RETINOPATHY OF PREMATURITY:

A CASE SERIES REPORT OF TREATED INFANTS

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Retinopathy of Prematurity: A Case Series of Treated Infants

MMED Report:

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Dedication

I dedicate this work to my family, Avette, Liam and Talia. Your love and support made this report possible.

Acknowledgements

I thank Prof Wayne Marais for the advice given in initiating and completing this research. It has been an honour to have such a decorated professor to guide me in my academic and clinical career to date.

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Declaration of Independent Work

I, Theunis Botha, hereby declare that this dissertation, submitted for the subject NAMB7900, degree MMED OPHTALMOLOGIST SPECIALIST SURGEON in the DEPARTMENT OF OPHTHALMOLOGY, UNIVERSITY OF THE FREE STATE, BLOEMFONTEIN, is my own independent work and that it has not been submitted before to any institution by me or anyone else as part of any qualification.

4.5.2017

Signature of student Date

Executive Summary

Retinopathy of Prematurity (ROP) is still a major contributor to vision loss in children and account for around 10% of children in schools for the blind in South Africa (SA). Around 14 000 infants are at risk for the development of ROP in SA each year.

Oxygen supplementation to the premature infant causes a relative hyperoxia within the retina which results in cessation of normal vascular proliferation. After the supplemental oxygen is stopped, a relative hypoxia causes an abnormal over proliferation of retinal vessels. ROP is the clinical entity which results from this abnormal vascular response.

Classification of ROP is clinical and includes three entities: vascular response, zone of retina involved and the presence of plus disease. Retinal detachments can result, and this comprises stage 4 and 5 of the classification.

Treatment is according to the ETROP study. The classification above is used to further classify the disease into Type 1 and 2, and then treated accordingly.

Many risk factors have been identified in contributing to the development of ROP. Some major risk factors include: gestational age, birth weight, poor postnatal weight gain and supplemental oxygen administration. Protective factors include human breastmilk and fresh frozen plasma.

Three ROP epidemics have been identified. The first epidemic was with the advent of supplemental oxygen in the 1950's. Infants with ROP in the United Kingdom at the time had birth weights of 1370g. In the 1970's neonatal care improved, and we saw the second epidemic as the birth weights of infants with ROP dropped to below 1000g. Now, at the turn of the century, we are seeing a 3rd epidemic in middle-income countries with infants having ROP with birth weights of 900g to 1500g. For comparison, infants with ROP in developed countries have birth weights of around 750g and below.

Screening for ROP is necessary but sometimes difficult in resource constraint environments. Therefore, algorithms have been developed to try and decrease the number of infants that need screening. A major successful algorithm is the WINROP algorithm. This algorithm is web based, and needs only the gestational age, birth weight and postnatal weight gain to

determine whether an infant is at risk for the development of ROP. It has proven 100% sensitive in some developed countries.

The aim of this study was to determine the risk factors present in infants with ROP in our province. Secondary objectives included: the comparison of the WINROP detection rate in our infants with those in developed countries; to identify major issues in neonatal care in the province; and to document the ROP stage prior to treatment and treatments given.

This was a case series. Records were reviewed of all infants treated for ROP at a single referral unit, Universitas Academic Hospital, during the time period of 2009 to 2015. Ethics approval was obtained for this study.

Most infants were of African race. All infants were from the two major referral centres within the Free State. The averages for gestational age and birth weight were 27.6 weeks (range 26 to 30 weeks) and 1061.2 grams (range 760 to 1405 grams) respectively. The day original birth weight was reached on average was on day 22 (range 9 to 56 days). Other parameters which showed a high presence factor were: oxygen supplementation, proven sepsis and breastmilk administration. The WINROP algorithm showed an alarm in 75% (n9) of cases. This means that 25% (n3) were not detected by 6 weeks of age when screening would already have been implemented. One unit showed a target oxygen saturation of >95% in all treated infants.

In conclusion, the study confirms that SA forms part of the third epidemic of ROP. The WINROP algorithm is not accurate in our population with larger infants. A site with poor post-natal oxygen saturation monitoring was identified. It is recommended that further study is needed before the implementation of the WINROP algorithm in SA. Education of staff involved with neonatal care concerning oxygen saturation targets is important.

List of Presentations

This work has been presented at the international annual Ophthalmology Society of South Africa (OSSA) Congress held in March 2017.

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List of Abbreviations

BEAT-ROP	Bevacizumab Eliminates the Angiogenic Threat of Retinopathy of Prematurity
BW	birth weight
CRIB-score	clinical risk index for babies score
CPAP	continuous positive airway pressure
CRYO-ROP	Cryotherapy for Retinopathy of Prematurity study
DNA	deoxyribonucleic acid
ETROP	Early Treatment for Retinopathy of Prematurity trial
GA	gestational age
HSREC	Health Sciences Reasearch Ethics Committee
IGF-1	insulin-like growth factor 1
NEC	necrotizing enterocolitis
OSSA	Ophthalmological Society of South Africa
PDA	patentus ductus arteriosus
ROP	Retinopathy of Prematurity
SA	South Africa
UAH	Universitas Academic Hospital
VEGF	vascular endothelial growth factor

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Chapter 1. Literature review

Introduction

The current body of knowledge on Retinopathy of Prematurity (ROP) is summarized in this review of the literature. Firstly, the history of the disease and how it has developed to become a major contributor to visual impairment in children will be discussed. South Africa's statistics are put into context. The mechanisms by which ROP develops in the premature infant are explored. Clinical presentation and classification for treatment purposes are looked at. Factors contributing to both development and protection are highlighted. Indications and protocols for screening are discussed and screening in our setting is outlined. Lastly, treatment modalities are considered for different stages of ROP.

History of Retinopathy of Prematurity

ROP was first described in 1942 by Terry and he coined the disease Retrolental Fibroplasia.[1] Interest in this previously unidentified entity grew rapidly among obstetricians, pediatricians and ophthalmologists. Subsequently many cases were described with some showing the typical history of the presence of prematurity.[2] In 1953, Bedrossian showed a connection between ROP and oxygen supplementation.[3] Since then, many more risk factors have been identified.

Epidemiology: Developed and Developing Countries

In this section, current global trends in epidemiology of ROP will be discussed. Differences in high, middle and low income countries are discussed. The South African context is discussed.

Three epidemics of ROP have been described.[4] The first was at the advent of supplemental oxygen use. At the time, the average birth weight of infants with ROP in the United Kingdom was 1370g.[4] Later, more immature infants were being saved and the second epidemic showed birth weights of less than 1000g.[4] Now, after the turn of the century, middle-income countries are saving less immature babies and we are seeing a combination of both the first and second epidemics.[4] One study showed that the mean

birth weights of babies with ROP in developed countries ranged from 737g-763g, while in less developed countries it ranged from 903g-1527g.[4] Gestational age differences in the same study was 25.3-25.6 weeks compared with 26.3-33.5 weeks.[4] An estimated 30 000 infants are visually impaired world-wide yearly from ROP and an estimated 65% of these are in middle-income countries.[5]

South Africa and Retinopathy of Prematurity

South Africa (SA) forms part of the third epidemic of ROP.[6] The mean birth weight of infants with ROP in SA is 1093g.[7] A paper published by Varughese et al in 2008 looked at the needs, resources and requirements for ROP screening programs in SA.[8] About 13000 to 15000 surviving premature infants are at risk of developing ROP in SA each year, while 10.6% of blindness in children in schools for the blind is due to ROP.[8] Shortage of equipment precludes continuous oxygen monitoring in public units.[8] Nursing levels are often below recommendations, and most nurses are unaware of target oxygen saturations. Conversely, private units are well staffed and adequately equipped.[8] Ophthalmologists only visited 4 of the 17 units for screening investigated in the 2008 research paper.[8]

Pathogenesis of Retinopathy of Prematurity

The following describes the normal growth of retinal blood vessels and how oxygen plays a role in the formation of abnormal vessels after birth.

Vascularization of the retina begins at approximately two months of gestation. Vascularization develops from the optic disc to the periphery and reaches the nasal retina at 36 weeks gestation and the temporal retina at 44 weeks after conception.[9] The fetal vascular system, emerging from the hyaloid artery, reaches its peak of development at approximately 10 weeks of gestation. It starts its process of apoptosis by the 5^{th} to 6^{th} month of gestation. This apoptotic process coincides with the growth of peripheral retinal vessels. The imbalance between the hyaloid artery disappearance and the peripheral growth of retinal vessels seems to be the main cause for the development of ROP.[9]

Vascular growth is comprised of two phases: vasculogenesis and angiogenesis. The vasculogenesis phase is characterized by the de novo growth of vessels from precursor

endothelial cells within the retina.[10] This growth forms the four major arcades of the retinal vasculature. The angiogenesis phase comprises the budding of new vessels from already formed vessels to form the peripheral circulation. This phase of vascular growth within the fetus is driven by vascular endothelial growth factor (VEGF).[10] The fetal circulation is relatively hypoxic to the infant's circulation. This hypoxia is the main stimulant for VEGF release and thus peripheral retinal vasculature growth.[10]

The development of ROP comprises of two phases.[11] Preterm infants are born before completion of the development of their peripheral circulation. And as a result, the degree of underdevelopment depends on the degree of prematurity. The fetus goes from a relative hypoxic state to a relative hyperoxic state as an infant when oxygen is administered soon after birth. This comprises phase I: hyperoxia. VEGF secretion from the avascular retina is down regulated. Phase II is a relative hypoxic state within the avascular retina as weaning of oxygen takes place. With the combined metabolic increase demand and vessel loss from phase I, VEGF secretion from the avascular retina is up regulated to such a degree that vessels proliferate abnormally.[11]

Classification of Retinopathy of Prematurity

In this section a description is given on how to classify ROP. An explanation is given to the importance of classification in the management of infants with ROP.

Three clinical entities are noted in the classification of severity of ROP[12]:

1. Stage: vascular response abnormality and retinal detachment changes (Table 1)
2. Zone: retina divided into three clinical zones (Figure 1)
3. Plus disease: the presence of additional signs of ROP

Table 1. ROP Stage: abnormal vascular response and retinal detachment classification of ROP.[12,13]

Stage Name	Clinical Description of Stage
1. Demarcation line	A thin but definite structure that separates avascular retina from vascularized retina. Vessels leading up to the demarcation line show abnormal branching. The line itself is relatively flat, white, and lies within the plane of the retina.
2. Ridge	The ridge arises at the site of the demarcation line. It has height and width, and extends above the plane of the retina. It may be pink with vessels leaving the plane of the retina to enter it. There may be so called "pop-corn" lesions present.
3. Extraretinal Fibrovascular Proliferation	Neovascularization extends from the ridge into the vitreous. The extraretinal proliferating tissue is continuous with the posterior aspect of the ridge.
4. Partial Retinal Detachment	Most detachments are concave and circumferentially orientated. The extent depends on the number of clock hours involved. Stage 4 is divided into: A – extrafoveal, and B – foveal.
5. Total Retinal Detachment	Detachments are usually tractional in nature, but can be exudative (effusive) or rhegmatogenous. They are generally funnel shaped. The shape of the funnel subdivides Stage 5. Anterior or posterior parts of the funnel can be open or closed with various combinations.

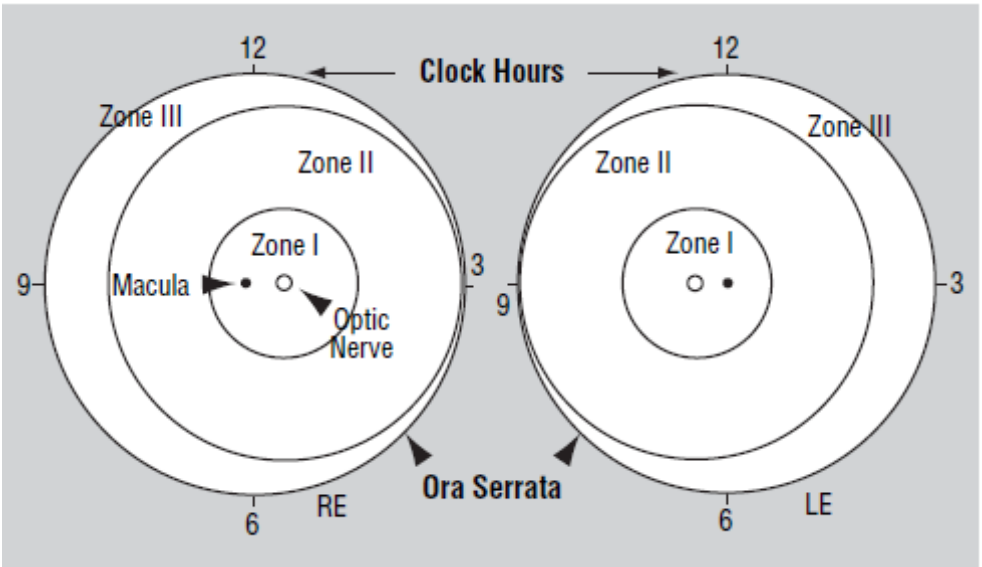

Figure 1. A figure depicting the three anatomical zones of the retina. Figure taken from the South African ROP screening guidelines.[6]

If plus disease is present, a + symbol is placed after the numerical stage, for example 3+. Plus disease is increased venous dilatation and arteriolar tortuosity of the posterior retinal vessels, according to a standard photograph and needs to be present in at least 2 quadrants.

Vitreous haze and pupil rigidity are also part of the plus disease entity. "Pre-plus" disease is described as the presence of these changes in the posterior pole, but not severe enough to meet the criteria of "plus disease".[12]

According to the Early Treatment for Retinopathy of Prematurity (ETROP) trial, ROP is divided into type I and type II disease. Table 2 below shows the difference between type I and type II disease. Type I ROP qualifies for treatment, but a "wait and watch" approach to type II ROP is supported. Eyes with type II ROP are only considered for treatment if they progress to type I.[13]

Table 2. Type I and Type II ROP according to the ETROP trial, with examples of short notations of classification.[14]

Type I		**Type II**	
Zone 1, 1/2/3, plus	Z1 S1/2/3+	Zone 1, Stage 1/2, without plus	Z1 S1/2-
Zone 1, Stage 3, without plus	Z1 S3-	Zone 2, Stage 3, without plus	Z2 S3+
Zone 2, Stage 2/3, plus	Z2 S2/3+		

The term "threshold" ROP came from the CRYO-ROP study and included any disease worse than and including 5 contiguous clock hours or 8 total clock hours of stage 3+ disease in zone 1 or 2.[13] This degree of disease was used as threshold for treatment with cryotherapy. "Prethreshold" is any stage of ROP less than threshold.[13] Classifying according to type I and type II disease is now preferred to the threshold system.[13]

An entity described as "Rush disease" or "Aggressive Posterior ROP" (APROP) is a form of ROP separate from the classification above.[12] It is an uncommon form of the disease seen mostly in the posterior pole within zone 1 and is recognized by the severity of plus disease without well-defined vascular retinopathy changes. It does not progress through the classic stages of ROP, but progresses quickly if untreated to total retinal detachment.[12]

Risk Factors

Many risk factors have been identified for the development of ROP. Some speak to the prematurity of the infant such as birth weight and gestational age. Oxygen supplementation has a clear pathophysiological mechanism for causing ROP. Other identified factors have

less clear mechanisms of contribution and could speak to the severity of general poor health of the infant. Furthermore, some factors even contribute to protecting the child against the development of ROP. This section looks at all of these contributing factors. Table 3 summarizes both risk and protective factors.

Prematurity: Gestational Age at Birth and Birth Weight

Birth weight (BW) and gestational age (GA) have been shown to be the major causative factors for the development of ROP.[13] Prematurity also contributes to the severity of disease.[15]

Not only is BW a risk factor, but growth restriction at birth (low weight for GA) is a risk factor by itself. Infants under the third percentile for weight for GA have four times greater odds of developing ROP than the babies within the 25^{th} to 75^{th} percentiles.[16] Furthermore, recent years have shown poor post-natal weight gain to be a major contributor and predictor for disease.[13,17] For each day delay in reaching the original BW after 10 days of age, an infant has a 6% risk of developing ROP.[18]

Oxygen Supplementation

Oxygen plays a major role in the pathogenesis of ROP. The relative hyperoxia created by supplemental oxygen soon after birth has been shown to be a major risk factor for the development of ROP.[13] Artificial ventilation itself has been shown to be an independent risk factor.[13] When a saturation target of 85% to 92% is maintained for a premature infant before 34 weeks GA, and a target of 85% to 95% is maintained for an infant after 34 weeks GA, then there is a reduction in ROP from 35% to 13%.[11]

Other Factors

Not only the smallest infants get ROP, but also the sickest.[19] Risk factors contributing to this are listed in Table 3.

It has been shown that human breast milk lowers the risk for the development of ROP and significantly lowers the chance of retinal detachment in advanced disease.[20] Oxygen toxicity has been shown to be reduced in infants fed human milk as compared to infants fed formula, as evident from the finding that urinary 8-hydroxydeoxyguanosine, a marker for

oxidative DNA damage, was significantly lower in infants fed human milk than in infants fed formula.[21]

Table 3. Summary of Factors in the development of ROP.[13,22–27]

Risk Factors	Controversial	Protective Factors
Gestational age	Maternal hypertension	Human milk
Birth weight	Race	Fresh frozen plasma
Poor postnatal weight gain		
Low IGF-1 levels		
Supplemental oxygen		
Repeated blood transfusions		
Sepsis		
Pulmonary disease		
Surfactant administration		
Intraventricular hemorrhage		
Hyperglycemia		
Hypoglycemia		
Genetics		
PDA		
Necrotizing enterocolitis		
Parenteral nutrition		
Hypotension		
Low CRIB score		
Post-natal steroid		

Screening for ROP

Differences in criteria and methods, as well as new developments in screening tools, are discussed below. Screening methods in South Africa and Bloemfontein are discussed.

Screening for ROP depends on the setting in which it is done. In the developed world it is widely excepted to screen premature infants less than 31 weeks GA or less than 1250g BW and infants bigger than these values at the discretion of the neonatologist.[5] In developing countries however, a BW of less than 1500g and a GA of less than 32 weeks, or at the

neonatologists discretion, are more prudent criteria.[6] Historically, screening has been done by an ophthalmologist with an indirect ophthalmoscope at the infant's bedside.[6]

By utilizing the RetCam® (fundus photography) and implementing telemedicine modalities, one can greatly reduce the costs and resources involved with screening programs. Large studies have proven the safety and validity of this newer modality.[28]

The WINROP study introduced an algorithm to detect the infants at risk for developing ROP needing treatment.[29] This algorithm used insulin-like growth factor I and weight gain for this prediction, but recently updated the algorithm to only use weekly weight gain and the degree of prematurity.[30]

South Africa uses the specifically designed 2012 guidelines produced by Visser et al.[6] A BW of less than 1500g or a GA of less than 32 weeks is used as cut off for screening. Interestingly, one study showed that the screening criterion based on BW can safely be lowered to 1250g for the South African population; however the 1500g cut-off is widely accepted and used.[7] A BW of 1500g to 2000g is acceptable to screen at the neonatologists discretion or when one of the following is present: family history of ROP, cardiac arrest, multiple (more than two) blood transfusions, exchange transfusions, or hypoxic ischemic encephalopathy.[6] If oxygen administration was suboptimal, then screening can be considered if resources allow, but ensuring appropriate oxygen monitoring is more cost effective.[6]

At our hospitals in Bloemfontein, the Visser et al guidelines are used for screening of premature infants with an indirect ophthalmoscope.[6] If an infant qualifies, screening is initiated 4 to 6 weeks after birth.

Criteria for discontinuation of screening are as follows:[6]

1. Vascularization reaches zone 3 without prior zone 2 or 1 disease
2. Full retinal vascularization
3. Postmenstrual age of more than 45 weeks without any pre-threshold disease (where pre-threshold disease is defined as zone 1 with any ROP stage or zone 2 with stage 3 disease)
4. Regression of ROP

Treatment

Different prevention categories and treatment modalities are summarized in this section.

Primary prevention of ROP requires meticulous neonatal care and adequately equipped and staffed units.[13] Secondary prevention requires efficient screening and treatment programs.[8]

Active management of ROP is initiated for type 1 disease as demonstrated in the ETROP study. Laser photocoagulation is used to ablate the avascular retina, and is the treatment of choice.[13] However, the BEAT-ROP study has demonstrated that for zone 1 stage 3+ disease, Bevacizumab (anti-VEGF) is beneficial.[13] Cryotherapy is now considered archaic as a routine treatment modality.[13]

Retinal detachments are individualized and best treated by experienced retinal surgeons. Management modalities can include: observation, lens sparing vitrectomy, scleral buckling procedures and a combination of vitrectomy with or without scleral buckle procedures.[13]

A debate is ongoing whether laser photocoagulation should be done under general anaesthesia by an anaesthetist in the operating theatre, or whether sedation should be done under neonatologist supervision in the neonatal unit.[31]

Conclusion

ROP is still a major contributor to visual impairment in children, especially in the middle-income countries like South Africa. Many risk factors have been identified to contribute to the development of the disease. Screening places strain on already resourced constraint environments. Algorithms have been developed to try and use the identified risk factors to decrease the number of infants that need screening. One of these algorithms, WINROP, has emerged as an excellent tool in identifying at risk infants.

Study Justification

There is a discrepancy between the infants with ROP in the developed world versus those in the developing world. Identification of the risk factors contributing to this discrepancy needs exploration to improve management of premature infants in South Africa.

Study Aim

The main aim of this study is to document the risk factors present in a population of infants treated for ROP, and to compare the major contributing factors with international statistics.

Study Objectives

- Identify major contributors to ROP in our population.
- Look at the prediction strength of the WINROP algorithm in our population and compare with international statistics.
- Document information about the ROP severity present in our infants and treatments given to these infants.
- Use the information gained from the study to educate personnel involved in the management of preterm infants and in doing so improve the quality of care.

Chapter 2: Article

Retinopathy of Prematurity: A Case Series Report of Treated Infants

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Keywords

Retinopathy of prematurity risk factors, Retinopathy of prematurity in developing countries, WINROP

Abstract

Objective

Retinopathy of Prematurity (ROP) is still a major contributor to childhood blindness, especially in middle-income countries. This study aimed to: identify risk factors for ROP in a population of treated infants; compare the detection of infants at risk for the development of ROP using the WINROP algorithm with international detection rates; find any major areas of concern in management of the premature infants in our setting; and to document the ROP stage and treatment given in the population.

Methods and Analysis

A case series was done. All infants treated for ROP at a single unit during the time period of 2009 to 2015 were included. Records were reviewed, data collected and data analysed.

Results

The average birth weight and gestational age of treated infants were 1061.2 grams and 27.6 weeks respectively. WINROP detected 9 (75%) of infants by 6 weeks when screening was initiated. One unit showed a lower limit for oxygen saturation to be set at 95% for all infants included in the study.

Conclusion

South Africa forms part of the third epidemic of ROP. The WINROP algorithm is not as accurate in our population as in the developed world where smaller premature infants get ROP. Further education is needed in our province concerning the management of at risk infants in the prevention of ROP.

Introduction

Retinopathy of Prematurity (ROP) is a major cause of childhood blindness in the world, especially in emerging middle income countries.[1] It is largely unknown in Africa, but in South Africa it accounts for up to 10.6% of childhood blindness, and 13 000 to 15 000 surviving infants are at risk for developing ROP each year.[2]

A relative hypoxic state developing in the retina after cessation of supplemental oxygen in premature infants cause an over proliferation of retinal vascular tissue.[3] To grade the severity of ROP, the retina is divided into 3 zones and severity is classified into 5 stages.[4] In addition, 'plus disease' denotes the presence of other signs of ROP.[4] The ETROP study further classified the disease into Type 1 and Type 2 disease for treatment purposes.[5]

Prematurity is a major risk factor for the development of ROP. Birth weight (BW) and gestational age (GA) are measurements of this. Together with these, oxygen supplementation has been well established as a causative factor for the development of ROP.[6] Many other risk factors have been identified as contributing factors: low post-natal weight gain, sepsis, necrotising enterocolitis, pulmonary disease, surfactant administration, intraventricular haemorrhage, multiple blood transfusions, mode and duration of oxygen administration and patentus ductus arteriosus.[7,8] Some protective factors have also been identified: breastmilk administration[9] and administration of fresh frozen plasma within the first week of life.[10]

Three ROP epidemics have been identified.[1,2] In the first epidemic, larger more mature infants survived with the advent of supplemental oxygen in the early 1950's. At the time, the average BW of infants with ROP in the United Kingdom was 1370g. In the late 1960's, survival of smaller infants (<1000g) caused the second epidemic. Currently, middle-income

countries are experiencing the third epidemic. This is a combination of the first two epidemics, as slightly less immature infants are surviving and getting ROP.

Screening for ROP places even more strain on already constraint resources.[2] As a result, risk development algorithms have been developed to try and minimize the infants screened. One of these algorithms, WINROP, has emerged as an excellent predictor for the development of ROP.[11]

The aim of this study was to identify the presence of risk factors in our population of premature infants and to put these statistics into context internationally. The study also aimed to explore the prediction of high risk ROP using the WINROP algorithm in our population. Documentation of ROP disease and treatment was done. Identification of any major issues in management of our population was seen as a secondary outcome. Data and information collected could then be used in improving care and education of staff involved with the management of premature infants.

Materials and Methods

Study Design

This was a case series.

Study Setting

Universitas Academic Hospital (UAH), in the city of Bloemfontein, is the only tertiary referral hospital for the Free State province. The Free State is one of nine provinces in South Africa. Multiple sites in the province are used for screening, but all infants needing treatment for ROP are referred to UAH.

Study Population

Infants treated for ROP at UAH, during the time period of January 2009 to December 2015, were included in the study.

Data Collection and Management

A retrospective review was conducted and medical records of all treated infants were included in the data set. Data collected included: demographics (sex and ethnicity); birth site information; prematurity parameters (birth weight and gestational age); weekly weight

gain for the first six weeks of life; the presence of risk factors for the development of ROP; breastmilk administration statistics; ROP stage prior to treatment, and treatment given.

Data Analysis

A descriptive analysis was done.

Ethics

Ethical approval was obtained prior to data collection via the Health Sciences Research Ethics Committee (HSREC) of the University of the Free State (HSREC 66/2016). The Department of Health of the Free State and the head of UAH granted permission for review of patient records. Patient information was kept confidential.

Results

There were a total of 18 infants who met the inclusion criteria, of which 5 data sets could not be traced and subsequently excluded. Seven (53.9%) were from the larger Bloemfontein area, 6 (46.1%) were from the Bethlehem region. Twelve (92%) infants were of African race while 1 (8%) was of mixed race. There were 8 (61.5%) females and 5 (38.5%) males. Table 1 shows a summary of the measured birth parameters.

Table 1. A summary of birth parameters measured.

Infant	Birth Weight in grams	Gestational Age in weeks	1 minute APGAR	5 minute APGAR	Birth HB in g/dL
1	1405	28	7	8	17.3
2	880	28	9	10	14.6
3	930	26	4	6	13.5
4	1250	29	6	8	14.3
5	1110	28	9	10	17.3
6	940	27	-	-	11.5
7	1120	28	5	8	17
8	760	25	7	6	18.7
9	1400	28	4	8	-
10	820	26	-	-	15.5
11	830	28	2	7	8.9
12	1200	28	6	8	13.3
13	1150	30	6	9	16.9
Average	**1061.2**	**27.6**	**5.9**	**8**	**14.9**
St Dev*	±217	±1.3	±2.1	±1.3	±2.8

*Standard Deviation

Post-natal day that BW was reached was on average on day 22 (range 9 to 56 days). Table 2 shows the percentage average gain/loss in weight for each infant at weekly intervals. It shows an average of 32.1% increase in weight at 6 weeks after birth for the population studied. When these weight gains were entered into the WINROP algorithm, 9 (75%) infants were detected to be at high risk for developing ROP before the age of 5 weeks. Most (8 infants, 66.7%) of these were detected before the age of 3 weeks, one included in this total even detected at birth. Of clinical importance, is the fact that 9 (69%) of the infants had less than 50% gain in birth weight at 6 weeks of age. Table 3 summarizes other contributing factors measured in the study.

Table 2. Average percentage weekly gain/loss in birth weight and WINROP algorithm detection of high risk for developing ROP at age in weeks (w) after birth.

Infant	Birth weight in grams	Day						WINROP detection
		7	14	21	28	35	42	
1	1405	-4.3	-5.3	+0.7	+6.4	+7.8	+12.1	Low risk at 6w
2	880	-	-	+11.4	+11.4	+11.4	+11.4	High risk at 3w
3	930	-	-	-	-	+19.4	+38.6	High risk at 5w
4	1250	-11.1	+11.1	+12	+24	+40	+48	Low risk at 6w
5	1110	-4.5	-0.9	+19.8	+34.2	+44.1	+53.2	High risk at 3w
6	940		+6.4	+13.8	+21.3	+34	+56.4	High risk at 3w
7	1120	-3.6	-3.6	+10.7	+25	+37.5	+42.9	High risk at 3w
8	760	-	-	-4.6	-2.6	-4.6	0	High risk at 3w
9	1400	-	-	-	+38.2	-	-	Missing data
10	820	-8.5	-3.7	+19.5	+29.3	+36.6	+45.1	High risk at 2w
11	830	-8.4	-8.4	-15.7	+10.8	+22.9	+18.1	High risk at birth
12	1200	-11.7	-9.2	-10.4	-	-	-9.6	High risk at 3w
13	1150	-	+5.2	+18.3	+36.5	+49.6	+68.7	Low risk at 6w

Table 3. Summary of contributing factors present in infants treated for ROP.

Factor	Percentage of presence in infants n (%) (N=13)
Oxygen supplementation Intubated ventilation CPAP	12[#] (100) 4 (33)[*] 8 (67)
Blood transfusions 2 or more Average amount transfused	6[#] (50) 77.25ml (Range 0-308ml)
Proven sepsis	10 (76.9)
Pulmonary disease Surfactant administered	12[#] (100) 4 (33)
Intraventricular haemorrhage[†]	4 (30.8) (unknown in 9)
Hyperglycemia 1st week of life[‡]	Average 3 of 7 days
PDA	5 (38.5) (unknown in 3)
Parenteral nutrition	5[#] (41.7)
NEC	3 (23.1)
Phototherapy	11 (84.6)
Breast milk	10 (76.9)

*The duration of intubation was longer than 7 days in all intubated infants.

†Intraventricular haemorrhage when present was grade 2 or less.

‡Hyperglycemia taken as a spike above 6.7mmol/L.

#N=12.

In addition to the above oxygen administration statistics, It was found that one unit in the referral system had a lower limit for oxygen saturation set at 95% for all infants included in the study.

The administration of breast milk was documented for each day up to 42 days after birth. The volume of breast milk given was measured, as well as the volume of breast milk as a percentage of the total fluid intake. 10 (76.9%) infants received breast milk. The average total intake of breast milk per infant was 899ml (range 281ml to 1348ml) in the 6 weeks

measured, which equates to 21.4ml/day. Average percentage breast milk intake of total fluid volume intake was 70.5% (range 30% to 91%) for the first 6 weeks of life.

ROP needing treatment was detected on average on day 71 (range 42 to 160 days) after birth. Seven eyes (30.4%) had ROP worse than Type 1. The two infants that had a weight more than 1250g, one with a weight of 1400g and the other of 1405g, both had stage 4 and worse. Twelve (52.2%) eyes had Type 1 disease. No eyes showed Type 2 disease. 4 (17.4%) eyes had ROP of better staging than Type 2 disease. 2 of these eyes (8.7%) were contralateral eyes that had Type 1 or worse disease, while 2 eyes were from one patient with bilateral Stage 2 Zone 2 with no plus disease. This patient was included as the infant still received treatment in the form of Bevacizumab injections. Cryotherapy was done in 1 eye (4%), while laser photocoagulation treatment was given to 22 eyes (88%). Bevacizumab was given in 9 eyes (36%) where it was used in conjunction with laser in all but two eyes, the two eyes mentioned above from the same patient with pre-threshold disease. One eye with Stage 5 disease was not treated, but included as the contralateral eye with Stage 4B was treated with laser photocoagulation. The outcome of treatments were difficult to measure accurately as more than half of patients' follow up notes after treatments could not be located.

Discussion

Birth Weights and the third epidemic of ROP

In the developed world, it is acceptable to have screening limits of <30 weeks gestation and <1250g for ROP, as infants with ROP show more prematurity with BW of 737g to 763g and GA of below 26 weeks.[1,12] Countries equivalent to South Africa in income show a GA of 26.3 to 33.5 weeks and BW of 903g to 1527g.[1] In South Africa, it has been shown that the mean GA for infants with ROP is 30.4 weeks with a mean BW of 1093.7g.[13] This study is in keeping with other statistics from South Africa. The results strengthen the fact that South Africa forms part of the third epidemic of ROP.[6] Brazil is seen as one of the countries that is part of the third epidemic.[1] In contrast with South African statistics, Brazil has managed to improve their outcomes and a study showed a mean BW of 972g for their infants with ROP.[14] Currently the screening guidelines of <32 weeks GA and <1500g BW is the acceptable standard in South Africa, although one study showed that the BW criterion could

be lowered to 1250g in our population.[6,13] This study suggests that the criteria should remain at 1500g, especially with the fact that the two infants with BW of 1400g and 1405g had stage 4 and worse disease.

Race and Breastmilk Administration

Race

The literature is conflicting in regard to race and the development of ROP. It has been shown that Caucasians have double the risk in reaching threshold disease compared with African infants.[15] In contrast, in 2010, a study from the United Kingdom showed a higher risk in African infants than in Caucasian infants for the development of ROP.[16] This same study however, showed a difference in birth weights between the two groups, in that African infants were smaller and more premature.[16] The clinical relevance of the difference is questioned in the paper.

Breastmilk Administration

Human breastmilk administration is a protective factor for both the development and severity of ROP.[9,17] One of these studies showed a major difference between a group developing retinal detachment and a group not developing retinal detachment concerning the amount of breastmilk administered as a total percentage of total fluid intake, being 38.4 ± 16.2% and 83.1 ± 10% respectively.[9] The current study's breastmilk administration statistics is comparable to the second group that had less retinal detachments.

Race, Breastmilk and Incidence

It is difficult to calculate the incidence of ROP in our population because of the lack of good statistics in screening. One South African study showed an incidence for threshold ROP to be 4.3% (3.2% in infants <1250g).[18] This incidence is similar to those for developed countries which are in the order of 3.9%.[19] Other developing nations show an incidence for treatment threshold ROP of up to 41%.[20] If one considers the fact that South Africa forms part of the third epidemic of ROP and has an incidence comparable to developed countries, then one could postulate that there are factors protecting our infants from developing threshold ROP. A possible explanation for this could be the fact that most of our infants are of African race, and an attempt is made to give most of our infant population human breastmilk.

WINROP and Post-natal Weight Gain

Early delay in weight gain seems to be an important risk factor. For each day delay in reaching the original BW after 10 days of age, an infant has a 6% risk of developing ROP.[8] This study shows a marked increase in delay of regaining BW. A practical way to measure this risk factor for clinicians, is to take note of infants not gaining at least 50% of their BW by 6 weeks of age.[21] The infants included in this study showed both of these clinical parameters: delay in reaching BW and gain percentage at 6 weeks of age.

Application of these weight gains in predicting the risk for developing ROP is under investigation. The WINROP group's algorithm has proved to be very accurate in predicting the risk for developing ROP. In developed countries it seems to be the most effective with sensitivities up to 100%.[22,23] In countries with developing Neonatal units, the sensitivity is lower at around 91% in one study while even lower at 55% in another study.[24,25] In the latter study, infants with BW below 1250g had a WINROP detection rate of 84.7% (83 of 98 infants) while infants with BW above 1250g had a detection rate of 5.3% (3 of 57 infants). The reasons for the difference in alarm for this algorithm in developing and developed countries could be explained by the same causative factors that outline the third epidemic of ROP. In our study the prediction rate for detecting infants at high risk for ROP falls within the developing country bracket.

APGAR scores

Low APGAR scores have been confirmed as an independent risk factor not only for the development of ROP but also ROP needing treatment.[26,27] In this study, 72.7% of infants fell into the high risk category (5 minute APGAR of <9) for mortality and morbidity according to a recent large Swedish study.[28] Of note, if the 5 minute APGAR high risk category is added to the WINROP algorithm results, a further 2 infants would have been detected as having a high risk of morbidity. This would have left only 1 infant (8.3%) undetected for the risk of development of ROP. Considering the difference in WINROP results in developing and developed countries, a possible adjustment with incorporation of the APGAR score could make the algorithm more accurate for infants with higher birth weights.

Oxygen Saturation Targets and Education

It has been proven that targets for oxygen saturation should be in the range of 88% - 92%.[6] Oxygen supplementation is a major contributor to the development of ROP and has a very clear pathophysiological basis for causation. Education of staff concerning this single important fact, especially at the identified unit with poor saturation targets, can have profound effects on prevention of ROP.

Limitations of the Study

The study population was small. The study was just a descriptive study.

Conclusion

The birth weights of our infants with ROP are above 1000g and the WINROP algorithm is not as accurate in detecting our infants as in the developed countries. Both of these two factors contribute to the statement that South Africa forms part of the third epidemic of ROP. Exactly what the cause is for the discrepancies in the developed and developing countries concerning these two facts are as yet uncertain. African race and human breastmilk administration could be major protective factors for the development of ROP in our population. Information gained from this study will be used to further educate staff involved in the care of our infants.

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Chapter 3. Discussion

The discussion in Chapter 2 of this report is written for the purposes of publication. This discussion builds on the discussion presented in Chapter 2 under the same headings.

Birth weights and the third epidemic of ROP

South Africa forms part of the third epidemic of ROP. Weights of infants with ROP are still above the 1000g mark.[1] This study confirms that fact. Another country to be part of the third epidemic, Brazil, has a mean weight of 972g for infants with ROP.[2] However, this value drops to 814g when mild disease in stage 1 and 2 is removed from the statistics.[2] South Africa has room for improvement before we can boast of statistics shown by the Brazilian study. However, as presented at the OSSA congress of 2016 by the department of ophthalmology of Kwa-Zulu Natal, (unpublished data) improvements have been made especially after the release of the 2013 South African ROP guidelines and education of all staff involved with oxygen administration.[3]

Race and Breastmilk Administration

The literature is conflicting in regard to race and the development of ROP. The major study where African race as a protective factor was realized was with the large CRYO-ROP study.[4] In a paper exploring the ethnic variations in ROP published by Yang in 2003, it is hypothesized that African infants are generally healthier than their Caucasian counterparts, and this causes African infants to develop ROP less.[4] Other papers have shown conflicting results.[4,5]

The current study's breastmilk administration statistics is comparable to a group of infants that showed breastmilk to be protective against the development of retinal detachments.[6] The complete results of breastmilk administration statistics for this study are attached as Addendum F.

South Africa has an incidence for treatment threshold ROP much lower than some other developing countries and similar to those of some developed countries.[7–9] If one considers this fact, then one could postulate that there are factors protecting our infants

from developing threshold ROP. A possible explanation for this could be the fact that most of our infants are of African race, and an attempt is made to give most of our infant population human breastmilk.

WINROP and post-natal weight gain

Infants should regain their birth weight by day 10 of life. Early delay in weight gain seems to be an important risk factor for the development of ROP.[10,11] The infants included in this study showed two clinical parameters of poor post-natal weight gain: delay in reaching birth weight and gain percentage at 6 weeks of age.

The WINROP algorithm uses post-natal weight gain to predict the risk for the development of ROP and was developed in Sweden.[12] Infants in Sweden with ROP have birth weights of around 740g.[13] Studies in developed countries have shown sensitivities of up to 100% in detecting ROP using the WINROP algorithm. [14,15] However, a nation based cohort in Sweden showed that the alarm was poor in detecting infants with weights above 900g.[13] Developing countries statistics are lower concerning the prediction rate; one study showed a WINROP detection rate of 5.3% in infants above 1250g.[16] The reasons for the difference in alarm for this algorithm in developing and developed countries could be explained by the same causative factors that outline the third epidemic of ROP. In our study the prediction rate for detecting infants at high risk for ROP falls within the developing country bracket.

APGAR scores, Oxygen saturation targets and education

This is discussed in Chapter 2.

Limitations of the study

The study population was small. The study was just a descriptive study.

Conclusion

The birth weights of our infants with ROP are above 1000g and the WINROP algorithm is not as accurate in detecting our infants as in developed countries. Both of these two factors contribute to the statement that South Africa forms part of the third epidemic of ROP. Exactly what the cause is for the discrepancies in the developed and developing countries concerning these two facts are as yet uncertain. African race and human breastmilk administration could be major protective factors for the development of ROP in our population. Information gained from this study will be used to further educate staff involved in the care of our infants.

Study Presentation at OSSA 2017

This study was presented at the annual Ophthalmological Society of South Africa (OSSA) Congress held in Port Elizabeth on 16 March 2017.

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Appendix A: Ethics Approval Letter

UNIVERSITY OF THE FREE STATE
UNIVERSITEIT VAN DIE VRYSTAAT
YUNIVESITHI YA FREISTATA

UFS·UV
HEALTH SCIENCES
GESONDHEIDSWETENSKAPPE

IRB nr 00006240
REC Reference nr 230408-011
IORG0005187
FWA00012784

25 May 2016

DR TC BOTHA
DEPT OPHTHALMOLOGY
FACULTY OF HEALTH SCIENCES
UFS

Dear Dr TC Botha

HSREC 66/2016
PROJECT TITLE: RETINOPATHY OF PREMATURITY: A CROSS SECTIONAL RISK FACTOR ANALYSIS OF TREATED INFANTS.

1. You are hereby kindly informed that, at the meeting held on 24 May 2016, the Health Sciences Research Ethics Committee (HSREC) approved the above project after all conditions were met.

2. The Committee must be informed of any serious adverse event and/or termination of the study.

3. Any amendment, extension or other modifications to the protocol must be submitted to the HSREC for approval.

4. A progress report should be submitted within one year of approval and annually for long term studies.

5. A final report should be submitted at the completion of the study.

6. Kindly use the **ECUFS NR** as reference in correspondence to the HSREC Secretariat.

7. The HSREC functions in compliance with, but not limited to, the following documents and guidelines: The SA National Health Act. No. 61 of 2003; Ethics in Health Research: Principles, Structures and Processes (2015); SA GCP(2006); Declaration of Helsinki; The Belmont Report; The US Office of Human Research Protections 45 CFR 461 (for non-exempt research with human participants conducted or supported by the US Department of Health and Human Services- (HHS), 21 CFR 50, 21 CFR 56; CIOMS; ICH-GCP-E6 Sections 1-4; The International Conference on Harmonization and Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Tripartite), Guidelines of the SA Medicines Control Council as well as Laws and Regulations with regard to the Control of Medicines, Constitution of the HSREC of the Faculty of Health Sciences.

Yours faithfully

.....
PROF W STEINBERG
VICE CHAIR: HEALTH SCIENCES RESEARCH ETHICS COMMITTEE

Health Sciences Research Ethics Committee
Office of the Dean: Health Sciences
T: +27 (0)51 401 7795/7794 | F: +27 (0)51 444 4359 | E: ethicsfhs@ufs.ac.za
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Appendix B: Approval letter from Department of Health

health
Department of Health
FREE STATE PROVINCE

13 May 2016

Dr TC Botha
Dept. of Ophthalmology
Faculty of Health Science
UFS

Dear Dr TC Botha

Subject: Retinopathy of prematurity: A cross sectional risk factor analysis of treated infants.

- Permission is hereby granted for the above – mentioned research on the following conditions:
- Serious adverse events to be reported and/or termination of the study.
- Ascertain that your data collection exercise neither interferes with the day to day running of Universitas Hospital nor the performance of duties by the respondents or health care workers.
- Confidentiality of information will be ensured and no names will be used.
- Research results and a complete report should be made available to the Free State Department of Health on completion of the study (a hard copy plus a soft copy).
- Progress report must be presented not later than one year after approval of the project to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- Any amendments, extension or other modifications to the protocol or investigators must be submitted to the Ethics Committee of the University of the Free State and to Free State Department of Health.
- **Conditions stated in your Ethical Approval letter should be adhered to and a final copy of the Ethics Clearance Certificate should be submitted to** khusemj@fshealth.gov.za or sebeelats@fshealth.gov.za **before you commence with the study**
- No financial liability will be placed on the Free State Department of Health
- Please discuss your study with the institution managers/CEOs on commencement for logistical arrangements
- Department of Health to be fully indemnified from any harm that participants and staff experiences in the study
- Researchers will be required to enter in to a formal agreement with the Free State department of health regulating and formalizing the research relationship (document will follow)
- You are encouraged to present your study findings/results at the Free State Provincial health research day
- Future research will only be granted permission if correct procedures are followed see http://nhrd.hst.org.za

Trust you find the above in order.

Kind Regards

Dr D Motau
HEAD: HEALTH
Date: 17/05/16

Appendix C: Data Collection Sheet

Retinopathy of Prematurity: A Cross Sectional Risk Factor Analysis of Treated Infants.

For office use

Infant reference study number _____

1. Gender

Male	1	☐ 1-2
Female	2	

2. Race

African	1	☐ 1-3
Caucasian	2	
Other _____	3	

3. Birth site

Hospital

Inside unit	1	☐ 1-2
Outside unit	2	

4. Birth site

Region ☐ 1-5

Bloemfontein region	1
Bethlehem region	2
Welkom region	3
Northern Free State	4
Other, Specify _____	5

5. Gestational Age at Birth _____ weeks

6. Birth Weight _____ grams

7. Weight gain

Day original birth weight reached Day _____

8. Weight gain

Day 7	_____ grams
Day 14	_____ grams
Day 21	_____ grams
Day 28	_____ grams
Day 35	_____ grams
Day 42	_____ grams

9. Oxygen supplementation

Route (most invasive)

Ventilated	1	☐	1-5
CPAP	2		
Box	3		
Nasal prongs	4		
Room air	5		

10. Oxygen supplementation

Days intubated

7 or less Days	1	☐	1-2
>7 Days	2		

11. Blood transfusions, 2 or more	Y	N	☐	1-2

12. Amount transfused _____ ml

13. Proven sepsis Y N ☐ 1-2

14. Pulmonary disease (RDS, BPD, HMD, apnoea) Y N ☐ 1-2

15. Surfactant administered Y N ☐ 1-2

16. Intraventricular haemorrhage Y N ☐ 1-3

Unknown

17. Intraventricular haemorrhage grade ☐ 1-4

Grade 1 1

Grade 2 2

Grade 3 3

Grade 4 4

18. Hyperglycemia (blood glucose spike >6.7mmol/l) within first week

Number of days _____

19. Patentus Ductus Arteriosus Y N ☐ 1-3

Unknown

20. Parenteral Nutrition Y N ☐ 1-2

21. Necrotizing Enterocolitis Y N ☐ 1-2

22. Breast Milk Y N

1-2

23. Average percentage breast milk of total volume intake per day during following week of life:

Week 1 _____

Week 2 _____

Week 3 _____

Week 4 _____

Week 5 _____

Week 6 _____

24. Average total breast milk intake volume per day during following week of life:

Week 1 _____

Week 2 _____

Week 3 _____

Week 4 _____

Week 5 _____

Week 6 _____

25. Age at diagnosis of treatment threshold ROP.

_____days

26. ROP stage prior to treatment.

OD _____

OS _____

27. Treatment

OD	Surgery	1	☐ 1-4
	Laser	2	
	Avastin	3	
	None	4	

28. Treatment

OS	Surgery	1	☐ 1-4
	Laser	2	
	Avastin	3	
	None	4	

29. Regression of disease after treatment.

OD	Y	N	☐ 1-2

30. Regression of disease after treatment.

OS	Y	N	☐ 1-2

Appendix D: Subsidiary results

Breastmilk Administration Statistics Table

Table 4. Breastmilk administration statistics table. Average intake for weeks 1 to 6: total volume breast milk intake per day and percentage of total fluid intake per day.

		Breast milk intake: average volume per day in millilitres.							Average percentage breast milk of total fluid intake per day.					
Infant		**1**	**2**	**3**	**4**	**5**	**6**		**1**	**2**	**3**	**4**	**5**	**6**
1		58	65	212	249	190	216		27	29	97	100	80	97
2		51	124	41	61	147	40		38	74	24	35	97	20
3		98	189	250	216	277	318		59	79	100	83	100	100
4		91	200	29	218	266	293		70	98	13	86	98	100
5		74	162	187	205	232	252		31	76	93	100	100	100
6		75	187	203	232	257	275		48	100	100	100	100	100
7		42	114	145	141	146	186		35	87	99	100	86	100
8		0	0	53	137	120	167		0	0	38	85	71	99
9		18	12	28	36	87	100		10	6	14	20	61	73
10		27	146	216	242	276	314		18	73	100	100	100	100

Appendix E: Anti-Plagiarism Report: Turn It In

Dr Botha tesis II

ORIGINALITY REPORT

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SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

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4	www.dos-times.org Internet Source	1%
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6	Alizadeh, Yousef; Zarkesh, Marjaneh; Moghadam, Reza Soltani; Esfandiarpour, Bahareh; Behboudi, Hassan; Karambin, Mohammad-Mehdi and Heidarzade, Abtin. "Incidence and Risk Factors for Retinopathy of Prematurity in North of Iran", Journal of Ophthalmic & Vision Research, 2015. Publication	1%

7	"Characteristics of Infants With Severe Retinopathy of Prematurity in Countries With Low, Moderate, and High Levels of Development: Implications for Screening Programs", PEDIATRICS, 05/01/2005 Publication	1 %
8	Ingele Casteels. "Educational paper : Retinopathy of prematurity", European Journal of Pediatrics, 11/04/2011 Publication	<1 %
9	Abdel Hadi, Ahmed Mahmoud, and ShereenHamdy. "Correlation between risk factors during the neonatal period and appearance of retinopathy of prematurity in preterm infants in neonatal intensive care units in Alexandria, Egypt", Clinical Ophthalmology, 2013. Publication	<1 %
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11	S Varughese. "Retinopathy of prematurity in South Africa: an assessment of needs, resources and requirements for screening programmes", British Journal of Ophthalmology, 07/01/2008 Publication	<1 %
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13	"The International Classification of Retinopathy of Prematurity Revisited", Archives of Ophthalmology, 2005 Publication	<1%
14	Wu, Wei-Chi, Hsi-Kung Kuo, Po-Ting Yeh, Chung-May Yang, Chi-Chun Lai, and San-Ni Chen. "An Updated Study of the Use of Bevacizumab in the Treatment of Patients with Prethreshold Retinopathy of Prematurity in Taiwan", American Journal of Ophthalmology, 2013. Publication	<1%
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19	Mosotho, Lehlohonolo, Dap Louw, F.J.W. Calitz, and K.G.F. Esterhuyse. "Clinical manifestations of mental disorders among Sesotho speakers", International Journal of Psychiatry in Clinical Practice, 2008. Publication	<1%

20	Shah, P. K., V. Narendran, and N. Kalpana. "Aggressive posterior retinopathy of prematurity in large preterm babies in South India", Archives of Disease in Childhood - Fetal and Neonatal Edition, 2012. Publication	<1 %
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