RISK FACTORS IN DEVELOPING RETINOPATHY OF PREMATURITY IN A NEWBORN

Arejenald U. Meollo M.D.
Principal Author

Marissa Salas MD, FPPS, FSPCCMP, FPSCCM
Co-Author

Our Lady of Lourdes Hospital Department of Pediatrics
Institutional Affiliation

ABSTRACT

I. OBJECTIVE: To identify the risk factors which predispose to retinopathy of prematurity.

II. DATA SOURCES: The population of this study consists of infants born premature admitted at the Neonatal Unit of a private tertiary institution. The medical records of 124 premature infants born from January 2011 to January 2013 were gathered. Presence of known and possible risk factors in developing Retinopathy of Prematurity (ROP) were evaluated using these medical records.

III. REVIEW METHOD: Data were analyzed using Stata version 10 software. Frequency tables were generated to show the distribution of prematures according to maternal obstetrical factors, neonatal factors, course of hospital stay and occurrence of ROP. To determine differences between those who developed and those who did not develop ROP, chi square test and Fishers exact test when applicable were utilized for qualitative variables and independent t-test for quantitative variables. Crude analysis was done to determine the association of selected factors independently with the development of ROP.

IV. RESULTS: Mothers had a mean age of 31 years. Majority had no pre-partum illnesses like preeclampsia, maternal pyrexia and PROM. Most delivered via caesarian section with preeclampsia as the most common indication. Majority of the preterms were 35-36 weeks AOG and weighed between 1500 to less than 2500 grams. Most had Apgar scores of 8 and 9 at 1 and 5 minutes of life, respectively. Almost equal distribution of males and females. Majority did not develop jaundice. The mean length of stay at the NICU was 19 days. For those needing oxygenation, it was given for 8 days on the average. Majority did not require mechanical ventilation. The maximum level of Fi02 (100%) was used in 26% of cases. Out of 124 preterm neonates, 31 (25%) developed ROP. The mean age at detection was 30 days.

V. CONCLUSION: Maternal age was older, duration of PROM was longer, and the proportion of those delivered by caesarian section was higher among those who had ROP. Gestational age was earlier, birthweight was lower and 1-minute Apgar scores were also lower among those who developed ROP. NICU stay and duration of O_2 therapy was longer, level of FiO_2 was higher and a greater proportion placed on mechanical ventilation was seen among those who developed ROP. The final regression model for factors associated with the development of ROP showed birthweight and FiO_2 to be significantly associated with developing ROP.

KEYWORDS: prematurity – retinopathy of prematurity – risk factors

INTRODUCTION

Retinopathy of prematurity (ROP) is a disorder of the developing retina and an important and potentially preventable cause of blindness in childhood. Although treatment options are available, the prevention of ROP is highly desirable. It is widely acknowledged that ROP is a multi-factorial disorder, with low gestational age, low birth weight, oxygen exposure, neonatal sepsis, and bronchopulmonary dysplasia being important risk factors. Some of the risk factors appear to contribute to ROP by affecting the systemic cytokine and growth factor milieu.[1]

ROP is characterized by abnormal neovascular development in the retina of premature infants. These abnormal blood vessels are fragile and can leak or bleed, scarring the retina and pulling it out of position. This causes a tractional retinal detachment, which is the main cause of visual impairment and blindness in ROP.[2] ROP is always correlated with the level of oxygen use in journals. However, some preterms that were not given oxygen support also developed this condition.

Retinopathy of prematurity (ROP) is the main cause of visual impairment in premature infants. The increased survival of extremely low birth weight (ELBW) infants in recent years, due to advances in neonatal care, has produced a population of infants at very high risk of developing ROP. It has been believed for many years that oxygen therapy increases the risk of ROP in preterm infants. However, ROP can occur even with careful control of oxygen therapy. Several factors increase the risk of ROP, especially those associated with short gestation and low birth weight. Other identified risk factors include sepsis, intraventricular hemorrhage, exposure to light, blood transfusions, and mechanical ventilation.[3]

Prematurity has been established as the major risk factor in development of retinopathy. Early diagnosis of retinopathy will give a better chance of preventing loss of sight in these infants. Establishing other conditions other than prematurity in the causation of retinopathy is therefore important in its prevention and management. This study identifies risk factors for ROP other than those established in previous papers.

REVIEW OF RELATED LITERATURE

Prematurity is a term for the broad category of neonates born at less than 37 weeks gestation.[4] The length of a normal pregnancy or gestation is considered to be 40 weeks (280 days) from the date of conception. Infants born before 37 weeks gestation are considered premature and may be at risk for complications.[5]

Retinopathy of prematurity is a serious complication of prematurity treatment and will lead to blindness if not recognized and treated early. It is an important cause of preventable blindness in children. A cohort study by Chen et. al. in 2011 suggests that neonatal sepsis, oxygen exposure and low gestational age are

not only independently associated with a significantly increased risk for ROP, but also interact in a fashion that suggests synergistic effects that go beyond additive and even multiplicative patterns between low gestational age and any sepsis.[6] The currently used international classification of ROP describes the location, extent, and severity of the disease. To delineate location, the retina is divided into three concentric zones, centered on the optic disc. Zone I, the posterior or inner zone, extends twice the disc-macular distance, or 30 degrees in all directions from the optic disc. Zone II, the middle zone, extends from the outer edge of zone I to the ora serrata nasally and to the anatomic equator temporally. Zone III, the outer zone, is the residual crescent that extends from the outer border of zone II to the ora serrata temporally, this area of the retina being vascularized. The extent of involvement is described by the number of circumferential clock hours involved. The phases and severity of the disease process are classified into five stages. Stage 1 is characterized by a demarcation line that separates vascularized from avascular retina. This line lies within the plane of the retina and appears relatively flat and white. Often noted is abnormal branching or arcading of the retinal vessels that lead into the line. Stage 2 is characterized by a ridge; the demarcation line has grown, acquiring height, width, and volume and extending up and out of the plane of the retina. It may change from white to pink. Vessels may leave the plane of the retina to enter the ridge. Stage 3 is characterized by the presence of a ridge and by the development of extraretinal fibrovascular tissue. Stage 4 is characterized by subtotal retinal detachment caused by traction from the proliferating tissue in the vitreous or on the retina. Stage 4 is subdivided into two phases: (1) subtotal retinal detachment not involving the macula and (2) subtotal retinal detachment involving the macula. Stage 5 is total retinal detachment. When signs of posterior retinal vascular changes accompany the active stages of ROP, the term plus disease is used. Patients reaching the point of dilatation and tortuosity of the retinal vessels also frequently demonstrate the associated findings of engorgement of the iris, pupillary rigidity, and vitreous haze.[7]

Advances in neonatal care in the last decade improved the survival rates for premature infants. Consequently, the incidence of ROP has increased in parallel. It is under constant epidemiological study around the world. Early identification of retinal damage and the institution of appropriate treatment prevents blindness and offers the child better overall development. Studies around the world have been conducted to find the relationship between comorbid conditions and maturity of newborns in developing retinopathy.[8]

In a retrospective cohort study by Narong Thongharn in 2010 at Thailand entitled Risk Factors of Retinopathy of Prematurity, data from medical records of premature babies with a gestational age (GA) of ≤32 weeks or a birth weight (BW) of ≤2,000 grams and who were admitted at Roi-Et Hospital between October 2006 and September 2010, were collected and analyzed to identify risk of

ROP by independent t-test and logistic. It concluded that the important risk factors associated with the development of ROP were Respiratory Distress Syndrome (RDS) and hypothermia. The means of gestational ages and birth weight were also noted to be lower in ROP patients than non ROP patients. Prevention of prematurity and avoidance of these risk factors can thus reduce the incidence of ROP.[9]

OBJECTIVES

GENERAL OBJECTIVES

To identify the risk factors which predispose to retinopathy of prematurity among premature infants.

SPECIFIC OBJECTIVES

1. To determine the relationship between retinopathy of prematurity and each of the following risk factors:
    a. Mode of delivery
    b. Age of gestation
    c. Birth Weight
    d. Gender
    E. APGAR score at 5 minutes of life
    f. Number of days on oxygen support
    g. Jaundice
    h. Number of days in phototherapy
    i. Number of days stay in neonatal unit
    J. FiO2 used
    K. Use of mechanical ventilator
    L. Age at which ROP detected
    m. Maximum stage of ROP reached
    n. Maternal age
    o. Preecclampsia in the mother
    p. Preterm Premature Rupture of membrane (PPROM)
    q. Presence of maternal pyrexia

2. To determine which of the abovementioned risk factors are significantly associated with ROP.

STUDY DESIGN

Cross-Sectional Study

PATIENTS AND METHODS

SETTING:

Private tertiary institution

SUBJECTS:

The population of this study consists of infants born premature admitted at the Neonatal Unit of a private tertiary institution.

INCLUSION CRITERIA:

Male and female preterm (<37 weeks AOG) infants born via Cesarean section or normal spontaneous delivery from January 2011-January 2013 in a private tertiary institution.

EXCLUSION CRITERIA:

Neonates who died before the first ophthalmologic examination and infants with congenital anomalies.

STUDY PROCEDURE:

The medical records of 124 premature infants born from January 2011 to January 2013 were gathered. Presence of known and possible risk factors in developing Retinopathy of Prematurity (ROP) were scrutinized using

these medical records. The risk factors included were: mode of delivery, age of gestation, birth weight, gender, APGAR score at 1 and 5 minutes of life, number of days on oxygen support, jaundice, number of days in phototherapy, number of days stay in neonatal unit, FiO2 used, use of mechanical ventilator, age at which ROP detected, maximum stage of ROP reached, maternal age, preecclampsia in the mother, preterm premature rupture of membrane (PPROM), and presence of maternal pyrexia.

Data were analyzed using Stata version 10 software. Frequency tables were generated to show the distribution of prematures according to maternal obstetrical factors, neonatal factors, course of hospital stay and occurrence of ROP. To determine differences between those who developed and those who did not develop chi square test and Fishers exact test when applicable were utilized for qualitative variables and independent t-test for quantitative variables. Crude analysis was done to determine the association of selected factors independently with the development of ROP.

SAMPLE SIZE

For determining factors associated with the development of ROP, current literature provided estimates only for gestational age and birth weight. In the absence of available information from the literature on Apgar score at 1 minute, need for mechanical ventilation, duration of oxygen therapy and level of Fi02, an initial run of the data provided values for these proportions which was used in power calculation and sample size estimation. The largest of these values was the final sample size requirement.

In a study on the incidence and risk factors for ROP (Alpay and Ugurbas, 2012), ROP developed in 43.2% of those <32 weeks AOG and in 50% of those weighing 1500 grams or less. Utilizing the formula for test of hypothesis between two proportions, incorporating the power of the test at 5% level of significance, the estimated sample size was 35 per group (Appendix A).

Appendix A:

$$n = \frac{\left(Z_{1-\alpha}\sqrt{2\bar{P}\bar{Q}} + Z_{1-\beta}\sqrt{(P_1Q_1 + P_2Q_2)}\right)^2}{(P_1 - P_2)^2}$$

Age of gestation:

Where P_1 is the proportion of preterms who developed ROP among those < 32 weeks AOG = .432 (Alpay and Ugurbas, 2012)

P_2 is the proportion of preterms who developed ROP among those ³ 32 weeks AOG = .093 (Alpay and Ugurbas, 2012)

$Z_{1-\alpha}$ is 1.96 corresponding to a two-tailed α error of .05

$Z_{1-\beta}$ is 0.84 corresponding to a one-tailed error of 0.2 or 80% power

$$\bar{P} = \frac{P_1 + P_2}{2} \qquad \bar{Q} = 1 - \bar{P} \qquad Q_1 = 1 - P_1 \qquad Q_2 = 1 - P_2$$

$$n = \frac{\left(1.96\sqrt{2(.263)(.738)} + .84\sqrt{(.432)(.568) + (.093)(.907)}\right)^2}{(.432 - .093)^2}$$

n = 25 per group of gestational age

Birthweight:

Where P_1 is the proportion of preterms who developed ROP among those < 1500 g = .50 (Alpay and Ugurbas, 2012)

P_2 is the proportion of preterms who developed ROP among those ³ 1500 g = .186 (Alpay and Ugurbas, 2012)

$$n = \frac{\left(1.96\sqrt{2(.343)(.657)} + .84\sqrt{(.50)(.50) + (.186)(.814)}\right)^2}{(.50 - .186)^2}$$

n = 35 per group of birthweight

For other selected factors:

The ability to detect a difference in the proportion of those who developed ROP based on the present sample size of the study for the other selected factors is given in the following table :

	Present sample size	Power for present sample size	Sample size needed to achieve 80% Power
Duration of O_2 therapy		100%	
³ 6 days	38		8
< 6 days	86		8
1 minute Apgar Score		NAN	
< 7	5		27
³ 7	119		27
Need for mechanical ventilation		99.9%	
Yes	37		10
No	87		10
Level of FiO_2		100%	
100%	32		7
<100%	92		7

The final sample size was 35 per group of the selected factors.

STATISTICAL ANALYSIS

Data was analyzed using Stata version 10 software. Frequency tables were generated to show the distribution of prematures according to maternal obstetrical factors (maternal age, presence of preecclampsia and maternal pyrexia, duration of PROM, mode of delivery, indication for CS), neonatal factors (gestational age, birthweight, apgar score and gender), course of hospital stay (occurrence of jaundice, length of phototherapy, duration of stay at the NICU, number of days on oxygen therapy, need for mechanical ventilation, level of Fi02 used) and occurrence of ROP (age at which ORP was detected, maximum stage of ROP reached and therapy given).

To determine differences between those who developed and those who did not develop ROP in terms of the above factors, chi square test and Fishers exact test when applicable was utilized for qualitative variables and independent t-test for quantitative variables. A p-value < 0.05 was used as cut-off for significance.

Crude analysis was done to determine the association of selected factors independently with the development of ROP. Risk ratios with 95% confidence intervals were likewise computed.

However, crude analysis has its limitations and so binary logistic regression using backward elimination procedure was carried out to determine factors significantly associated with the development of ROP.

RESULTS

I. General Data

There were a total of 124 preterms delivered from January 2011 to January 2013. Table 1 shows their distribution as to gender, birthweight, and age of gestation.

Table 1: General data Preterm Neonates

Gestational Age	n	%
< 32 weeks	21	17
³ 32 weeks	103	83
total	124	100
Birthweight		
< 1500 grams	22	18
³ 1500 grams	102	82
total	124	100
Gender		
Male	63	51
Female	61	49
total	124	100

II. Profile of Cases

Mothers of the preterm neonates had a mean age of 31 SD ± 5 years, the youngest being 18 and the oldest being 45 years old. Majority had no pre-partum illnesses like preeclampsia, maternal pyrexia and PROM. Most delivered via caesarian section with preeclampsia as the most common indication *(Table 2).*

Table 2: Distribution of Preterm Neonates according to Maternal Obstetric Factors

Maternal Obstetric Factors	No. (%)
Maternal Age (in years)	
Mean, sd	30.9, 5.0
Median (min, max)	31 (18, 45)
Preeclampsia	
With	32 (25.8)
Without	92 (74.2)
total	100
Maternal Pyrexia	
With	1 (0.8)
Without	123 (99.2)
total	100
Duration of PROM (in hours)	
0	107 (86.3)
10	2 (1.6)
12	8 (6.5)
13	2 (1.6)
14	2 (1.6)
18	3 (2.4)
total	100
Mode of Delivery	
Caesarian Section	81 (65.3)
Normal Spontaneous Delivery	43 (34.7)
total	100
Indications for Caesarian Section	
Preeclampsia	32 (39.5)
Twin pregnancy	12 (14.8)
PPROM	11 (13.6)
Repeat CS	10 (12.3)
Non-reassuring Fetal Heart Rate Pattern	7 (8.6)
Placenta Previa	4 (4.9)
Breech	3 (3.7)
Placental Insufficiency	1 (1.2)
Failure of Descent	1 (1.2)
ACD	1 (1.2)
total	100

Table 3: Distribution of Preterm Neonates according to Neonatal Factors

Neonatal Factors	No.(%)
Gestational Age (in weeks)	
24	1 (0.8)
26	1 (0.8)
27	1 (0.8)
28	2 (1.6)
29	4 (3.2)
30	2 (1.6)
31	10 (8.1)
32	6 (4.8)
33	16 (12.9)
34	15 (12.1)
35	34 (27.4)
36	32 (25.8)
total	100
Birthweight (in grams)	
< 1500	22 (17.7)
1500 to < 2500	95 (76.6)
≥ 2500	7 (5.7)
total	100
Apgar Score at 1 minute	
2	1 (0.8)
3	2 (1.6)
5	2 (1.6)
7	26 (21.0)
8	93 (75.0)
total	100
Apgar Score at 5 minute	
7	1 (0.8)
8	19 (15.7)
9	101 (83.5)
	100
Gender	
Male	63 (50.8)
Female	61 (49.2)
total	100

Majority of preterms were aged 35-36 weeks and weighed between 1500 to less than 2500 grams. Most had Apgar scores of 8 and 9 at 1 and 5 minutes of life, respectively. There was almost equal distribution of males and females *(Table 3).*

Majority did not develop jaundice. For those who did, phototherapy was given for a mean duration of 3 SD ± 2 days. The mean length of stay at the NICU was 19 SD ± 16 days, the shortest being 2 days and the longest being 68 days. For those needing oxygen

therapy, it was given for 8 SD ± 7 days on the average, the shortest being a day and the longest being 28 days. Majority did not require mechanical ventilation. The maximum level of FiO_2 (100%) was used in 26% of cases while majority were subjected to room air and FiO_2 ranging from 30% to 90% *(Table 4).*

Table 4: Distribution of Preterm Neonates as to Conditions During Course of Hospital Stay

Conditions during Course of Hospital Stay	No. (%)
Jaundice	
Yes	46 (37.1)
No	78 (62.9)
total	100
Length of Phototherapy (in days)	
Mean, sd	2.6, 2.2
Median (min, max)	2 (1, 9)
NICU stay (in days)	
Mean, sd	18.7, 16.0
Median (min, max)	12 (2, 68)
Duration of Oxygen Therapy (in days)	
Mean, sd	7.5, 7.2
Median (min, max)	4.5 (1, 28)
Need for Mechanical Ventilation	
Yes	37 (29.8)
No	87 (70.2)
total	100
Level of FiO_2 Used (in %)	
21	39 (31.5)
30	49 (39.5)
45	1 (0.8)
60	1 (0.8)
70	1 (0.8)
90	1 (0.8)
100	32 (25.8)
total	100

Out of 124 preterm neonates, 31 (25%) developed ROP. The mean age at detection was 30 SD ± 16 days. The highest stage or most severe ROP in either eye was noted to be commonly stage 2. Observation was the usual therapy given *(Table 5)*. The lone stage 4 case was detected longest at 53 days while stage 1 was detected earliest at 24 SD ± 6 days *(Table 6)*. All of stages 1 and 3 and majority of stage 2 were managed with observation alone while two of stage 2 and the lone stage 4 underwent laser treatment *(Table 7)*.

Table 5: Incidence and Profile of ROP

ROP	No. (%)
With	31 (25.0)
Without	93 (75.0)
	100
Age detected (in days)	
Mean,sd	30.2, 15.5
Median (min,max)	27 (7, 60)
Maximum Stage reached	
Stage 1	6 (19.4)
2	17 (54.8)
3	7 (22.6)
4	1 (3.2)
	100
Therapy given	
Observation	28 (90.3)
Laser IO	3 (9.7)
	100

Table 6: Mean Age detected by Stage of ROP

Stage of ROP	Age Detected (Mean, sd)	No.
1	23.5, 6.2	6
2	30.7, 17.2	17
3	31.6, 15.7	7
4	53.0	1
total		31

Table 7: Therapy given by Stage of ROP

Stage of ROP	Therapy Given			No.
	Laser	Laser , Avastatin	Observation	
1			6	6
2	2		15	17
3			7	7
4		1		1
total				31

III. Comparison between those with and without ROP

There were significant differences in maternal age, duration of PROM and mode of delivery between those who did and those who did not develop ROP (p-value <0.05). Maternal age was older, duration of PROM was longer, and the proportion of those delivered by caesarian section was higher among those who had ROP (Table 8).

As to neonatal factors, there were significant differences in gestational age, birthweight and 1-minute Apgar score. Gestational age was earlier, birthweight was lower and 1-minute Apgar scores were also lower among those who developed ROP. There was no significant difference in gender distribution (Table 8).

Likewise, there were significant differences in length of NICU stay, duration of oxygen therapy, need for mechanical ventilation and level of FiO_2 between the two groups. NICU stay and duration of O_2 therapy was longer, level of FiO_2 was higher and a greater proportion placed on mechanical ventilation was seen among those who developed ROP. No differences were noted on the occurrence of jaundice and duration of phototherapy (Table 8).

Table 8: Comparison by Maternal Obstetric and Neonatal Factors and Course of Hospital Stay

Maternal Obstetric Factors	ROP	No ROP	p-value
Maternal Age in years (mean, sd)	32.7, 3.9	30.2, 5.3	0.0197[a]
Duration of PROM in hrs (mean, sd)	4.5, 6.3	0.9, 3.5	0.0001[a]
Preeclampsia (%)	29.0	24.7	0.6355[b]
Maternal Pyrexia (%)	3.2	0	0.0820[b]
Mode of Delivery (%)			0.0007[b]
CS	90.3	65.4	
NSD	9.7	34.6	
Neonatal Factors			
Gestational Age in weeks (mean, sd)	30.9, 2.6	34.8, 1.3	0.0000[a]
Birthweight in grams (mean, sd)	1412.5, 343.5	2106.9, 323.9	0.0000[a]
1 minute Apgar score (mean, sd)	7.1, 1.3	7.8, 0.8	0.0009[a]
Gender (%)			0.2540[b]
Male	41.9	53.8	
Female	58.1	36.2	

Course of Hospital Stay			
Jaundice (%)	38.7	36.6	0.8300[b]
Length of phototherapy in days (mean, sd)	1.5, 2.2	0.9, 1.7	0.0858[a]
NICU stay in days (mean, sd)	39.4, 14.0	11.8, 9.2	0.0000[a]
Duration of O_2 therapy in days (mean, sd)	12.7, 7.9	2.6, 4.1	0.0000[a]
Need for mechanical ventilation (%)	77.4	14.0	0.0000[b]
Level of FiO_2 in % O_2 (mean, sd)	83.9, 30.3	33.9, 22.6	0.0000[a]

[a]Independent t-test [b]Chi square test

IV. Crude Analysis on the association between selected factors and ROP

Gestational age, birthweight, duration of O_2 therapy, mechanical ventilation and level of FiO_2 were independently significantly associated with ROP (p-value <0.05). ROP was 6 times more among those with gestational age less than 32 weeks, 7 times more among those with birthweight was less than 1500 grams, 12 times more among those on O_2 therapy for more than 6 days, 6 times more among those on mechanical ventilation and 10 times more among those exposed to 100% FiO_2. ROP was 3 times more among those with 1-minute Apgar scores less than 7 but the association was not significant (p-value =.0992) (Table 9).

Table 9: Association between Selected Factors and Development of ROP

Selected Factors	ROP	No ROP	Risk Ratio (95% CI)	p- value
Gestational Age			5.96 (3.51, 10.11)	0.0000[b]
< 32 weeks	17 (81.0)	4 (19.0)		
³ 32 weeks	14 (13.6)	89 (86.4)		
Birthweight			7.34 (4.21, 12.81)	0.0000[b]
< 1500 grams	19 (86.4)	3 (13.6)		
³ 1500 grams	12 (11.8)	90 (88.2)		
Duration of O_2 therapy			11.76 (4.89, 28.3)	0.0000[b]
³ 6 days	26 (68.4)	12 (31.6)		
< 6 days	5 (5.8)	81 (94.2)		
1 minute Apgar score			2.55 (1.16, 5.59)	0.0992[c]
< 7	3 (60.0)	2 (40.0)		
³ 7	28 (23.5)	91 (76.5)		
Need for mechanical ventilation			8.06 (3.81, 17.05)	0.0000[b]
Yes	24 (64.9)	13 (35.1)		
No	7 (8.1)	80 (91.9)		
Level of FiO_2			9.86 (4.70, 20.65)	0.0000[a]
³100%	24 (75.0)	8 (25.0)		
<100%	7 (7.6)	85 (92.4)		

[a]Independent t-test [b]Chi square test [c]Fishers exact probability test

V. Logistic Regression Analysis

Taking into account all of the above selected factors, the final regression model for factors associated with the development of ROP showed birthweight and FiO_2 to be significantly associated with ROP. Those whose birthweight was less than 1500 grams were 47 times more likely to have ROP than those weighing more than or equal to 1500 grams. Likewise those exposed to more than 100% Fi02 were 36 times more likely to have ROP than those exposed to less than 100% Fi02 (Table 10).

Table 10: Final Logistic Regression Model for Factors Associated with the Development of ROP

Factor	Coefficient (b)	Odds Ratio (95% CI)	p-value
Constant	-3.403		
Birthweight <1500 grams	3.846	46.81 (8.20, 267.12)	0.000
Fi02 100%	3.583	35.98 (8.52, 151.99)	0.000

DISCUSSION

Retinopathy of prematurity (ROP) is a major treatable cause of blindness worldwide. The rate of blindness varies considerably in different care units, depending on their level of development and whether effective screening and treatment programs exist.[10]

In this study there were a total of 124 preterms included. Mothers had a mean age of 31 (see table 2). Majority had no pre-partum illnesses like preeclampsia, maternal pyrexia and PROM (see table 2). Most delivered via caesarian section due to preeclampsia (see table 2). According to Yu et. al.[11] preeclampsia was not associated with ROP in preterm births, however, this was not proven in our study.

Majority of the pre terms were aged 35-36 weeks and weighed between 1500 to less than 2500 grams (see table3). Most had Apgar scores of 8 and 9 at 1 and 5 minutes of life, respectively (see table3). Almost equal distribution of males and females (see table3).

Majority did not develop jaundice, but for those who did, phototherapy was given for a mean duration of 3 days (see table 4). The mean length of stay at the NICU was 19 days (see table 4). For those needing oxygen therapies, it was given for 8 days on the average (see table4). Majority did not require mechanical ventilation (see table 4). The maximum level of Fi02 100% was used in 26% of cases while majority were subjected to FiO_2 ranging from 21% to 90% (see table 4).

Out of 124 preterm neonates 31 developed ROP (see table 5). The mean age at detection was 30 days (see table 5). Although guidelines for ROP screening recommends age of gestation less than or equal to 32 weeks, there were 4 neonates 33 weeks AOG, 2 neonates 34 weeks AOG, and 1 neonate 36 weeks AOG who developed ROP in our study.

Retinopathy of prematurity primarily occurs in extremely low birth weight (ELBW) infants. Most research suggests that a low birth weight, a young gestational age, and the severity of illness are associated factors.

Retinal vasculature begins to develop around 16 weeks age of gestation. It grows circumferentially and becomes fully mature at term. Premature birth results in the cessation of normal retinal vascular maturation. Exposure of newborn premature infants to hyperoxia downregulates retinal vascular endothelial growth factor (VEGF). Blood vessels constrict and can become obliterated, resulting in delays of normal retinal vascular development. This hyperoxia-vasocessation is the underlying cause of retinopathy of prematurity.[12]

There were significant differences in maternal age, duration of PROM and mode of delivery between those who did and those who did not have ROP (see table 8). Maternal age was older, duration of PROM was longer, and the proportion of those delivered by caesarian section was higher among those who had ROP (see table 8).

According to a study by Wu et. al. entitled "Retinopathy of Prematurity and Maternal Age": older maternal age is a newly identified risk factor for the development of ROP in premature babies.[13] This is similar with our study. The average age of marriage continues to increase, this might be one of the reasons why advanced maternal age was not an issue in the past and this risk factor was not identified in previous studies.

There are more patients who developed ROP who were delivered via cesarean section which is in contrast with the study by Manzoni et. al. which concluded that vaginal delivery is a significant and independent predictor of threshold ROP in preterm infants.[14] As to neonatal factors, there were significant differences in gestational age, birthweight and 1-minute Apgar score (see table 8). Gestational age was earlier, birthweight was lower and 1-minute Apgar scores were also lower among those who developed ROP. There was no significant difference in gender distribution (see table 8). Although gender is not a significant factor in developing ROP, there were more males than females noted in our study. According to Walsh in 2009: Both birth weight and gestational age were independently associated with severe retinopathy, but gestational age was a stronger predictor.[15] This is comparable with our study where infants born earlier and those with low birth weights developed ROP. This may be due to advancements during the recent years where improvements in neonatal intensive care lead to greater survival among infants born at extremely low gestational ages.

There were significant differences in length of NICU stay, duration of oxygen therapy, need for mechanical ventilation and level of Fi02 between the two groups. NICU stay and duration of O2 therapy was longer, level of Fi02 was higher and a greater proportion placed on mechanical ventilation was seen among those who developed ROP (see table 8). These finding are the same with that of Hakeem et. al. in "Retinopathy of Prematurity: A Study of Prevalence and Risk Factors" which stated that higher level of oxygen during oxygen therapy and use of mechanical ventilator were significant risk factors for ROP.[8] In 1954, Ashton and Cook were the first to establish

that oxygen is important in disrupting retinal blood vessel development.[16] Several recent studies have shown a relationship between a high-oxygen saturation and ROP. It seems that a SaO2>93% increases the risk for severe ROP and need for therapy.[17]

No differences were noted on the occurrence of jaundice and duration of phototherapy (see table 8). Gestational age, birthweight, duration of O_2 therapy, mechanical ventilation and level of FiO_2 were independently significantly associated with the development of ROP (see table 8), which also concurs with the study of Hakeem et. al.[8] ROP was 6 times more among those with gestational age less than 32 weeks (see table 8), 7 times more among those with birthweight was less than 1500 grams (see table 8), 12 times more among those on O_2 therapy for more than 6 days (see table 8), 6 times more among those on mechanical ventilation (see table 8) and 10 times more among those exposed to 100% FiO_2 (see table 8). ROP was 3 times more among those with 1-minute Apgar scores less than 7 but the association was not significant (see table 8).

CONCLUSION

An older maternal age, a longer duration of PROM, and a larger proportion of those delivered by caesarian section are likely to have ROP. Earlier gestational age, lower birthweight, and lower 1-minute Apgar scores were also noted in those babies that developed ROP. Furthermore, a longer NICU stay, a longer duration of O_2 therapy, a higher level of FiO_2, and a greater proportion placed on mechanical ventilation was also seen among those who have ROP.

The final regression model for factors associated with the development of ROP showed birthweight and FiO_2 to be significantly associated with ROP.

LIMITATION OF THE STUDY

Limitation of this study is the short duration of the period included from January 2011 to January 2013, however, adequate sample size was reached. The study only involved one private tertiary hospital. We believe that this is an advantage since there is little variability in practice. In particular, the ophthalmologic examinations were consistent since all neonates were seen by the same ophthalmologist for the entire duration of the study. This study was made to determine risk factors for ROP, but not to test prior hypotheses.

RECOMMENDATIONS

As this is a single hospital-based study, a comprehensive countrywide survey on ROP in the Philippines is recommended to determine any regional differences in ROP prevalence. Larger sample size and additional risk factors is also recommended to yield higher statistical power.

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