this study, and could represent the degree of prematurity, clinical condition, and O_2 exposure which made infants receive the drugs. Possibly, the total number of drugs used had an independent effect on the development of ROP as some drugs have been reported to do so (Hammer, 1986). But the univariate analysis really cannot tell the relation in depth and it only demonstrated that this variable had a very strong relation with severe ROP (Table 4-34) that cannot be simply explained by the effect of drugs themselves.

All of the significant factors identified in this study are risk factors for development of severe ROP, except for the TTN. TTN is a self-limited condition characterized by tachypnea, mild retractions and grunting respiration, usually without signs of severe respiratory distress, and TTN is usually noted in larger premature infants (Kliegman, 1990). So, it is quite understandable that TTN is not a risk factor for severe ROP.

ROP is a multifactorial disease and the risk factors identified in univariate analysis are possibly inter-related. Based on the basic knowledge of medical science, the effect chain of risk factors (not necessary linear or single chain) could be that more premature infants (low birthweight and shorter gestation) will be more likely to have adverse clinical condition (BPD, PDA, sepsis et al) and a higher number of follow-up criteria, then they will be more likely to receive longer and higher O_2 exposure, longer hospital stay

and then a higher chance to develop severe ROP. It was obvious that univariate analysis used in this study did not control for inter-relationships among some of the variables studied. The multivariate analysis will be better way to explore that. Since the limitations in both timing and knowledge of the writer, effort was made to perform bivariate analysis (stratification analysis) on selected variables. The selection of the variables was based on expertise suggestions, strength of association, biologic plausibility or clinical importance, as well as the comparison value to the literatures. The follow up risk criteria, total days of hospital stay, the total days of O_2 (or the days of O_2 administration), maternal race as well as bronchopulmonary dysplasia (BPD) were chosen for stratification analysis. The purpose of stratification analysis was to re-examine the associations between these selected variables and severe ROP after controlling for the influence of prematurity (birthweight and gestational age respectively) which are the most important factors in development of severe ROP. The following discussion will focus on these five selected variables.

1) Maternal race

The study found that infants' ethnic origin determined by mother' race, was significantly associated with the development of severe ROP. The composition of mothers race for 325 subjects involved in the analysis is Caucasians (276), Blacks (10), Native (10) and others (29). The highest incidence of severe ROP was found in infants with native ethnic origin (70%), and the lowest incidence rate was in infants with black ethnic origin. So, having a Native mother would generate a significant 7-fold increase in risk in development of severe ROP compared to having a Black mother, although the number of both were low (Table 4-26). When the

ethnic origin of the mother was broken in to binary categories, Native vs non-native, the Native mother was associated with an 4-fold increase risk for severe ROP, compared to non-native mother. This significant association still existed but with weaker strength after stratifying on the birthweight (RR_{MH}=3.4) and on gestational age (RR_{MH}=3.1).

Racial difference in ROP was first reported by Monos et al in 1987. They found that a higher incidence of stage 1, but no stage 2 and stage 3 acute ROP in Bedouin rather than in Jewish infants.

A population-based study in England (Ng et al, 1988) revealed differences of incidence of severe ROP in different infant ethnic origins. In a cohort of 505 infants studied, although prematurity distribution for Caucasian and Asians did not differ significantly and Asians were not smaller than their counterparts for a fixed gestation, severe ROP was more likely to develop in Asians than in Caucasians (14.1% vs 2.7%). They explained that this difference was largely due to the better survival for Asians. Another important finding of that study was that black infants had shorter gestation, but any stage of ROP was less likely to develop, and severe stages of ROP occurred in 4.2%. Compared to this study, Ng's study had much larger sample size of Blacks (24 subjects, 4.8% of 505) and Asians (64, 12.7% of 505), and hence the results were more valid and reliable. The way to determine the infants' ethnic origin in Ng's study was different this study. Infants of Black or Asian origin were determined by either parent's race, and Caucasian origin was determined by both parents' race. Once more, Ng's study had Asia ethnic origin as a subgroup in which the highest incidence rate of severe ROP was found, but in this thesis project, Natives was identified as a subgroup and was found to have highest rate of severe ROP. The Ng's study analyzed the effect of survival rate of infants

in different ethnic origin on the development of severe ROP, but we do not have enough infants survival information to answer this question.

Palmer et al (1991) also reported the racial differences in occurrence of the severe ROP. In their study, race of infants was determined by the race of mother. The incidence rate of severe ROP in Black infants was lowest across the board (13.2%); in white infants was second (20.8%); in others was highest (25.2%). The report did not examined further for this difference since the study emphasis was not on this point.

In summary, our study finding support the previous studies results that racial origin of infants was associated with the development of severe ROP. Usually, the black infants were less likely to develop severe ROP ; Asian and Native origin infants were more likely to develop severe ROP. The relationship was still significant after controlling for the influence of the degree of prematurity. This study finding of racial difference should be interpreted cautiously because of the small sample size for Native as well as Black infants. Further study on this relation with large sample size will be necessary to examine wether the biological nature of the race effect on the severe ROP development or social-demographic aspects connected with the race brings the difference.

2) Follow-up risk criteria and hospital stay

Follow-up risk criteria as well as the days of hospital stay were newly defined and first examined in this study and could be taken as complex variables marking the effect of a collection of covariates. Both of them were highly significantly associated with the development of severe ROP in

univariate analysis (Table 4-34).

The follow-up risk criteria accumulated all six risk criteria under which the infant was selected into the follow-up program. Among them are "on ventilator, congenital infection, neurological abnormality, retinopathy of prematurity and low birth weight" and others. This factor could be the complex marker for the degree of prematurity and clinical condition which was related to the prematurity as well as others factors. Possibly, it will predict the O_2 exposure and finally the development of severe ROP. The Univariate analysis gave a strong association among all the factors (Table 4-34). The RR was 15.6 when infants with 4 risk criteria or more were compared to the infants with LBW risk criteria only. This association was influenced by the prematurity, but still significant after control the influence of the degree of prematurity (Table 4-35). Based on the analysis performed, it really can not answer how well this variable will present the covariates expect for the prematurity, and wether it is an independent factor to development of severe ROP.

Like the number of Follow up risk criteria, days of hospital stay is a newly identified risk factor to development of ROP with very strong association (RR=13.3, when infants had more than 120 days stay compared with infants had less than 60 days stay, Table 4-34) and is a complex variable inter-related with other variables, such as the degree of prematurity ($R=-0.5650$, $P<0.001$ with birthweight; $R=-0.5475$, $P<0.01$). And possibly, it will related to the O_2 exposure as well as some infants' clinical conditions keeping the infants in hospital. Previous researchers had demonstrated the adverse relation between the prematurity and days of hospital stay (Yu et al, 1991; Harding & Howie, 1987). It was rarely reported as related to ROP. Stratification analysis showed that

association between days of hospital stay and development of severe ROP is a risk factor independently from the degree of prematurity, although the degree of prematurity did increase this association (Table 4-35). Limitation of the analysis performed is the same as was discussed in follow-up risk criteria.

The significant associations identified in the study for the number of follow up criteria as well as the days of hospital stay to the development of severe ROP were not previously reported. It will benefit the research in this area in terms of strong association, the biological plausibility, possible importance of predictive value as well as enriching the literature.

3) Duration of O_2 supplementation

Previous investigations suggested a relation between ROP and duration of exposure to supplemental oxygen (Kinsey, 1956; Yu et al, 1982; Bossi et al, 1984), although most of these studies were done before the availability of ICROP system. Bossi et al (1984) in a retrospective study found that days of oxygen administration was significantly longer (Mean 25 days) in infants who developed ROP than that in infants who did not develop ROP (mean 18.7 days) when univariate analysis was performed. The covariate variable like prolonged elevated oxygen, days of artificial ventilation were also associated with the ROP in univariate analysis. When a multivariate statistical method was used, the duration of oxygen administration lost it association, but the prolonged elevation of oxygen supplementation (FiO_2>0.4), duration of artificial ventilation remains in the regression. Using ICROP (1984), Charles et al (1991) compared the mean days of O_2 supplementation between severe ROP and no ROP groups infants (not severe ROP vs non-severe ROP), and they found

that duration of O_2 supplementation was significantly longer in severe ROP group.

This study result supported the previous study findings what showed the significant relation of O_2 exposure duration and the development of severe ROP. There were 93.6% infants received O_2 supplementation in this study. This variable was selected as a complex variable which could reflect a collection of covariates like the degree of maturity, the ventilatory assistance duration, ventilatory assistance episodes, maximal inspiratory pressure, episodes of arterial PO_2>100, and complication of ventilatory support and possible some clinical condition. The majority of these covariates are significantly associated with severe ROP in univariate analysis. The relation between duration of O_2 administration (>90 days vs ≤ 90 days) were further evaluated stratifying on degree of prematurity (birthweight and gestational age respectively). Before and after stratification, the result were all significant, but unstratified association (RR=6.3, 95%CI 2.8-14.2) was stronger than stratified ones (RR=4.1, 95% CI 1.6-10.5 stratifying on birthweight; RR=3.9, 95% CI 1.5-9.8 stratifying on gestational age) (Table 4-35). But the stratification analysis did not answer whether it is the key component among other possible interrelated variables except for the degree of prematurity. Since the days of oxygen supplementation lost its association with severe ROP in Bossi's study (1984), it was really highly suggested that a multivariate analysis should be applied.

4) Bronchopulmonary dysplasia (BPD)

The data of the study showed that bronchopulmonary dysplasia was typically highly prevalent in the very low birthweight population (60%) and it was significantly associated with the development of severe ROP (RR=4.8). This

association was influenced by the degree of prematurity, but could be independent of it (Table 4-35). The relation between BPD and ROP have been widely reported (Brown et al, 1990; Zierler, 1988) but not as its relation to the development of severe ROP. Our data confirmed the importance of this risk factors for severe ROP. Brown et al (1990) thought that O_2 administration as well as the ventilatory assistance were the two components of BPD. When multivariate analyses were performed on a collection of covariates which were significant risk factors for severe ROP in univariate analysis, including the birthweight, BPD (included duration of oxygen exposure, duration of ventilatory assistance) as well as the intraventricular haemorrhage (IVH), only the ventilatory therapy can be singled out as the most important associated with the development of sever ROP. In other words, the time spent on a ventilator in the key component among these interrelated variables. This result called the need for the further data analysis on the BPD and its covariates to see what will be the most important predictor to severe ROP, BPD itself or the components covariated with it.

III Others

Besides answering the two research questions addressed by this study, data obtained can also provide the estimate of cicatricial ROP as well as the visual outcomes at 4 months adjusted age as well as 12 months adjusted age. The results show the cicatricial ROP affected 13.8% followed infants or 47.7% of infants with previous severe ROP at 4 months adjusted age and affected only 7.7% of followed infants or 25% of infants with previous severe ROP at 12 months adjusted age. The data available for visual outcome were visual acuity, refraction error and strabismus. The major adverse visual

outcomes at 4 months as well as the four months adjusted age was refraction error (including suspect cases, 51.7% in 4 months AA and 40% in 12 months AA). The prevalence rate of abnormal visual acuity including suspect cases was 20 % for both time cut-offs (Table 4-36,38,40,42).

Severe ROP was associated with the development of cicatricial ROP at 4 months AA (RR=6.5, 95% CI 3.7-11.6) (Table 4-37) and the latter significantly attributed to the adverse visual outcomes (including the suspect cases): abnormal visual acuity (RR=3.4, 95% 2.0-5.7), abnormal refraction (RR=1.38, 95% CI 1.04-1.83) and strabismus (RR=2.7, 95% CI 1.25-5.60) (Table 4-39b). Since all eyes with progressive stage 3b+ ROP were intervened with cryotherapy which was considered as a most effective intervention in terms of the reduction of unfavourable retinal and functional outcome to date (Cryo-ROP, 1988; 1990; White et al, 1991), the cicatricial ROP and adverse visual outcomes could be much severe if this intervention was not applied.

The relation of severe ROP and the cicatricial ROP and visual ROP at 12 months adjusted age are similar to that at 4 month AA.

The high loss to follow up for 4 months AA (298/458 followed, loss 35%) as well as the 12 months AA (218/458 followed, loss 52.4%) were noticed. High incomplete information on both cicatricial ROP (not graded cases) and visual outcome (suspected cases) at both time cut-off was also recognized. The generalizability as well as the internal validity of the results in Part IV of the results was highly affected and interpretation and application of the results should be very conservative.

IV Strength and Weakness of the Study

This study had the advantage of comprehensive longitudinal follow-up of a relative large number of high-risk infants for development of severe ROP in a geographical area. The ophthalmologic examination strategies to detect the timing of various stages of ROP reduced the probability of missing ROP cases. The well established and maintained SA-PNFU program database had provided an excellent information for the study and make the risk factor analysis on an extensive area base possible, both prenatal and postnatal, biological and therapeutic. The large sample size allowed the accurate estimates for most independent variables, the incidence as well as the risk factors. The longitudinal design provided information about changes over time. Generally, the results of the study are considered as reliable as well as valid. Comprehensive analyzing the risk factors to develop severe ROP in very high risk infants population in this longitudinal population based cohort study will be the contribution to the current research literatures in this area.

Several limitations and weakness were identified in this study. The major limitation for longitudinal cohort study in general is that validity of the results can be affected by losses to follow-up (Hennekens & Buring, 1987). The losses to follow-up rate was 18.7% when estimating the incidence of various stages of ROP as well as associations between the risk factors and severe ROP development. The analysis for lost and followed infants showed that lost babies were a 'positively biased' infants. Relative speaking, this lost rate is not a surprising figure for a follow-up study, but the results will overestimated the true incidence and associations. Therefore , the interval validity as well as the external validity will be affected.

The loss to follow-up for four months adjusted age and 12 months adjusted age were much higher, 35% and 52% respectively. So the validity and the generalizability of the results from this two time cut-off were really limited.

Another limitation was the incomplete information which were the reflection of the weakness of secondary data analysis and affect the validity of the study results.

The first aspect of this limitation was that the majority of data required by the study, such as all independent variables, were obtained from a pre-existing database - SA-PNFU program database. This database were well established and maintained for program as well as research activities built within the program, and provided the excellent core of information. But it was not exactly designed for this study purpose. The problems encountered by this study were: a) some cases who met the eligibility criteria of study population, had not yet been registered in the computer database at the time this study was carried out; b) Some information, which is important in data analysis, such as the survival experience of followed infants were not completely entered into computer database; c) missing information for some variables were identified and as this investigator can do nothing to make it complete. Examples were the maternal race as well as the total days of hospital stay which had a certain proportion of missing information.

The second aspect of this limitation was that the data collection for ophthalmologic examination was based on the review of pre-existing ophthalmologic consult sheets for every infant. Information was easily missed when the baby was transferred between hospitals. Although the ophthalmologist examined and recorded the findings of the retina in a standard manner, the problems came out because the routine

ophthalmologic examination were not specially designed for this specific study. For some cases, the reason for later start or early stopping of eye examination was not provided, but this information will help to judge if the ophthalmologic data for ROP detection is complete or not. Some cases did not have a clear record about the termination of observation for each stage of ROP. This is why only 344 of all 374 followed infants had information for ROP incidence estimating; and only cumulative incidence rate rather than incidence density could be provided.

The third aspect of this limitation for this study was that there was large proportion of uncertain status of "suspect" in cicatricial ROP as well as the visual outcomes. This makes the study vulnerable to classification errors. So, the results of analysis on the association between previous severe ROP and adverse visual outcomes were obvious different before and after taking "suspect" cases as abnormal. The application of this part of results should be very conservative.

One possible limitation of this study is the device used for retina examination. It differed from other reported studies which used the indirect ophthalmoscope to examine the retina. This study used the direct ophthalmoscope with infant gonia lens. The comparability of examination findings of retina for these two devices need to be discussed.

Finally, since the study population is intensely selected and the observation method was well defined, the application of the results to other studies and other region would require a careful comparison for selection criteria as well as the eye examination strategies. Slightly difference in one of them will bring the difference in the results of interest.

CHAPTER 6 CONCLUSIONS

The development of ROP as well as the risk factors associated with the development of severe ROP were studied prospectively in a geographically defined area of the Southern Alberta. Over 6 years, 374 infants weighing 500-1250g at birth in this area were studied. The results follow:

1 The Development of Severe ROP

Acute ROP developed in 70.3% of infants and severe ROP attacked 19.2% of infants. The incidence of severe ROP in infants of birth weight less than 1000g was 22.7% and in infants birthweight 500g and over and less than 750g was 41.3%. The more premature the infants, the higher incidence of severe ROP will be. Compared to other relevant studies, the incidence rates found in this study is reliable and valid in terms of the study design and the strategies of eye examination.

Age of onset for various stages of ROP were detected. Mild stages of ROP were first observed at CA 47 to 56 days and AA -44 to -40 days. Severe ROP was first observed at CA 60-73 days and AA -26.5 to -24 days. Smaller infants were found to take longer CA for ROP event to occur, but infants in all birthweights took almost the same adjusted AA to develop ROP. This implied that level of maturity was more important than postnatal environmental influences in governing the timing of the vascular events.

Prevalence rate of ROP in four different time points were provided in the study, and analysis shows the prevalence at near term was most important in terms of identifying the status of severe ROP. The severe ROP was found in 8.6% of

followed infants and the overall acute ROP was found in 51.1% of followed infants at this time point.

2 Risk Factors Associated with the Development of Severe ROP

Thirty six of all 85 potential risk factors are identified as risk factors for development of severe ROP. Those with RR more than 4.0 are summarized in table 4-34. The majority of those factors are valid in terms of the strength of the association, the biological plausibility as well as the comparability to the literatures.

After stratifying on birth weight as well as gestational week, the associations between the five variables selected form all 34 risk factors was further examined and the results showed that association between maternal race, the total hospital stay, the follow-up risk criteria, the days in oxygen as well as the BPD are significant associated with the development of severe ROP after controlling the degree of prematurity.

3 Others

Cicatricial ROP affected 13.8% of followed infants at four months AA and 7.7% of followed infants at 12 months AA. The refraction errors were the most prevalent adverse visual outcomes among three measurements investigated, visual acuity, refraction errors and strabismus, for both time points. Severe ROP was significantly associated with the cicatricial ROP and adverse visual outcomes. The validity of these findings were highly affected by the high rate of loss to follow-up at 4 and 12 months AA as well as the large number of not graded cicatricial cases and suspect adverse visual outcomes cases involved.

Further data analysis could be made on the data set obtained in this study. Firstly, the multivariate analysis is desirable to control the confounders at the same time and to examine what are independent risk factors to severe ROP among the risk factors identified in univariate analysis. Secondly, it will be interesting to determine if the complex variables defined in the study really represent the collection of the covariates, and how will they do it. The way to do it could be multivariate analysis on a collection of covariates, to see what variables or variable will be identified. It will be nice to have an independent study on infants' ethnic origins and development of severe ROP with enough sample size in each ethnic group; to see if the nature of the race bring the difference in severe ROP occurrence, or the socio-demographic factors and other connected with race brings the difference.

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Appendices

THE UNIVERSITY OF CALGARY
Health Sciences Centre
3330 Hospital Drive N.W., Calgary, Alberta, Canada T2N 4N1

Faculty of MEDICINE

1992-03-10

Dr. R. S. Sauve
Department of Community Health Sciences
Faculty of Medicine
The University of Calgary
Calgary, Alberta

Dear Dr. Sauve:

Re: **Development and Risk Factors of Severe Retinopathy (ROP) in Very Low Birthweight Infants**

Student: Ms. Ying Mei-Ding

Degree Program: M.Sc.

The above-noted thesis proposal has been submitted for Committee review and found to be ethically acceptable.

Yours sincerely,

E. D. Burgess, MD, FRCPC, FACP
Chairman, Conjoint Medical Ethics
Committee

EDB:smh

c.c. Dr. R. B. Church, Assistant Dean
(Medical Science)
Dr. E. J. Love (information)

DATA COLLECTION FORM FOR OPHTHALMOLOGIC EXAMINATION

Name: _____ (first) _____ (last) FH# _____

Date of Birth (M-D-Y)_____ BW (gram) _____

GW at birth (week) _____

Examination Order		First Exam	Near Term
Date of Exam.		MM1 DD1 YY1	MM2 DD2 YY2
Chronological age (day)		CA1	CA2
Adjusted age (day)		AA1	AA2
Anterior Exam.	Rt.	AE1_R	AE2_R
	Lt.	AE1_L	AE2_L
Media Exam.	Rt.	ME1_R	ME2_R
	Lt.	ME1_L	ME2_L
Fundus Exam.	Rt.	FE1_R	FE2_R
	Lt.	FE1_L	FE2_L
Calgary Code	Rt. 1)	CODE1_R1	CODE2_R1
	2)	CODE1_R2	CODE2_R2
	3)	CODE1_R3	CODE2_R3
	4)	CODE1_R4	CODE2_R4
	5)	CODE1_R5	CODE2_R5
	Lt. 1)	CODE1_L1	CODE2_L1
	2)	CODE1_L2	CODE2_L2
	3)	CODE1_L3	CODE2_L3
	4)	CODE1_L4	CODE2_L4
	5)	CODE1_L5	CODE2_L5
ROP	Rt.	ROP1_R0/ROP1_R1	ROP2_R0/ROP2_R1
		ROP1_R2	ROP2_R2
	Lt.	ROP1_L0/ROP1_L1	ROP2_L0/ROP2_L1
		ROP1_L2	ROP2_L2
RLF	Rt.	RLF1_R	RLF2_R
	Lt.	RLF1_L	RLF2_L
Diagnosis		DIAG1	DIAG2
Treatment		TREAT1	TREAT2
# of Exam.			EXAMA#
Date Verification		VERIFY1	VERIFY2

ROP	CA	AA	Verify
Stage 1	CA_ROP1R CA_ROP1L	AA_ROP1R AA_ROP1L	OK_ROP1R OK_ROP1L
Stage 2	CA_ROP2R CA_ROP2L	AA_ROP2R AA_ROP2L	OK_ROP2R OK_ROP2L
Stage 3a	CAROP3AR CAROP3AL	AAROP3AR AAROP3AL	OKROP3AR OKROP3AL
Stage 3b	CAROP3BR CAROP3BL	AAROP3BR AAROP3BL	OKROP3BR OKROP3BL
Stage 3c	CAROP3CR CAROP3CL	AAROP3CR AAROP3CL	OKROP3CR OKROP3CL
Stage 4	CA_ROP4R CA_ROP4L	AA_ROP4R AA_ROP4L	OK_ROP4R OK_ROP4L

RLF	CA	AA
Grade1	CA_RLF1R CA_RLF1L	AA_RLF1R AA_RLF1L
Grade2	CA_RLF2R CA_RLF2L	AA_RLF2R AA_RLF2L
Grade3	CA_RLF3R CA_RLF3L	AA_RLF3R AA_RLF3L
Grade4	CA_RLF4R CA_RLF4L	AA_RLF4R AA_RLF4L
Grade5	CA_RLF5R CA_RLF5L	AA_RLF5R AA_RLF5L
Cryotherapy	CA_CT	AA_CT
Overall ROP Diagnosis	DIAGNOSE	

Appendix 2b: Coding Menu for Ophthalmologic Examination Data

Field name	Length	Type	Explanation and coding
BACKGROUND INFORMATION			
CASE#	3	numerical	- the data input order, same number as shown on the screen when entering the data in SPSS DATA ENTRY. - this is reference number,in case of need go back to the original data.
ID	4	numerical	- identification number. - range 8501-9090 the first two digits are the subject birth year and last two digits are the subject number in that year.
FH#	6	numerical	- Foothill Hospital number - if baby never born in Foothill hospital, record the assigned number. - 999999, means subject are not included in the subject list of PNFU Data Base. - the key variable to connect this data base to the PNFU data base.
YY0	2	numerical	- year of birth - 99, unknown 88, not applicable.
MM0	2	numerical	- month of birth - 99, unknown 88, not applicable.
DD0	2	numerical	- Day of birth - 99, unknown 88, not applicable.
BW	4	numerical	- birth weight, gram - 8888, not applicable 9999, unknown.
GW	4 1	numerical decimal	- gestational week at birth - 88.8, not applicable 99.9, unknown/missing
FIRST OPHTHALMOLOGIC EXAMINATION INFORMATION			
			- the first examination is defined as the first successful ophthalmologic examination applied to the subject.

YY1	2	numerical	- year of the first examination - 99 means unknown 88 not applicable
MM1	2	numerical	- month of the first examination - 99 means unknown 88 not applicable
DD1	2	numerical	- day of the first examination - 99 means unknown 88 not applicable
CA1	3	numerical	- chronological age (days) for first examination. - 999, unknown/not assessed 888, not applicable
AA1	3	numerical	- adjusted age (days) for first ophthalmologic examination. - 999, unknown/not assessed. 888, not applicable - AA = age at assessment-days of premature delivery.
AE1_R	1	numerical	- first anterior examination for right eye - 0, normal, 1, TVL zone 1,2,3, 2, TVL zone 2,3, 3, TVL zone 3, 4, TVL partial in zone 3, 5, TVL trace in zone 3, 6, TVL + other problems, write down the details, 7, other problems, write down the exactly disorder. 8, not applicable, 9, unknown/not assessed;
AE1_L	1	numerical	- first anterior examination for left eye, - codes are the same as AE1_R;
ME1_R	1	numerical	- first media examination for right eye - 0, normal or clear, fairly clear, 1, slight haze or mild, some haze, 2, median haze, 3, haze, 6, other problems or disorder at the same time, write down the details, 7, other problems or disorder only, write down the details, 8, not applicable, 9, unknown/not assessed;
ME1_L	1	numerical	- first media examination for left eye, - codes are the same as the ME1_R;
ME1_R	1	numerical	- first fundus examination for right eye, - 0, normal,

1, vascularizing in zone 1,2,3,
2, vascularizing in zone 2, 3,
3, vascularizing in zone 3,
4, can see the retina but can't clearly record it, sure no ROP,
5, under cryotherapy, can't record it formally,
6, vascularization incomplete + other problems or disorders, write down the details,
7, other problems or disorders only, write down the details,
8, not applicable,
9, unknown/unassessed;

FE1_L 1 numerical - first fundus examination for left eye,
- codes are the same as the FE1_R;

Code1_R1 9 numerical - Calgary code for the ROP of right eye at first examination,
Code1_R2 9 numerical
Code1_R3 9 numerical - Code1-R1 to Code1-R6 record the all findings of ROP for right eye at first examination,
Code1_R4 9 numerical
Code1_R5 9 numerical
Code1_R6 9 numerical - refer to the reference article for detail explanation of the Calgary Code,
- 999999999, unknown/not assessed,
888888888, not applicable,
555555555, post Cryotherapy, out of Calgary Code,
444444444, seen well, no ROP, but can't be well coded,
312121111, vascular completed.
222222222, type II disease
000000000, normal,
xxxxx0000, vascular not completed in specific zone(x) and specific clock hours(xxxx),
xxxxx1000, completed vascularization in specific zone(x) and specific clock hours(xxxx)

- 1st digit, zone,1,2,3
2nd to 5th digits, clock hours,
6th digit, type1 or type 2
7th-8th digits, stage1
10, rop stage1
20, rop stage2
31, rop stage3a
32, rop stage3b
33, rop stage3c
40, rop stage4

		9th digit, status (r or h,p); 1, active 2, resolving 3, progressive 4, haemorrhage 5, others problems, write down the details,
Code1_L1	9 numerical	- the Calgary code for the ROP of left
Code1_L2	9 numerical	eye at first examination,
Code1_L3	9 numerical	- Code1-L1 to Code1-L6 record the all
Code1_L4	9 numerical	findings of ROP for left eye at
Code1_L5	9 numerical	first examination,
Code1_L6	9 numerical	- refer to the reference article for detail explanation of the Calgary Code, - codes are the same as right eye,
ROP1_R0	2 numerical	- ROP stages for the right eye at first examination, - for the retina had different stages of ROP at the same time, record the worst condition, - 0, no ROP, 10, stage 1 ROP, 20, stage 2 ROP, 31, stage 3a ROP, 32, stage 3b ROP, 33, stage 3c ROP, 40, stage 4 ROP, 22, type II disease 55, under or post Cryotherapy, 66, had ROP but resolved, 77, has ROP but not staged, 88, not applicable, 99, unknown/not assessed;
ROP1_R1	1 numerical	- the status of ROP for the right eye at first examination, - 0, no ROP at all, 1, active ROP, 2, resolving ROP, 3, progressive, 4, haemorrhage 5, under or post cryotherapy, 6, previous ROP, resolved at time of examination, 7, others, write down the details, 8, not applicable, type disease 9, unknown/not assessed;
ROP1_R2	1 numerical	- the plus disease for the right eye at first examination, - 0, no plus disease, 1, plus disease yes,

5, had plus disease, but under Cryotherapy treatment,
6, resolved plus disease,
8, not applicable, type II disease
9, unknown/not assessed;

ROP1_L0 2 numerical - ROP stages for left eye at first examination,
- codes are the same as ROP1-R0;

ROP1_L1 1 numerical - ROP status for left eye at first examination,
- codes are the same as ROP1-L1;

ROP1_L2 1 numerical - ROP plus disease for left eye at first examination,
- codes are the same as ROP1-R2;

RLF1_R 1 numerical - cicatricial ROP for right eye at first examination,
- 0, no RLF,
1, yes, grade 1,
2, yes, grade 2,
3, yes, grade 3,
4, yes, grade 4,
5, yes, grade 5,
7, yes, but not graded,
8, not applicable,
9, unknown/not assessed;

RLF1_L 1 numerical - cicatricial ROP for left eye at first examination,
- codes are the same as RLF1-R;

Diag1 5 numerical - the diagnosis at first examination,
- record the worst ROP condition among both eyes,
- 1st digits, ROP or RLF,
0, ROP
1, RLF
2nd to 3rd digits, stage or grade,
00, no ROP or RLF
01, RLF grade1
02, RLF grade2
03, RLF grade3
04, RLF grade4
05, RLF grade5
10, ROP stage1
20, ROP stage2
31, ROP stage3a
32, ROP stage3b
33, ROP stage3c
40, ROP stage4
4th digit, status of ROP
0, no ROP
1, ROP active
2, ROP resolving
3, progressive

4, haemorrhage
5, other problems, write down the details,
5th, plus disease,
0, no
1, yes
- 00000, normal,
22222, type II disease,
55555, under or post cryotherapy
66666, resolved ROP,
77777, other disorder or problem, write down the details,
88888, not applicable
99999, unknown/not assessed;

Treat1 1 numerical - eye related treatment applied at first examination,
- 0, none,
1, previous cryotherapy,
2, under treatment for refraction error,
3, under treatment for strabismus,
4, under treatment for amblyopia,
5, under treatment for other
6, combination of above treatment
8, not applicable
9, unknown,

Verify1 2 numerical - timing verification for first examination,
- 00 OK, CA range 10-40 days,
- 10-19 code for reasons too late or missed OE:
10, too premature, cannot apply examination
11, transferred from other hospital where the OE late or don't practise OE,
12, transfer to other hospital in Calgary,
13, transfer to other hospital out of calgary
14, transfer to home
15, directly admitted to other hospital where don't have routine OE,
16, ...
18, medical problem, cancelled
19, OE should be done or early in FH, but no reason can be found so far,
- 20-29 code for missing information.
21, missing information in FH
22, missing information in CGH

23, missing information in ACH
24, missing information in H+H
25, missing information in PLH
26, missing information in Grace H.
27, missing information in others within calgary
28, missing information out calgary
29, missing information in Rockview
- 30-39 code for loss to follow up:
31, discharge to home, no follow up
32, transfer to other hospitals in calgary, no ophthalmologic examination done there
33, transfer to other hospital out of calgary
34,
- 40-49 missing for unknown reasons:
40, whole case missing, index case
41, whole case missing, not index case.
43,
50, die during the course of observation.

NEAR TERM OPHTHALMOLOGIC EXAMINATION INFORMATION

YY2	2	numerical	- year of the near term examination - 99 means unknown 88 not applicable
MM2	2	numerical	- month of the near term examination - 99 means unknown 88 not applicable
DD2	2	numerical	- day of the near term examination - 99 means unknown 88 not applicable
CA2	3	numerical	- chronological age (days) for near term examination - 999, unknown/not assessed 888, not applicable
AA2	3	numerical	- adjusted age (days) for near term ophthalmologic examination. - 999, unknown/not assessed. 888, not applicable - AA = age at assessment-days of premature delivery.
AE2_R	1	numerical	- near term anterior examination for right eye; - codes are the same as AE1_R,
FE2_L	1	numerical	- near term anterior examination for left eye, - codes are the same as AE2-R;

ME2_R	1	numerical - near term media examination for right eye - codes are the same as ME1_R,
ME2_L	1	numerical - near term media examination for left eye, - codes are the same as the ME2-R;
FE2_R	1	numerical - near term fundus examination for right eye, - codes are the same as FE1_R,
FE2_L	1	numerical - near term fundus examination for left eye, - codes are the same as the FE2-R;
Code2_R1	9	numerical - the Calgary code for the ROP of right
Code2_R2	9	numerical eye at near term examination,
Code2_R3	9	numerical - Code1-R1 to Code1-R6 record the all
Code2_R4	9	numerical findings of ROP for right eye at
Code2_R5	9	numerical first examination,
Code2_R6	9	numerical - refer to the reference article for detail explanation of the Calgary Code, - codes are the same as Code1_R1 to Code1_R6.
Code2_L1	9	numerical - the Calgary code for the ROP of left
Code2_L2	9	numerical eye at near term examination,
Code2_L3	9	numerical - Code1-L1 to Code1-L6 record the all
Code2_L4	9	numerical findings of ROP for left eye at
Code2_L5	9	numerical first examination,
Code2_L6	9	numerical - refer to the reference article for detail explanation of the Calgary Code, - codes are the same as right eye,
ROP2_R0	2	numerical - ROP stages for the right eye at near term examination, - codes are the same as ROP1_R0P,
ROP2_R1	1	numerical - the status of ROP for the right eye at near term examination, - codes are the same as ROP1_R1,
ROP2_R2	1	numerical - the plus disease for the right eye at near term examination, - codes are the same as ROP1_R2,
ROP2_L0	2	numerical - ROP stages for left eye at near term examination, - codes are the same as ROP2-R0;
ROP2_L1	1	numerical - ROP status for left eye at near term examination, - codes are the same as ROP2-L1;
ROP2_L2	1	numerical - ROP plus disease for left eye at near term examination, - codes are the same as ROP2-R2;
RLF2_R	1	numerical - cicatricial ROP for right eye at near term examination,

- codes are the same as RLF1_R,

RLF2_L 1 numerical - cicatricial ROP for left eye at near term examination,
- codes are the same as RLF2-R;

Diag2 5 numerical - the diagnosis at near term examination,
- codes are the same as Diag1;

Treat2 1 numerical - eye related treatment applied at near term examination,
- codes are the same as Treat1;

Verify2 2 numerical - timing verification for near term examination,
- 00 OK, AA range -20 - +20 days,
- 10-19 code for reasons to stop ophthalmologic examination too early:
  10, no further examination necessary
  the rest codes are the same as verify1;

Eaxama# 2 numerical - the total number of ophthalmologic examinations during observations.
- 88, not applicable
  99, missing/unknown

TIMING OF FINDING THE ROP

For all of the following variables, code guide are:
- 000, or 0 normal
  888, or 8 not applicable,
  999, or 9 unknown/not assessed,

CA_ROP1R 3 numerical - chronological age (days) for the first time detection of stage1 ROP at right eye

AA_ROP1R 3 numerical - adjusted age (days) for the first time detection of stage1 ROP at right eye

OK_ROP1R 1 numerical - time verification for ROP stage1 at right eye
- 1, OK, two weeks interval or within the physician's prescription.
- 2, not Ok, interval too long

CA_ROP1L 3 numerical - chronological age (days) for the first time detection of stage1 ROP at left eye

AA_ROP1L 3 numerical - adjusted age (days) for the first time detection of stage1 ROP at left eye

OK_ROP1L 1 numerical - time verification for ROP stage1 at left eye

			- 1, OK, two weeks interval or within the physician's prescription.
			- 2, not Ok, interval too long
CA_ROP2R	3	numerical	- chronological age (days) for the first time detection of stage2 ROP at right eye
AA_ROP2R	3	numerical	- adjusted age (days) for the first time detection of stage2 ROP at right eye
OK_ROP2R	1	numerical	- time verification for ROP stage2 at right eye
			- 1, OK, two weeks interval or within the physician's prescription.
			- 2, not Ok, interval too long
CA_ROP2L	3	numerical	- chronological age (days) for the first time detection of stage2 ROP at left eye
AA_ROP2L	3	numerical	- adjusted age (days) for the first time detection of stage2 ROP at left eye
OK_ROP2L	1	numerical	- time verification for ROP stage2 at left eye
			- 1, OK, two weeks interval or within the physician's prescription.
			- 2, not Ok, interval too long
CAROP3AR	3	numerical	- chronological age (days) for the first time detection of stage3a ROP at right eye
AAROP3AR	3	numerical	- adjusted age (days) for the first time detection of stage3a ROP at right eye
OKROP3AR	1	numerical	- time verification for ROP stage3a at right eye
			- 1, OK, two weeks interval or within the physician's prescription.
			- 2, not Ok, interval too long
CAROP3AL	3	numerical	- chronological age (days) for the first time detection of stage3a ROP at left eye
AAROP3AL	3	numerical	- adjusted age (days) for the first time detection of stage3a ROP at left eye
OKROP3AL	1	numerical	- time verification for ROP stage3a at left eye
			- 1, OK, two weeks interval or within the physician's prescription.
			- 2, not Ok, interval too long
CAROP3BR	3	numerical	- chronological age (days) for the first time detection of stage3b ROP at right eye
AAROP3BR	3	numerical	- adjusted age (days) for the first time detection of stage3b ROP

			at right eye
OKROP3BR	1	numerical	- time verification for ROP stage3b at right eye - 1, OK, two weeks interval or within the physician's prescription. - 2, not Ok, interval too long
CAROP3BL	3	numerical	- chronological age (days) for the first time detection of stage3b ROP at left eye
AAROP3BL	3	numerical	- adjusted age (days) for the first time detection of stage3b ROP at left eye
OKROP3BL	1	numerical	- time verification for ROP stage3b at left eye - 1, OK, two weeks interval or within the physician's prescription. - 2, not Ok, interval too long
CAROP3CR	3	numerical	- chronological age (days) for the first time detection of stage3c ROP at right eye
AAROP3CR	3	numerical	- adjusted age (days) for the first time detection of stage3c ROP at right eye
OKROP3CR	1	numerical	- time verification for ROP stage3c at right eye - 1, OK, two weeks interval or within the physician's prescription. - 2, not Ok, interval too long
CAROP3CL	3	numerical	- chronological age (days) for the first time detection of stage3c ROP at left eye
AAROP3CL	3	numerical	- adjusted age (days) for the first time detection of stage3c ROP at left eye
OKROP3CL	1	numerical	- time verification for ROP stage3c at left eye - 1, OK, two weeks interval or within the physician's prescription. - 2, not Ok, interval too long
CA_ROP4R	3	numerical	- chronological age (days) for the first time detection of stage4 ROP at right eye
AA_ROP4R	3	numerical	- adjusted age (days) for the first time detection of stage4 ROP at right eye
OK_ROP4R	1	numerical	- time verification for ROP stage4 at right eye - 1, OK, two weeks interval or within the physician's prescription. - 2, not Ok, interval too long
CA_ROP4L	3	numerical	- chronological age (days) for the

			first time detection of stage4 ROP at left eye
AA_ROP4L	3	numerical	- adjusted age (days) for the first time detection of stage4 ROP at left eye
OK_ROP4L	1	numerical	- time verification for ROP stage4 at left eye - 1, OK, two weeks interval or within the physician's prescription. - 2, not Ok, interval too long

TIMING OF FINDING RLF AND CRYOTHERAPY

For all of the following variables except "Diagnose", the coding guide are: - 000, normal
777, irregularly recorded
888, not applicable,
999, unknown/not assessed,

CA_RLF1R	3	numerical	- chronological age (days) for first time detection of grade1 RLF for right eye
AA_RLF1R	3	numerical	- adjusted age (days) for first time detection of grade1 RLF for right eye
CA_RLF1L	3	numerical	- chronological age (days) for first time detection of grade1 RLF for left eye
AA_RLF1L	3	numerical	- adjusted age (days) for first time detection of grade1 RLF for left eye
CA_RLF2R	3	numerical	- chronological age (days) for first time detection of grade2 RLF for right eye
AA_RLF2R	3	numerical	- adjusted age (days) for first time detection of grade2 RLF for right eye
CA_RLF2L	3	numerical	- chronological age (days) for first time detection of grade2 RLF for left eye
AA_RLF2L	3	numerical	- adjusted age (days) for first time detection of grade2 RLF for left eye
CA_RLF3R	3	numerical	- chronological age (days) for first time detection of grade3 RLF for right eye
AA_RLF3R	3	numerical	- adjusted age (days) for first time detection of grade3 RLF for right eye
CA_RLF3L	3	numerical	- chronological age (days) for first time detection of grade3 RLF for left eye

AA_RLF3L	3	numerical	- adjusted age (days) for first time detection of grade3 RLF for left eye
CA_RLF4R	3	numerical	- chronological age (days) for first time detection of grade4 RLF for right eye
AA_RLF4R	3	numerical	- adjusted age (days) for first time detection of grade4 RLF for right eye
CA_RLF4L	3	numerical	- chronological age (days) for first time detection of grade4 RLF for left eye
AA_RLF4L	3	numerical	- adjusted age (days) for first time detection of grade4 RLF for left eye
CA_RLF5R	3	numerical	- chronological age (days) for first time detection of grade5 RLF for right eye
AA_RLF5R	3	numerical	- adjusted age (days) for first time detection of grade5 RLF for right eye
CA_RLF5L	3	numerical	- chronological age (days) for first time detection of grade5 RLF for left eye
AA_RLF5L	3	numerical	- adjusted age (days) for first time detection of grade5 RLF for left eye
CA_CT	3	numerical	- chronological age (days) for applying cryotherapy for the eyes
AA_CT	3	numerical	- adjusted age (days) for applying cryotherapy for the eyes
Diagnose	5	numerical	- the diagnosis for the ROP over the time of observation, - record the worst condition among both eyes, - codes are the same as Diag1.

Appendix 3a : NICU Discharge Summary Form

N.I.C.U. DISCHARGE SUMMARY

Name: _____
I.D.#: _____
B.D.: _____
B.W.: _____

Baby's Name: _____
Last First Middle

GENERAL DATA

F.H. Hosp. # or assigned # _____ (1-6)
Card 0 1 (7-8)

Birthdate (Yr-month) _____ (9-12)

*Follow-Up Criteria _____ (13-17)

*0 = none
1 = low birth weight
2 = compl. ventilator course
3 = congenital infection
5 = neuro disorders
6 = other _____ specify
7 = ROP
8 = special study
9 = unknown

*Birthplace _____ (18)

*Where Hospitalized _____ (19)

Age at admission (hrs) _____ (20-22)

Transported _____ (23)

*Days hospitalized: Acute _____ (24-26)
: Other ICN _____ (27-29)
: Other hospital _____ (30-32)

*000 = none
001 = ≤ 24 hrs.
002 = 2 days, etc.
999 = unknown

*Disposition _____ (33)

*1 = home
4 = other hospital _____ specify
5 = died
8 = other
9 = unknown

Autopsy? _____ (34)

Basic Codes

0 = no 4 = suspect
1 = yes 9 = unknown
(Code changes denoted by *)

*Place Codes

*1 = Foothills Hospital
2 = Other Calgary Hospital
3 = Other Alberta Hospital
4 = Out of Province Hospital
5 = Non-Hospital (eg. home, ambulance)
6 = Other _____

BASIC METHOD FOR DETERMINING # OF DAYS

The number of days are determined by subtracting the date of commencement of treatment (or date of admission) from the date of termination of treatment (or date of discharge), or, in other words, by counting calendar days and subtracting one day. If treatment begins and ends on the same day, count as 1 day. Otherwise the above method applies.

e.g. Ventilation begins on July 7 and stops July 9: number of days = 2

Admitted to Acute care July 7 and died July 7: Days hospitalized = 1

Admitted to Acute care July 7, transferred to Prem II on July 10, discharged home on August 3: Days in Acute = 3; days in Prem II = 24

Phototherapy begins July 7, stops July 10, recommences July 12, stops July 14: Total days on phototherapy = 5

Date Completed: _____

*Cause of Death (35-38)

*0000=not applicable (39-42)
9999 = unknown
Use H - ICDA codes for causes

_____ specify
_____ specify

*Sex (43)
*1 = Male
2 = Female

*Multiple Birth (44)
*0 = singleton
1 = twins
2 = triplets or greater

DEMOGRAPHIC DATA

Maternal:
Name: _____

Age at delivery (Yrs): (45-46)

*Marital Status (47)
*1 = two parent family
2 = single parent family
9 = unknown

*Race (48)
*1 = Caucasian
2 = Black
3 = Canadian Indian/Metis
4 = Other _____ specify
9 = unknown

Transported PTD? (49)

*If so, hospital of origin: (50)
*0 = N/A
Use place codes

*Total years in school (51-52)
*99 = unknown

Paternal:
Name: _____

Age at delivery (yrs) (53-54)

Occupation: _____

*Blishen Index (55-56)
*(see manual)

*Total years in school (57-58)
*99 = unknown

*Midparent height (cm) (59-61)
*999 = unknown

*Mother's Obstetrical History (Biological)

(T) # of previous term births (62)

(P) # of previous pre-term births (63)

(A) # of spontaneous abortions (64)

(A) # of therapeutic abortions (65)

(L) # of living children (66)
(not counting this one)
* 8 = ⩾ 8
9 = unknown

LABOUR AND DELIVERY

Drugs in Labor & Delivery

Antibiotics (67)

Steroids (68)

Analgesics (69)

Drugs to arrest Labor (70)

Antihypertensives (71)

Sedatives (72)

Prostaglandins (73)

Other _____ (74)
(specify)

*Anaesthesia for Delivery (75)
*0 = none
1 = pudendal, local, paracervical
2 = caudal
3 = epidural
4 = spinal
5 = general
9 = unknown

Meconium staining? (76)

*Rupture of Membranes (77)
*1 = < 24 hrs PTD
2 = ⩾ 24 hrs PTD
9 = unknown

Monitor? (78)

*Presentation at Delivery (79)
*0 = vertex
1 = breech
8 = other
9 = unknown

CARD 2

Duplicate columns (1-6)

Card 0 2 (7-8)

C - Section (9)

*If so, indications (10-12)
- *0 = n/a
- 1 = fetal distress
- 2 = breech presentation
- 3 = abnormal lie
- 4 = failure to progress
- 5 = APH
- 8 = Other _____ (specify)
- 9 = Unknown

PERINATAL INFECTION

Foul smelling liquor (13)

Maternal fever (14)

Other evidence of maternal infection _____ (specify) (15)

*Risk Score (Coopland's) (16)
- *0 = average
- 1 = increased
- 9 = unknown

*Resuscitation Required (17)
- *0 = none
- 1 = O_2 ± bag and mask
- 2 = intubation
- 3 = cardiac massage
- 4 = yes, type unknown
- 9 = unknown

*Apgars: 1 minute (18-19)

5 minutes (20-21)
- *99 = unknown

*Admission temp. (rectal °C) (22-24)
- *34.9 = too low to record
- 99.9 = unknown

*B.P. on admission (mmHg) (25-26)
- *99 = unknown

Gestational Age (wks) (27-28)

*Intrauterine Growth Status (29)
- *1 = SGA
- 2 = AGA
- 3 = LGA
- 9 = unknown

*MEASUREMENTS *Percentiles

Birthweight (gms)	(30-35)
Birthlength (cm)	(36-40)
Head Circ. (cm)	(41-45)
Chest Circ. (cm)	(46-48)

*9's = unknown
- 04 = < 5th percentile
- 96 = > 95th percentile

*Ponderal Index (49-50)
- *9.9 = unknown

NUTRITION

Minimum Wt. (gms)	(51-54)
Total Wt. lost (gms)	(55-57)
% b.w. lost	(58-59)
*Age b.w. regained (days)	(60-61)
Discharge Wt. (gms)	(62-65)
Parenteral (days)	(66-67)
*Age all feeds taken p.o.	(68-70)
*Formula Used	(71-74)

*Age b.w. regained (days)
- *01 = birthdate or Day 1
- 97 = ≥ 97 days
- 98 = not regained prior to discharge
- 99 = unknown

*Age all feeds taken p.o.
- *001 = birthdate or Day 1
- 998 = not prior to discharge
- 999 = unknown

*Formula Used
- *0 = none
- 1 = EBM
- 2 = BBM
- 3 = 20 cal. formula
- 4 = 24 cal. formula
- 5 = Prosobee
- 6 = Pregestimil
- 7 = Nutramigen
- 8 = Other _____ (specify)
- 9 = unknown

(List in order of frequency of use - i.e. in box 71 enter most frequent; in box 74 least frequent)

*Formula at Discharge
*Cocoes as above
(2 = breast feeding) [ ] (75)

CARD 3
Duplicate columns (1-6)
CARD [0][3] (7-8)

Feeding Problems
Blood in Stools [ ] (9)
Frequent Regurgitation [ ] (10)
Amino Aciduria (tyrosinemia) [ ] (11)
NEC [ ] (12)
Late Edema [ ] (13)
Rec. Abd. Distention [ ] (14)
Other _____ (specify) [ ] (15)

*DRUG UTILIZATION
*0 = not used
1 = used once
2 = used > once
9 = unknown if used

Penicillin [ ] (16)
Ampicillin [ ] (17)
Cloxacillin [ ] (18)
Gentamycin [ ] (19)
Kanamycin [ ] (20)
Other antibiotic or antifungal _____ (specify) [ ] (21)
Mycostatin [ ] (22)
Steroids [ ] (23)
Digoxin [ ] (24)
Lasix [ ] (25)
Other diuretic _____ (specify) [ ] (26)
Indocid [ ] (27)
Atropine [ ] (28)
Pavulon (Pancuronium) [ ] (29)
Dopamine [ ] (30)

Priscoline [ ] (31)
Morphine [ ] (32)
Codeine [ ] (33)
Phenobarbital [ ] (34)
Dilantin [ ] (35)
Theophylline (Aminophylline) [ ] (36)
$NaHCO_3$ [ ] (37)
Iron [ ] (38)
Multivitamins [ ] (39)
Vitamin E [ ] (40)
Calcium (p.o) [ ] (41)
NaCl (p.o.) [ ] (42)
MCT [ ] (43)
Polycose [ ] (44)
*Other [ ][ ] (45-46)
*Specify number used
00 = none
01 = one, etc.
99 = unknown

Total Drugs Used [ ][ ] (47-48)

*Adverse drug reactions [ ] (49)
*0 = none
1 = yes, BPD +/or ROP, RLF only
2 = other than BPD, ROP, RLF
3 = combination of 1 & 2 above
9 = unknown

HEMATOLOGY
*Blood Products (times given)
Packed rbc &/or whole blood [ ][ ] (50-51)
Plasma [ ][ ] (52-53)
Platelets/WBC [ ][ ] (54-55)
*00 = not given
99 = unknown
Hematocrit: max. (SI) [ ][ ][ ] (56-58)
: min. (SI) [ ][ ][ ] (59-61)

Partial Exchange ☐ (62)

*Clotting Disorder ☐ (63)
*0 = none
1 = thrombocytopenia only
2 = DIC (Incl. Thrombocytopenia)
3 = Other _____ (specify)
9 = unknown

JAUNDICE ☐ (64)

Days on phototherapy ☐☐ (65-66)

Exchange Transfusion ☐ (67)

*Etiology ☐ (68)
*0 = n/a
1 = blood group incompatibility
2 = other
9 = unknown

Max. bili: total(SI Units) ☐☐☐ (69-71)

: conj.(SI Units) ☐☐☐ (72-74)

CARD 4
Duplicate columns (1-6)
CARD 0 4 (7-8)

SEPSIS? ☐ (9)

Sepsis Work-ups
More than 2? ☐ (10)

*Work-ups on Day of Delivery
Blood ☐☐ (11-12)
CSF ☐☐ (13-14)
Stool ☐☐ (15-16)
Urine ☐☐ (17-18)
Auger/Trachea ☐☐ (19-20)
Skin ☐☐ (21-22)
Other _____ (specify) ☐☐ (23-24)

*First Postnatal Work-up
Blood ☐☐ (25-26)
CSF ☐☐ (27-28)
Stool ☐☐ (29-30)

Urine ☐☐ (31-32)
Auger/Trachea ☐☐ (33-34)
Skin ☐☐ (35-36)
Other _____ (specify) ☐☐ (37-38)

*Work-up codes
00 = not done
01 = no growth
02 = staph. albus/epidermidis/coagulase neg
03 = stap. aureus/coagulase pos
04 = E. Coli 05 = Klebsiella
06 = pseudomonas
07 = Bacteriodes
08 = Proteus
09 = Group A Strep
10 = Group B Strep
11 = Strep fecalis/gamma strep
12 = Other _____ (specify)
13 = Other _____ (specify)
99 = no report

NEUROLOGIC
*Seizures ☐ (39)
*0 = no
1 = yes, one only
2 = yes, more than one
9 = unknown

*Onset ☐ (40)
*0 = N/A
1 = ≤ 4 days
3 = > 4 days
9 = unknown

*EEG ☐ (41)
_____ (Interpretation)

*CT Scan ☐ (42)
_____ (Interpretation)

*CUS ☐ (43)
_____ (Interpretation)

*0 = not done
1 = normal
2 = abnormal
4 = suspect
9 = unknown if done

*APNEA (44)
*0 = no apnea
1 = apnea, no treatment
2 = apnea, drug treatment
3 = apnea, vent. treatment
4 = apnea, drug, & vent. treatment
6 = apnea, unknown if treated
9 = unknown

*Age of onset (days) (45-47)

*Age resolved (days) (48-50)
*000 = n/a
001 = birthdate or Day 1
998 = not prior to discharge
999 = unknown

VENTILATORY ASSISTANCE (51)

*Age of Onset (52)
*0 = N/A
1 = < 1 hour
2 = 1 to 24 hours
3 = > 24 hours
9 = unknown

Type and Duration
Pos. press. vent.? (53)

*Number of days (54-55)
*00 = N/A
01 = ⩽ 24 hrs
02 = 2 days, etc.
98 = ⩾ 98 days
99 = unknown

Other (CPAP-ET, CPAP-prongs,CNP)? (56)

*Number of days (57-58)
*00 = N/A
01 = ⩽ 24 hrs.
02 = 2 days etc.
98 = ⩾ 98 days
99 = unknown

Tracheostomy (59)

Orotracheal Tube (60)

Nasotracheal Tube (61)

*Max. insp. pressure (cm) (62-63)
*00 = N/A

*Max. end exp. pressure (cm) (64-65)
*00 = N/A

art. pO_2's > 100 (66-67)

cap. pO_2's > 50 (68-69)

Complications During Vent. Asst.

Atelectasis (70)

Prolonged Hypoxia (pO_2 art < 50) (71)

Prolonged acidosis (pH < 7.2) (72)

Nasal narrowing (73)

Post-extubation airway obstruction (74)

Pneumopericardium (75)

Emphysema (76)

Other extrapleural air (77)

Other _____ (specify) (78)

CARD 5

Duplicate Columns (1-6)
Card 0 5 (7-8)

Vessel Catheterization and Duration

Umbilical artery cath. (9)

*Days Catheterized (10-11)
*00 = N/A
01 = ⩽ 24 hrs.
02 = 2 days, etc.
98 = ⩾ 98 days
99 = unknown

Other artery Cath. (12)

*#Days catheterized (13-14)
*00 = N/A
01 = ⩽ 24 hrs.
02 = 2 days, etc.
98 = ⩾ 98 days
99 = unknown

*Complications of Catheterization (15)
*0 = none
1 = vasc. trans.
2 = vasc. perm.
8 = other
9 = unknown

Total days in O_2 (16-18)

Days in O_2 & art. line (19-21)

>1 episode vent. support (22)

DIAGNOSES

Cardiovascular

*PDA (23)
*0 = no
1 = yes, treated surgically
2 = yes, not treated surgically
4 = suspect
9 = unknown

VSD (24)

Persistent Fetal Circulation (25)

*Other (26)
*0 = none
1 = ASD
2 = pulmonic stenosis
3 = transposition
4 = coarctation
8 = other _____ (specify)
9 = unknown

Pulmonary

RDS (27)

Meconium aspiration (28)

Atelectasis (29)

*Pneumothorax - right (30)

- left (31)
*0 = no
1 = yes, spont. with tube
2 = yes, post-op. with tube
3 = yes, spont. no tube
4 = yes, post-op. no tube
9 = unknown

Transient Tachypnea (32)

Pulmonary insufficiency of prematurity (33)

[redacted] &PD (34)

Emphysema (35)

*Other (36-37)
*0 = none
1 = aspiration, not meconium
2 = hypoplastic lung
3 = pulm. hemorrhage
4 = pneumonia, pneumonitis
5 = bronchial stenosis
8 = other _____ (specify)
9 = unknown

*Gastrointestinal (Congenital) (38-39)
*0 = none
1 = Inguinal hernia
2 = diaphragmatic hernia
3 = TE fistula
4 = gastroschisis or omphalocele
5 = small bowel obst.
6 = large bowel obst.
7 = mec. plug
8 = other _____ (specify)
9 = unknown

*Gastrointestinal (Acquired) (40-41)
*0 = none
1 = obstruction
2 = perforation
8 = other _____ (specify)
9 = unknown

*Genitourinary (Congenital) (42)
*0 = none
1 = cryptorchidism
2 = ambiguous genitalia
3 = neurogenic bladder
4 = hydronephrosis
5 = hypoplastic kidney
6 = polycystic kidney
7 = hypospadias
8 = other _____ (specify)
9 = unknown

*Genitourinary (Acquired) (43-44)
*0 = none
1 = UTI
2 = hematuria
3 = renal failure
8 = other _____ (specify)
9 = unknown

Neurology

Peripheral Nerve Injuries (45)

*Malformations of CNS (46)
*0 = none
1 = anencephaly
2 = hydrocephalus with ICH
3 = hydrocephalus without ICH
4 = microcephaly
5 = hydranencephaly
6 = meningomyelocele
7 = encephalocele
8 = other _____ (specify)
9 = unknown

Hemorrhages

Subarachnoid (47)

Cerebral (48)

*Intraventricular (49)
*0 = no
1 = grade 1 (mild)
2 = grade 2 (moderate)
3 = grade 3 (moderate)
4 = grade 4 (large)
8 = yes, grade unknown
9 = unknown

Hypoxic Ischemic Encephalopathy (50)

*Musculoskeletal Abnormalities (51)
*0 = none
1 = CDH/hip click
2 = club foot
3 = supernumary digits
4 = cong. amputation
8 = other _____ (specify)
9 = unknown

*Mouth, Larynx, Trachea Abnormalities (52)
*0 = none
1 = cong. stridor
2 = subglottic stenosis
3 = cleft palate &/or lip
4 = supraglottic/glottic acquired abnormalities
8 = other _____ (specify)
9 = unknown

Miscellaneous

Dysmorphic Features not listed elsewhere (53)

Choanal atresia (54)

*Trisomy (55)
*0 = no
1 = yes, 21
2 = yes, other
3 = yes, type unknown
4 = suspect
9 = unknown

Other syndrome _____ (specify) (56)

ASSESSMENTS IN N.I.C.U.

EYE

Ophthalmologic consult (57)

Vascularization Complete? (58)

*Cong. Abnormality (59)
*0 = none
1 = cataract, unilateral
2 = cataracts, bilateral
8 = other
9 = unknown

Chorioretinitis (60)

Conjunctival hemorrhage (61)

Retinal hemorrhage (62)

Vitreous hemorrhage (63)

*Retinopathy of prematurity (64)
*0 = no
1 = yes, grade 1
2 = yes, grade 2, etc.
3 = yes, grade 3
4 = yes, grade 4
6 = yes, grade 3+
8 = yes, grade unknown
9 = unknown

*Retrolental fibroplasia (65)
*0 = no
1 = yes, grade 1
2 = yes, grade 2
3 = yes, grade 3
4 = yes, grade 4
8 = yes, grade unknown
9 = unknown

Cryopexy? (66)

PHYSIO

*Gest. age at assess. (wks) (67-68)
*41 = > 40
99 = unknown

*Outcome (69)
*0 = normal
1 = profoundly abnormal
2 = abnormal
4 = suspect
9 = unknown

*GM Reflex (months) (70-71)
*99 = unknown

*Tone - upper (72)

- lower (73)

- trunk (74)
*0 = normal
1 = increased
2 = decreased
9 = unknown

*Primitive Reflexes (75)
*0 = normal
1 = abnormal
4 = suspect
9 = unknown

*N.I.C.U. HEARING (76)
*0 = normal
1 = abnormal
4 = suspect
9 = unknown

DISCHARGE SUMMARY FORM # 2 (77)

Appendix 3b: Independent Variables for the Study
(variables collected in NICU Discharge Summary Form)

Parents Social Demographic Factors:

Maternal age
- age (years) of biological mother at delivery.

Maternal race
- race of biological mother; is broken down into Caucasian (represents persons of European ancestry), Black, Canadian/Meti, others(includes Oriental, Arabs, East Indians, etc).

Marital status
- two parent families indicate any type of arrangement with a mother and father figure in the home, whether married or not; single parent family indicates any arrangement other than a mother and father figure in the home, whether married or not.

Maternal school years
- total years of education sociological mother has.

Paternal school years
- total years of education sociological father has.

Blishen Index
- socioeconomic index for sociological father's occupation (Blishen & McRoberts, 1976).

Maternal Factors:

OBSTETRICAL HISTORY

Parity
- # of total previous pregnancies. It is the sum of previous term birth, previous preterm birth, previous spontaneous abortion and previous therapeutic abortion.

Previous preterm birth
- number of premature (<37 weeks of gestation) babies biological mother has given birth to prior to this birth.

# of living children
- all living children whether or not in the home, including the twins or triplets of this baby and previously adopted children.

LABOUR AND DELIVERY

# of total drugs used
- record the total number of drugs used during labour and delivery. Drugs include antibiotics, steroids, drugs to arrest labour, antihypertensives, sedatives, Prostaglandins, and others.

Fetal heart monitor
- whether a fetal heart monitor was used prior to delivery.

C-section
- whether a Cesarean section was performed

C-section indications:

Fetal distress
- fetal distress, or fetal bradycardia, tachycardia, variable deceleration was an indicator for C-section.

Antepartum haemorrhage (APH)
- antepartum haemorrhage, or placenta previa, abruptio placenta was an indicator for C-section.

# of indications
- the total number of indications for C-section, including fetal distress, antepartum haemorrhage, breech presentation, abnormal lie, failure to progress, and others(such as cord prolapse, prolonged ROM).

Perinatal infection:

Foul smelling liquor
- indicated by amniotic fluid foul smelling, or chorioamnionitis.

Maternal fever
- whether mother had a temperature of >38°C.

Other infection
- whether there was any other evidence of maternal infection, such as positive cultures, increased WBC, foul smelling discharge.

Coopland Risk Score
- a score system to determine obstetrical risk score of average or increased.

Neonatal Characteristics:

Sex - male or female

Multiple birth
- defined as twins, triplets or greater.

Gestational age
- gestational age at birth (weeks), using Dubowitz score if done, clinical assessment or mother's dates. If discrepant, use sure dates as first choice. (Dubowitz, et al., 1970)

Birth weight
- birth weight in grams

Ponderal's Index
- determined by the formula, and round off to one decimal place. [birth weight(gms)*100]/[birth length(cm)^3]

Intrauterine growth status
- classified as small for gestational age (SGA), average for gestational age (AGA) and large for gestational age (LGA) based on following criteria:
  SGA = BW <10th percentile +/or Ponderal's index <2.0
  AGA = 10th percentile=< BW =< 90th percentile + ponderal's index >=2.0
  LGA = BW >= 90 percentile and Ponderal's index >=2.0

1 minute Apgar
- Apgar score at one minute of age

5 minutes Apgar
- Apgar score at five minutes of age

Resuscitation required
- whether resuscitation required or not. The procedure was broken down into O_2 with/without bag and mask; intubated; cardiac massage. If more than one procedure used, record the most vigorous one.

Birth place
- record the place of infants birth and categorized as: Foothills Hospital, other Calgary hospital, other non-Calgary hospital, non-hospital.

Place of hospitalization
- place where NICU treatment primarily provided and categorized as Foothills Hospital, other Calgary hospitals, other non-Calgary-hospital, non-hospital.

Disposition
- the location, either home or other hospital, to which infants was discharged.

Neonatal Follow-up Criteria and Hospital Stay:

FOLLOW-UP RISK CRITERIA

# of risk criteria
- total number of risk criteria under which the baby has enroled into study. There are six different risk criteria taken into account: on ventilator, congenital infection, neurological disorder, ROP, low birth weight, others. Four significant risk criteria were recorded separately and explained as follows:

on ventilator
- whether baby had been on a ventilator at least 8 days and/or have had a complicated ventilator course.

congenital infection
- whether baby had an infection at birth, includes such congenital infections as toxoplasmosis, rubella, cytomegalovirus, herpes, syphilis, gonorrhoea, or others.

neurological disorder
- whether baby had exhibited seizures or other abnormal neurological signs or symptoms.

Retinopathy of prematurity
- whether baby developed ROP stage 1

HOSPITALIZATION

Acute NICU days of stay
- number of days baby was in most acute level of care in NICU

Total NICU days of stay
- number of days baby was in both most acute level and less acute level of care in NICU.

Total hospital days of stay
- total NICU days of stay plus other hospital stay.

Neonatal Ventilatory Assistance and O_2 Supplementation:

Ventilatory assistance
- defined as positive pressure ventilator, CPAP (by ET or nasal prongs) or CNP, excluding ventilatory assistance for resuscitation purpose in Case room, if discontinued before admission to NICU.

Age hours of onset
- age in hours at which ventilatory assistance (PPV, CPAP or

CNP) was first begun.

Days of PPV
- number of days baby was on PPV. PPV defined as intubated and having both inspiratory and expiratory pressures controlled. "0" means that PPV was never used.

Days of other ventilatory assistance
- number of days baby received any combination of CPAP (ET or nasal prongs) or CNP. On CPAP, baby inhales on own, but exhalation was controlled so functional residual capacity of lungs does not go below a specified level. CNP is essentially an iron lung.

Maximum inspiratory pressure
- the highest inspiratory pressure (cm H_2O) used during ventilatory assistance. "0' means that a PPV was not used.

Maximum expiratory pressure
- the highest end expiratory pressure (cm H_2O) used during ventilation. "0' means that the baby was never ventilated.

# of arterial PO_2>100
- the number of arterial PO_2 were >100.

# of capillary PO_2>50
- the number of capillary PO_2 were >50.

Complication during Ventilatory Assistance:

Atelectasis
- atelectasis was occurred during ventilatory assistance or within 24 hours of being removed from assistance.

Prolonged hypoxia
- defined as more than two successive times PO_2's <50.

Prolonged acidosis
- defined as more than two successive times pH's <7.2.

Post extubation airway obstruction
- an airway obstruction occurred after extubation.

Emphysema
- emphysema was occurred during ventilatory assistance, excluding subcutaneous emphysema.

Other extrapleural air
- presence of other extrapleural air, such as pneumomediastinum or subcutaneous emphysema.

Others

- other complications were occurred during ventilatory assistance.

Total days in O_2
- total days of baby was receiving oxygen. "0' means that baby received none.

Episodes of ventilatory support >1
- baby was taken off assisted ventilation and restarted after a period of time.

Neonatal Respiratory Problems:

Apnea
- apnea is defined as the apnea or bradycardia which occurs more than 2 episodes per day for more than one day and requires stimulation. It is broken down into 3 categories depends on treatment procedures:
  1) treated only by cutaneous stimulation or alteration of environmental temperature;
  2) treated by drug but no oxygen;
  3) treated by oxygen, bag and mask ventilation, CPAP and/or assisted ventilation. Treat water beds is equivalent to assisted ventilation.

Apnea age of onset
- age in hours at which episodes of apnea or bradycardia requiring stimulation first occurred.

Apnea duration (days)
- duration between the apnea onset and apnea resolved.

Respiratory distress syndrome
- whether RDS or Hyaline membrane disease (HMD) was diagnosed.

Meconium aspiration
- whether meconium aspiration confirmed by X-ray was existed.

Pneumothorax
- whether pneumothorax was diagnosed for either lung.

Atelectasis
- whether baby had atelectasis which was confirmed by X-ray, or diagnosed as "collapsed lung". This includes the atelectasis as a complication of ventilatory assistance.

Transient tachypnea
- wether a transient tachypnea, wet lung or delayed resorption of lung fluid was diagnosed.

Pulmonary insufficiency of prematurity (PIP)
- whether PIP or respiratory insufficiency of prematurity was observed.

Bronchopulmonary dysplasia (BPD)
- whether a BPD or chronic obstructive pulmonary disease (COPD or CPD) confirmed by X-ray was noted.

Emphysema
- whether baby had emphysema confirmed by X-ray. This includes the complication of ventilatory assistance.

Other pulmonary problems
- whether baby had any other confirmed pulmonary disorders.

Neonatal Drug Utilization :

Total drugs used
- the number of drugs used during NICU stays. Drugs being observed are: penicillin, Ampicillin, Cloxacillin, Gentamycin, Kanamycin, other antibiotic or antifungal, Mycostatin, Steroids, Digoxin, Lasix, other diuretic, Indocid, Atropine, Pavulon, Dopamine, Priscoline, Morphine, Codeine, Phenobarbital, Dilantin, Theophyllline, $NaHCO_3$, Iron, Multivitamins, Vitamin E, Calcium (p.o.), NaCl(p.o.), Median chain Triglycerides oil (MCT), Polycose and others.
  All of these drugs were all observed as separate variables to examine their relationship to severe ROP.

Other Neonatal Factors:

CARDIOVASCULAR PROBLEM:

Patus ductus arteriosus(PDA)
- diagnosis was confirmed only by X-ray or cardiology consult, otherwise considered as "suspect". For established PDA, treated surgically or not was recorded.

Ventricular septal defect (VSD)
- whether a diagnosis of VSD was made. Diagnose should be confirmed by X-ray or cardiology consult.

Persistent fetal circulation (PFC)
- whether PFC was diagnosed.

NUTRITION AND FEEDING

Parenteral days

- the number of days of baby received parenteral nutrition including both total and partial. "0" means that baby never had parenteral feeding.

Age of all food taken orally
- age in days at time all feeds taken orally. Baby must not be receiving parenteral nutrition during this time.

HAEMATOLOGY

# of blood products given
- number of times baby received packed red blood cells, whole blood or both.

Maximum hematocrit
- the highest hematocrit value in SI unit obtained.

Minimum hematocrit
- the lowest hematocrit value in SI unit obtained.

HAEMORRHAGE

Subarachnoid
- haemorrhage outside brain was observed.

Cerebral
- haemorrhage into brain tissue (IVH grade 4) was diagnosed.

Intraventricular (IVH)
- whether IVH was diagnosed. If IVH is diagnosed, further assessment of grades is made.
  Grade 1 is mild or subependymal; grade 2 is a moderate bleed with no dilatation of ventricles and no hydrocephalus; grade 3 is moderate with dilatation of ventricles and early hydrocephalus; grade 4 is severe or large with intracerebral extension (cerebral haemorrhage).

OTHERS

Hypoxic ischemic encephalopathy(HIE)
- whether baby had a diagnosis with HIE

Sepsis
- whether sepsis was observed. Sepsis is defined as a positive blood or cerebral-spinal fluid (CSF) at any time during NICU stay.

Seizure
- whether seizure was occurred. Seizure is defined by specific diagnoses or "seizure-like activity" which can not be stopped by restraint.

Appendix 4: Follow-up Outcome Form

ID number: _____ Birth weight (g): _____
Chronological age (month) _____ Adjusted age (month) _____
Months since last report _____
Date of Assessment/death (yr/mo) _____
Source of information _____
Cause of death _____

OPHTHALMOLOGY:

Ophthalmology	0 -normal (normal ocular motility, fudus, refraction at lest 20/30 bilaterally) 1 -profoundly abnormal (blind or major visual impairment) 2 -abnormal (strabismus requiring treatment or refractive error requiring glasses) 4 -suspect (? strabismus; ? visual acuity; major arterial tortuosity or persistent retinopathy) 5 -presumed normal based on previous assessment 6 -presumed suspect based on previous assessment 7 -presumed abnormal based on previous assessment 8 -presumed profoundly abnormal based on previous assessment 9 -unknown/not assessed
Visual acuity	0 -normal 1 -abnormal. bilaterally 2 -abnormal, right eye only 3 -abnormal, left eye only 4 -suspect 9 -unknown/not assessed
Referaction	0 -normal 1 -abnormal. bilaterally 2 -abnormal, right eye only 3 -abnormal, left eye only 4 -suspect 9 -unknown/not assessed
Strabismus	0 -no 1 -abnormal(including nystagmus) 4 -suspect 9 -unknown/not assessed
ROP-right eye	0 -none 1 -yes, stage 1

	2 -yes, stage 2
	3 -yes, stage 3
	4 -yes, stage 4
	5 -yes, vascular irregularity (grade 1 RLF)
	6 -plus disease
	7 -previous ROP, now resolved
	9 -unknown/not assessed
-left eye	0 -none
	1 -yes, stage 1
	2 -yes, stage 2
	3 -yes, stage 3
	4 -yes, stage 4
	5 -yes, vascular irregularity (grade 1 RLF)
	6 -plus disease
	7 -previous ROP, now resolved
	9 -unknown/not assessed
RLF-right eye	0 -none
	1 -yes, grade 1
	2 -yes, grade 2
	3 -yes, grade 3
	4 -yes, grade 4
	5 -yes, grade 5
	6 -yes, not graded
	9 -unknown/not assessed
-left eye	0 -none
	1 -yes, grade 1
	2 -yes, grade 2
	3 -yes, grade 3
	4 -yes, grade 4
	5 -yes, grade 5
	6 -yes, not graded
	9 -unknown/not assessed
Treatment	0 -none
	1 -previous cryotherapy
	2 -under treatment for refractive error
	3 -under treatment for strabismus
	4 -under treatment for amblyopia
	5 -under treatment for other condition
	8 -combination for above
	9 -unknown/not assessed