OCULAR BIOMETRY, OPTIC NERVE HEAD PARAMETERS AND RETINAL NERVE FIBER LAYER THICKNESS IN SEVERE PRETERM MALAY CHILDREN

By

ALSHAARAWI M.A. SALEM

THESIS SUBMITTED IN FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF MASTER OF SCIENCES (CLINICAL OPHTHALMOLOGY)

SCHOOL OF MEDICAL SCIENCES
UNIVERSITI SAINS MALAYSIA
2012

Disclaimer

I hereby certify that the work in this thesis is my own except for the quotations and summaries which have been duly acknowledged.

……

Dated: 19 March 2012 **Alshaarawi M.A. Salem**

P-UM00006

ACKNOWLEDGEMENT

Alhamdulillah, Praise is only to Allah for endless giving us his mercy and blessing that we can still breathe the fresh air and survive in this world for gratis. Allah said in Holy Quran:

"Your Lord is best aware of you. If He will, He will have mercy on you, or if He will, He will punish you" (Holy Quran 17:54).

I wish to express my deepest gratitude to my supervisor, Associate Professor Dr Shatriah Ismail for her excellent supervision and providing me with interesting project to develop my own analytical skills. I am also indebted to her for her helpful discussions and constructive criticism.

Besides, my healthiest and greatest appreciation to my co-supervisors Associate Professor Dr Wan Hazabah Wan Hitam, Associate Professor Dr Zunaina Embong and all the Lecturers in the department of Ophthalmology, School of Medical Sciences, Universiti Sains Malaysia for their outstanding guidance and encouragement throughout my study research. I would like also to thank Associate Professor Dr. Fawwaz Al Joudi for advising me to continue my study in Universiti Sains Malaysia. Not forgotten to all my colleagues and every single person those have contribute to this thesis directly or indirectly.

My Acknowledgments will not be complete without specifically mentioning names of the following sponsors for their financial support. They include Mr. Haji Hussin Ismail head office of YAYASAN AMAL MALAYSIA (AMAL MALAYSIA) and Mr. Ausaini Ibrahim deputy chairman of SECRETARIAT FOR PALESTINE CONCERN MISSION.

I would like to aknowledge Universiti Sains Malaysia for providing a research university (RU) grant USMKK/PPP/JEPeM [228.4.(1.9)] to support these studies. I would like to express my sincere appreciation to Universiti Sains Malaysia for the award of graduate assistant (GA). I'm very grateful to universiti Sains Malaysia which has provided me platform to learn academically and acquire research skills.

Finally, I would like to acknowledge my dearest parents, Sheikh Mohamad Rajab Ahmed Salem and Madam Naima Salem for their many sacrifices and hardships in bringing me up to this world. I am very fortunate to have both of you. This day would not have arrived without the enormous support and constant inspiration from both of you. I do not have enough words to say how grateful I am to you both.

May Allah bless all of us

TABLE OF CONTENT

LIST OF TABLES

List of figures

PARAMETER BIOMETRIK OKULAR, PARAMETER KEPALA SARAF OPTIK, DAN KETEBALAN LAPISAN RETINA DALAM BAYI LAHIR PRAMATANG YANG TERUK DENGAN KANAK-KANAK MELAYU

ABSTRAK

Pengenalan: Kelahiran pramatang yang teruk ditakrifkan sebagai bayi yang dilahirkan pada minggu ke-32 atau kurang kehamilan. Semakin awal bayi itu dilahirkan, semakin kurang kemungkinan bayi itu untuk terus hidup. Mereka yang terselamat berada pada risiko yang lebih tinggi untuk masalah kesihatan sepanjang hayat, seperti mendapat komplikasi oftalmik yang merangkumi retinopati pramatang, myopia, amblyobia, strabismus dan keabnormalan saraf optik.

Objektif: Kajian ini adalah untuk membandingkan parameter biometrik okular, parameter kepala saraf optik, dan ketebalan lapisan retina antara bayi lahir pramatang yang teruk dengan kanak-kanak Melayu yang lahir cukup bulan yang berusia 8-16 tahun.

Metodologi: Kajian perbandingan keratan rentas ini menilai 64 pesakit, 32 orang pesakit telah dilahirkan kurang daripada 32 minggu kehamilan dan 32 pesakit yang dilahiran cukup bulan. Kesemua pesakit telah menjalani pemeriksaan mata yang menyeluruh. Okular biometri dilakukan menggunakan A-Scan ultrabunyi biometri, manakala

parameter saraf optik dan lapisan retina telah dijalankan dengan menggunakan Heidelberg Tomograph Retina III.

Keputusan: Terdapat perbezaan statistik yang signifikan terhadap kedalaman struktur *vitreous* antara kumpulan pramatang yang teruk dengan kumpulan cukup bulan, (p = 0.04).Walau bagaimanapun, tidak ada perbezaan statistik yang signifikan terhadap kedalaman structur hadapan bola mata, ketebalan kanta dan panjang bola mata antara kumpulan pramatang yang teruk dan kumpulan cukup bulan. Isi padu rim, ukuran bentuk cawan, variasi ketinggian kontur, dan kedalaman cawan maxima antara kumpulan pramatang yang teruk dan kumpulan cukup bulan ketara secara statistik (p <0.05). Walau bagaimanapun, purata keluasan cawan, cawan / cakera, isi padu cawan, min keluasan rim, cawan / keluasan cakera, cawan linear / keluasan cakera dan kedalaman cawan maksimum antara kumpulan pramatang yang teruk dan kumpulan cukup bulan tidak signifikan secara statistik (p> 0.05). Terdapat perbezaan statistik yang signifikan untuk kuadran hidung, hidung / kuadran nasal,dan hidung / kuadran yang lebih rendah antara kumpulan pramatang yang teruk dan kumpulan cukup bulan (p <0.05). Sebaliknya, tiada perbezaan yang signifikan telah dilaporkan dalam kuadran yang sementara, sementara / unggul, dan sementara / kuadran yang lebih rendah antara kumpulan pramatang yang teruk dengan kumpulan cukup bulan (p> 0.05).

Kesimpulan: Kajian ini mendapati bahawa kedalaman kebuk kaca ketara lebih rendah dari kalangan kanak-kanak kelahiran pramatang yang teruk. Terdapat perbezaan ketara

yang signifikan pada ukuran saraf optik dari kalangan kanak-kanak kelahiran pramatang yang teruk berbanding kelahiran biasa seperti isipadu rim, isipadu cawan, ukuran bentuk cawan, variasi ketinggian kontor dan purata kedalaman cawan. Ukuran saraf retina di sebelah kuadran nasal adalah lebih nipis secara signifikan dari kalangan kanak-kanak kelahiran pramatang yang teruk, sementara ukuran ketebalan keseluruhan saraf retina, nasal/kuadran atas, nasal/kuadran bawah adalah lebih tebal secara signifikan berbanding kanak-kanak kelahiran normal.

OCULAR BIOMETRY, OPTIC NERVE HEAD PARAMETERS AND RETINAL NERVE FIBER LAYER THICKNESS IN SEVERE PRETERM MALAY CHILDREN

ABSTRACT

Introduction: Severe preterm delivery is defined as babies born at 32 weeks or less of gestation. The earlier the baby is born, the less likely he or she is to survive. Those who do survive are at a higher risk of lifelong health problems, of which the ophthalmic complications include retinopathy of prematurity, myopia, amblyobia, strabismus and optic nerve abnormalities.

Objective : This study is to compare the ocular biometric parameters, optic nerve head parameters, and retinal nerve fiber layer thickness parameters between severe preterm and term Malay children aged 8-16 years old.

Methodology: This comparison cross sectional study evaluated 64 patients, 32 patients were born less than 32 weeks of gestation and 32 patients were full term. All patients underwent thorough eye examination. Ocular biometry was performed using A- Scan ultrasound biometry, whilst optic nerve head parameters and retinal nerve fiber layer thickness were performed using Heidelberg Retinal Tomograph III.

Results: There was a statistically shorter vitreous chamber depth between severe preterm group and term group, (p=0.04). However, there was no statistically significant difference of anterior chamber depth, lens thickness and axial length between severe preterm group and term group. The rim volume, cup shape measurement, height variation contour, and mean cup depth in severe preterm group were statistically increased compared to the term group and (p<0.05). However, the mean cup area, cup/disc, cup volume, mean rim area, cup/disc area, linear cup/disc area and maximum cup depth between severe preterm group and term group were not statistically significant (p>0.05). The mean nasal quadrant of retinal nerve fiber layer is significantly thinner in severe preterm children, whilst global retinal nerve fiber layer of nasal/superior quadrant and nasal/inferior quadrant are significantly thicker in severe preterm compared to term children. On the other hand, no significant differences have been reported in temporal quadrant, temporal/superior, and temporal/inferior quadrant between severe preterm group and term group (p>0.05).

Conclusion: This study shows the vitreous chamber is significantly shorter in severe preterm children. The rim volume, cup volume, cup shape measurement, height variation contour and mean cup depth of optic nerve head are significantly different between severe preterm and term children.

The nasal quadrant of retinal nerve fiber layer is significantly thinner in severe preterm compared to term Malay children, whilst global retinal nerve fiber layer thickness, nasal/superior quadrant and nasal/inferior quadrant are significantly thicker in severe preterm children compared to term Malay children aged 8-16 years old.

CHAPTER ONE
INTRODUCTION

1.0 INTRODUCTION

1.1 Preterm

A preterm child is defined as a child born at less than 37 weeks of gestation (Silvia and Eve, 1991; WHO, 1992). The causes of preterm birth are elusive and unknown in most situations; many factors appear to be associated with the development of preterm birth, making the reduction of preterm birth a challenging proposition. Silvia and Eve (1991) defined premature delivery as that occurring before 37 completed weeks of gestation, starting from the first day of the last menstrual period.

Preterm birth rates have been reported to range from 5% to 7% of live births in some developed countries, but are estimated to be substantially higher in developing countries (Lawn *et al.,* 2006). Preterm birth accounts for 10% of births in Malaysia and results in about 75% of neonatal deaths not associated with congenital malformation (Annual Report Ministry of Health, 1998).

Severe preterm or early preterm delivery is defined as babies born at 32 weeks or less of gestation (Gallo *et al.,* 1991; Keith *et al.,* 1983; Dowdeswell *et al.,* 1995). Low birth weight has been defined by the World Health Organization (WHO) as weight at birth at less than 2500 grams or 5.5 pounds. More common in developing countries than developed countries, a birth weight below 2500 grams contributes to a range of poor health outcomes (WHO, 1992).

Low birth weight can be either due to preterm birth (before 37 weeks of gestation) or intrauterine growth restriction. Generally, low birth is closely associated with increased fetal and neonatal mortality. It also causes inhibited growth and cognitive development, and may predispose to certain chronic diseases later in life. In an Asian population based study, Fikree *et al.* (1994) reported that significant risk factors for low birth weight could be attributed to a lower socioeconomic status, lower maternal education level, source of water supply and paternal.

Globally, more than 20 million infants are born with low birth weight (World Health Organization 2011). The percentage of low birth of developing countries (16.5%) is two- fold greater than that observed in the developed countries (7%). More than 95% of low birth weight occurs in developing countries. In Malaysia, the incidence of low birth weight is estimated at 10% (Department of Statistics, 1999) and this contributes to 66.2% of 6,038 estimated perinatal deaths (Ministry of Health Malaysia Annual Report, 1999).

1.2. Pathophysiology of preterm labour

Preterm labour is identified as occurrence of regular uterine contractions with cervical priming in women at less than 37 weeks of gestation. The pathological mechanisms leading to preterm labour are poorly understood. However one postulation is that it occurs as a result of early activation of the normal labour process. Another theory suggests that preterm labour sets in due to certain pathological insults to the body

system. In normal circumstances, the initiation of labour in a pregnant woman is postulated to be due to withdrawal of progesterone, initiation and release of oxytocin and activation of the decidual membrane. These hormonal changes usually occur at term. Theoretically speaking, it is thought that the possible mechanisms of initiation of labour are local reduction in progesterone levels and the reduction of progesterone receptors. As such serum progesterone levels do not increase near the time of parturition.

Oxytocin may not be directly involved in initiation of labour, because blood concentrations of oxytocin remain constant throughout and even at the onset of labour. However the infusion of oxytocin in pregnant women has been shown to cause uterine contractions, indicating that it may be involved in the mechanism of initiation of labour (Robert *et al.*, 2008).

The decidua is the endometrium of the pregnant uterus, which gets almost completely shed off at parturition, except for the innermost layer. Decidual activation usually occurs near term, and is thought to play an important role in the initiation of labour. Premature activation of the deciduous membrane is caused by occult intrauterine infections or intrauterine bleeding. These lead to spontaneous preterm labour and subsequent preterm birth (Romero *et al.*, 2006b).

1.3 Preterm labour: Obstetric causes

As mentioned previously, a preterm birth is defined as birth at less than 37 completed weeks of gestation. Preterm births are responsible for more than 75% perinatal mortality and account for more than 50% long term morbidity. Prematurity predisposes to various anomalies pertaining to the neurodevelopmental, respiratory and gastrointestinal system (McCormick, 1985).

The main obstetric causes for premature delivery of an infant are as follows (Tucker *et al.*, 1991) :

1. Spontaneous preterm labour (45%)
2. Premature preterm rupture of membranes (PPROM) (25%), and
3. Premature delivery secondary to maternal or foetal infections (30%).

1.3.1 Spontaneous preterm labour

Spontaneous preterm labour is that which is non-medically or surgically induced, and which results in spontaneous delivery. However the onset of labour is earlier than the expected date. Usually in these patients the membranes are intact at the onset of labour. Preterm labour has an ethnic variation and therefore it has been observed that preterm births occurring as a result of spontaneous preterm labour are more commonly seen in Caucasian women (Ananth and AM., 2006).

1.3.2 Premature preterm rupture of membranes

Premature preterm rupture of membranes (PPROM) is defined as the spontaneous rupture of membranes at less than 37 weeks of gestation, with the onset of contractions occurring at least 1 hour later. Compared to spontaneous preterm labour, PPROM is more commonly seen in Black women (Ananth, 2006). In most cases, the cause of PPROM cannot be identified. However certain risk factors predisposing to PPROM are cigarette smoking or other forms of exposure to tobacco and asymptomatic intrauterine infections (Mercer *et al.*, 2000). Usually intact membranes protect the foetus from ascending infections, and the breakdown of this protective barrier predisposes to ascending infections such as chorioamnionitis. The presence of infection leads to preterm labour and subsequent preterm birth (Romero *et al.*, 2004).

1.3.3 Premature delivery secondary to maternal or foetal infections

Various microorganisms have been linked to the pathogenesis of preterm birth. Microbes may reach the amniotic cavity and fetus by ascending from the vagina and cervix, by hematogenous distribution through the placenta, by migration from the abdominal cavity through the fallopian tubes, or through invasive medical procedures. Organisms commonly cultured from the amniotic cavity following preterm delivery include Ureaplasma urealyticum, Mycoplasma hominis, Bacteroides spp., Gardnerella vaginalis, Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis, and group B hemolytic streptococci. Several trials have examined the effect of antibiotic

administration to patients with preterm labor and intact membranes, preterm premature rupture of the membranes, genital mycoplasmal infection, asymptomatic bacteriuria, and bacterial vaginosis (Pararas *et al.*, 2006).

1.4 Preterm labour: Non-Obstetric causes

1.4.1 Maternal risk factors

According to statistics, women of African origin are at higher risk of preterm delivery compared to Caucasian women. In fact, women of African origin have the highest likelihood of having preterm children when considering all other ethnic groups (Goldenberg *et al.*, 1996). On the other hand, women of South Asian origin, including those of the Indian subcontinent have low preterm birth rates. Instead, these women have a high incidence of low birth weight due to intrauterine foetal growth restriction (Robert *et al.*, 2008). Low socioeconomic and a poor educational status of the pregnant mother are contributing factors to preterm births. Maternal age also seems to influence prematurity, with both young age and elderly age leading to increased incidence of preterm births. Single mothers have been observed to be at higher risk of giving birth to premature babies. The relationship between these demographic factors and the increased incidence of preterm birth remains largely unknown. Nevertheless, these factors need to be identified early and modified if possible (Smith *et al.*, 2007).

Women who work under stressful conditions may be more prone to preterm labour. (Saurel-Cubizolles *et al.,* 2004). Heavy physical work and long working hours have also been postulated to increase the likelihood of preterm labour and birth (Launer *et al.*, 1990). However several observational studies have given conflicting results and therefore a proper inference is difficult to make owing to the presence of several confounding factors (Pompeii *et al.,* 2005).

Another important risk factor that has been identified is birth spacing. Several studies have shown that a pregnancy occurring at less than 6 months' interval of a previous delivery is 50% more likely to result in a preterm birth (Smith *et al.,* 2003). Moreover those women who have previously given birth to a preterm are at higher risk of having a subsequent preterm child, presumably because of the closer temporal proximity between the two pregnancies. If pregnancies are not properly timed and occur at less than 6 months' interval, the uterus does not have enough time to completely recover from its previous inflammatory status. In addition the depleted maternal stores during the previous pregnancy are unable to get completely replenished and this also contributes to preterm labour (Conde *et al.*, 2006).

The nutritional status of the mother is very important in successfully carrying out a pregnancy to term. Women with a low prepregnancy body mass index are at higher risk of developing spontaneous preterm labour. On the other hand, prepregnancy obesity may be protective against preterm labour (Hendler *et al.*, 2005). Low serum

concentrations of certain minerals like iron and zinc and vitamins such as folate have also been associated with preterm births (Tamura T *et al.,* 1992).

1.4.2 Pregnancy related risk factors

It has been reported that women with a previous preterm birth are two and a half times more likely to have a premature child in their subsequent pregnancies (Mercer *et al.*, 1999). Furthermore the risk of another preterm birth is inversely proportional to the gestational age of the previous preterm birth. The occurrence of repeated spontaneous preterm births may be explained by the presence of intrauterine infections (Goldenberg *et al., 2006).*

Multiple gestations have been increasingly associated with higher incidence of preterm births. It is believed that as many as 60% of twins are born preterm. The possible mechanism for preterm labour in multiple gestations is uterine over distension leading to earlier onset uterine contractions and PPROM. This leads to an increased incidence of premature spontaneous labour and delivery (Romero *e*t *al.,* 2006).

A high incidence of preterm birth has also been linked to per vaginal bleeding in the first and second trimester of pregnancy. The main causes of bleeding in the ante partum period are placental abruption and placenta previa. However certain local pathologies which cause vaginal bleeding are also thought to contribute to increased risk of preterm

labour and delivery (Krupa *et al.*, 2006).

As has been previously mentioned, PPROM is a major cause of preterm birth. This phenomenon is a common occurrence in amniotic fluid disorders. Polyhydramnios is excessive amniotic fluid, whereas oligohydramnios is scanty amniotic fluid. These two amniotic fluid disorders can precipitate PPROM and therefore preterm labour will get initiated (Tucker *et al.*, 1991).

A pregnant woman undergoing abdominal surgeries during the second or third trimester of pregnancy is at increased risk of suffering preterm labour, because the surgical procedure may stimulate uterine contractions leading to preterm labour (Robert *et al.*, 2008).

Anomalies of the female reproductive system have been associated with increased incidence of preterm labour. These anomalies may be restricted to the uterus itself (e.g. presence of a septum), or to other structures like deformities of the cervix following electrocautery or biopsy for a premalignant cervical lesion (Jakobsson *et al.*, 2007).

Clinical depression has been shown to adversely affect pregnancy outcomes. It is increasingly common in the recent times and may result in preterm births, although most studies have given inconsistent results. Depression in pregnant women leads to behavioural changes like increased use of tobacco and increased consumption of

alcohol. Hence the risk of premature labour secondary these altered social habits is higher in these women (Schoenborn and J., 1993). Certain other studies have also demonstrated that depression increases the serum concentration of inflammatory cells, leading to increased vasoconstriction which further increases the chance of preterm labour and birth (Gennaro *et al.*, 1997). Around 35 % of women experience depressive symptoms during their pregnancy and this constitutes a substantial proportion of the pregnant population (Gavin *et al.*, 2005).

The use of tobacco during pregnancy carries a two folds increased risk of preterm delivery (Andres and MC, 2000). Tobacco smoke contains a very large number of harmful chemicals. Among these, nicotine and carbon monoxide are potent vasoconstrictors. They cause widespread vasoconstriction, particularly so at the placental level and reduce the uteroplacental blood flow. This reduces placental tissue perfusion leading to placental damage. As a result both intrauterine growth restriction and preterm labour occur. Smoking is also known to induce a systemic inflammatory response leading to the release of toxic free radicals which can lead to spontaneous preterm labour (Bermudez *et al.*, 2000).

Intrauterine infections are well known to increase the risk of preterm labour. Certain studies have shown that 25-40% of preterm births are linked to intrauterine infection (Goldenberg *et al.*, 2000). The causative organisms that have commonly been isolated in the amniotic cavity are the genital Mycoplasma species, particularly Ureaplasma

urealyticum (Watts *et al.*, 1992*)*. Certain other micro organisms of the lower genital tract like Streptococcus agalactiae have also been isolated, although their occurrence is relatively rarer. It should be noted that these organisms are of low virulence, and thus their infection follows a more chronic course. Owing to the chronicity and low virulence of these organisms, the resulting infections are asymptomatic and may remain largely undetected (Goldenberg *et al.*, 2000).

Other genital tract infections have been proposed as possible underlying pathological risk factors for preterm labour; however their mechanism still remains unclear (Goldenberg *et al.*, 2005a). A few of these infections are Chlamydia, trichomoniasis, syphilis and gonorrhoea (Donders *et al.*, 1993). Chlamydia will lead to preterm labour only in the presence of a maternal immune response (Sweet *et al.*, 1987). In certain cases periodontal disease has been implicated (Offenbacher *et al.*, 1996). One theory suggests that micro organisms within the gingival crevices may enter the maternal circulation, leading to bacteraemia and placental colonisation.

1.4.3 Biological risk factors

The use of biological markers has been useful in predicting the risk of preterm births. Chemical such as cytokines and chemokines contained in amniotic fluid or cervical mucus, as well as serum alkaline phosphatase and alpha fetoprotein have been used as biological markers. Among all these biomarkers, a substantial number have shown clinical significance (Goldenberg *et al.*, 2005b). Of all these biomarkers, the most

powerful predictor of preterm birth is foetal fibronectin (Goldenberg *et al.*, 1996b). It is a glycoprotein which is characteristically present in the cervicovaginal fluid in the early weeks of pregnancy. It later disappears from the cervicovaginal fluid as from 24 weeks of gestation and beyond. If foetal fibronectin is detected after 24-26 weeks of gestation, it indicates that there is choriodecidual disruption. Therefore preterm labour can accurately be detected early. It also has high negative predictive value (Lu *et al.*, 2001).

1.4.4 Genetic risk factors

Women with a strong family history of preterm birth are more prone to give birth to premature babies. Interestingly those women whose sisters had a preterm birth have an 80% increased chance of also delivering a preterm baby (Winkvist *et al.*, 1998). Preterm births not only affect siblings but also influence future generations of the family tree as well. In fact certain grandparents of women who have had a preterm birth may themselves have been born before 37 completed weeks of gestation. This means that a person who is born preterm is more prone to have a future preterm great grandchild (Porter *et al.*, 1997).

1.5 Complications of prematurity

Survival for extremely or severe premature infants has increased significantly during the last two decades. Complications of prematurity are becoming more common as more survivors are spending time in newborn intensive care units (NICUs). Most

premature infants born at <32 weeks gestation will remain in the NICU until close to term to allow for sufficient organ maturation so that the infant can be cared for independent of intensive care. Immaturity of multiple organ systems places them at high risk for a variety of complications during these prolonged hospital stays (Ward, and Beachy., 2003).

However, Ward, and Beachy., 2003 reported that CNS hemorrhage and/or ischaemia, necrotizing entercolitis (NEC), chronic lung disease, and retinopathy of prematurity (ROP) are the most specific complications in long term of babies who delivered extremely preterm.

In addition, Critchley *et al*., 2004, Terzidou & Bennett 2002, Woods et al., 2005, and Phillip and Keith., 2007 reported the most common complications of prematurity in babies who deliver preterm. They reported the followings complications:

a- Respiratory Distress Syndrome (RDS)

b- Intrventricular Hemorrhage (IVH)

c- Nectrotizing Entero-Colitis (NEC)

d- Cerebral Palsy (CP)

e- Physical disability

f- Hearing loss

g- Retinopathy of Prematurity (ROP)

h- Peri-ventricular Leucomalacia

i- Mental Disability / Neurodevelopmental delay and Learning difficulties at school

j- Neonatal seizures

k- Neonatal sepsis and neonatal death

1.5.1 Ophthalmic complications

Ophthalmic complications include ROP, myopia, amblyobia, strabimus and optic nerve abnormalities (Gallo *et al.,* 1991; Keith et al 1983; Dowdeswell *et al.,* 1995). These complications are dependent upon the degree of prematurity (Snir *et al.,* 1988) and the occurrence of cerebral damage (Hungerford *et al.,* 1986).

Choi *et al.,* (2000) studied the prevalence of myopia, strabismus and amblyopia in premature children in South Korea. Thirty one premature children and 31 full-term children were examined when they were 3 years of age from 1993 to 1996. They reported that uncorrected visual acuity of 0.6 or better was noted in 27 (43.55%) eyes of the premature children and 35 (56.45%) eyes of the full-term children. A total of 17 (27.42%) eyes of preterm and 8 (12.9%) eyes of full-term children had myopic refractive error (0.25 diopters or greater) and 6 (9.68%) eyes of preterm and 11 (17.74%) eyes of full-term children had hyperopic refractive error (2.0 diopters or greater). The astigmatism (1.0 diopter or greater) was found in 21 (33.87%) eyes in preterm as compared with 10 (16.13%) eyes in full-term children.

Similarly, Choi *et al.* (2000) observed the binocularity, and it was evaluated from Titmus and TNO stereo test. Fifteen (48.4%), 12 (38.7%) premature children and 25 (80.6%), 23 (74.2%) fullterm children passed the Titmus 200 seconds of arc and TNO 240 seconds of arc each. Strabismus was not found in full-term children and 4 (6.45%) of premature group. Premature infants without retinopathy of prematurity had higher rates of ocular abnormalities than full-term children (Choi *et al.,* 2000).

1.5.1.1 Retinopathy of prematurity

Retinopathy of prematurity ROP is a process of abnormal neovascularisation due to extreme prematurity, hyperoxia and retinal ischaemia (Ward, and Beachy, 2003). The incidence and severity of ROP is inversely related to gestational age.

Chiang *et al.,* (2004) determined the current incidence of (ROP) in New York State. This study reported that the overall incidence of any ROP among all newborn infants in New York state during the study period 1996-2000 was 0.2% (2284 of 1 167 427), or 1 in 511. The incidence of any ROP in the study population of newborns with initial hospital length of stay >28 days was 20.3% (2152 of 10 596) among infants with birth weight <1500 g and 27.3% (1839 of 6745) among infants with birth weight <1200 g. Among study patients with any ROP, the proportion who underwent laser photocoagulation during initial hospital stay was 9.5% (218 of 2284), and the proportion who underwent scleral buckle or vitrectomy surgery was 0.5% (12 of 2284). Seventeen study newborns with birth weight ≥2000 g had a discharge diagnosis of ROP,

although none of these patients required laser or incisional surgery during hospitalization.

In addition, Karkhane *et al.* (2008) have reported the incidence of the incidence and risk factors of ROP in premature infants referred to a tertiary eye hospital during 2003-2007 to provide preliminary evidence about ROP in Iran. They reported in this study that among 953 premature infants, there were 329 (34.5%) different stages of ROP. Severe ROP was seen in 22.6% (215/953) of infants (16.5%: treatable, 6.1%: advanced untreatable). The mean gestational age (GA) and birth weight (BW) of infants with severe ROP were 28.8 (SD 2.4) weeks and 1256 (389) g respectively.

ROP is rarely identified in infant with birthweight >1500 g or >32 weeks gestational age. Severe ROP leading to retinal detachment and blindness has a much higher incidence in infants with birth weight <1000 g (Wheatley *et al.*, 2002). Compared to fetal oxygen levels, the extra uterine environment is relatively hyperoxic to the premature infant even if no supplemental oxygen is required. The choroidal circulation, unlike the retinal circulation, does not auto regulate in response to changes in oxygen tension. Thus, under conditions of hyperoxia, excess blood and oxygen move from the choroidal to the retinal circulation. This increase in oxygen can cause the retinal vessels to constrict to the point of obliteration.

In addition, oxygen promotes creation of free radicals that can overwhelm the available antioxidants. Genetic factors also play a role in the incidence of severe ROP, as African-American preterm infants are less likely to develop ROP than caucasia preterm infants, controlling for gestational age and severity of illness (Wheatley *et al.*, 2002).

Retinopathy of prematurity can be diagnosed beginning at 32–34 weeks postconceptional age regardless of the gestational age at the time of delivery. The international classification of ROP describes the location of the lesion in concentric rings relative to the optic nerve (zones I, II, III), the degree of abnormality (stage), the extent of the developing blood vessels (clock hours), and the presence of engorged and tortuous vessels (plus disease).

Retinal blood vessels develop from the optic nerve to the periphery. Zone I is the area immediately surrounding the optic nerve and macula. Retinopathy of prematurity in zone I is the most concerning as progression leads to scar formation, visual impairment, and retinal detachment. Lesions in zone III do not usually lead to severe visual impairment. ROP is classified into five stages. In stage 1, there is a line of demarcation between the vascular and a vascular retina. In stage 2, the line of demarcation develops into a rolled ridge of scar tissue. Stage 3 is characterized by the development of extra-retinal blood vessels and fibrous tissue. In stage 4, the retina is partially detached due to scar tissue pulling the retina away from the orbit.

Total retinal detachment is defined as stage 5. The number of clock hours affected determines the extent of ROP. The more clock hours involved, the more likely that the lesion will progress to retinal detachment and will not spontaneously resolve. Threshold disease is defined as stage 3 disease in zone I or II with five contiguous or eight non-contiguous clock hours. Greater than 50% of eyes with threshold ROP will progress to retinal detachment. Stage 3 blood vessels that are tortuous and engorged (plus disease) often progress to scarring and retinal detachment (Wheatley *et al.*, 2002).

1.5.1.2 Non-Retinopathy of prematurity complications

These children have also been reported to have an increased incidence of long-term impairment in color vision (Dobson *et al.*, 1985, Abramov *et al.*, 1996) and contrast sensitivity (Dowdeswell *et al.*, 1995). It is also not uncommon for adolescents with a history of prematurity to have mild deficits in letter acuity which cannot be corrected by careful refraction. This problem is present even in the absence of clinical prematurity in the macula and early high refractive errors (Reisner *et al.*, 1997).

Visual impairment, occulomotor abnormalities, and refractive errors are prevalent among children with a history of preterm birth. These conditions may result from exposure of the immature visual system to early visual stimulation, from nutritional deficits that occur following the abrupt loss of placental maternal-to-fetal transfer of essential nutrients, and as secondary effects of systemic disease or complications

associated with preterm birth (Eileen and Anna 2001).

1.6 Ocular development

The ocular development of the infant eye is puzzling, yet very interesting. The average eye in a new born is about 17mm in length (Larsen, 1971; Fledlius 1992), with a corneal curvature of about 49D (Inagaki, 1986). During the first 5 years of life, on average, the eye grows another 4mm in length. This increase in length would result in a refractive error of -18D, provided that it is uncompensated by changes in the ocular component.

Ocular biometry parameters can be measured with quantitative A-scan ultrasound of the techniques available, applanation A-scan biometry is the one commonly employed. An ultrasonic transducer crystal placed in front the eye emits the receive sound waves along the patient's optical axis. Rapid emission of sound waves by the crystal in the probe, alternating with the emission suppression and subsequent retinal-rebound wave reception, yield a time-amplitude recording. This is converted into an electrical distance measurement and displaced on an oscilloscope screen along with other pertinent patient's information (Atlas of primary eye care procedures, 1997). A primary use of A-scan ultrasound (biometry) is to determine the appropriate dioptric power of the intraocular lens (IOL) implanted the time of cataract extraction surgery.

1.6.1 Axial Length

Compared to the rapid changes occurring during the first 2 years of life, ocular growth is much slower in the later years of childhood. Normally, during this period of slow growth, increase in the axial length should present little challenge to the compensating mechanism of the eye. However, it is surprising to note that during this period, the prevalence of myopia increases from 2% at the age 4 to 10.9% by 12 years of age (Junghans and Crewther 2005).

Fledlius, (1992) has reported that during the pubertal period, extending from 8 until 18 years of age, the so-called statistic eye has a basic axial length growth of 0.4-0.5mm. This assumed pubertal growth appears to be divided almost harmoniously between the anterior (20% increase from baseline) and posterior eye segment (80% increase from baseline). Thus the ratio of increase in axial length of the anterior eye segment to that of the posterior eye segment is 1:4. In progressive myopia, this ratio subsequently falls due to an increase in vitreous length, while the anterior segment grossly maintains its size.

1.6.2 Lens thickness

Concerning lens development, the infant lens is about 3.4-4.0 mm thick at birth. Lens wet weight can be directly determined by direct examination. The detectable changes in lens wet weight indicate that the lens grows most rapidly during the first year of life. It

is observed that doubling in wet weight occurs during the first 8-10 years. Thereafter, lens growth from age 10 until adulthood is relatively much slower. Once adulthood is reached, the growth rate of the lens picks up again in speed, and further doubling of the lens weight occurs (Zadnik *et al.*, 1995).

Interestingly, despite the rapid increase in lens substance during infancy, the thickness of the lens is fairly stable throughout this time. On an average, it remains around 3.6mm in size, until the age of 6 years. As from 6 to 10 years, the lens actually thins out, and the thickness gradually reduces to about 2.0mm (Larsen, 1971, Zadnik *et al.*, 1995). After 10 years of age, on average, lens thickness remains constant throughout childhood. It may begin to increase once more in the early teens.

1.6.3 Anterior chamber depth

In a study on the sagittal growth of the eye, Ultrasonic measurement of the depth of the anterior chamber from birth to puberty, Larsen (1971) observed that the anterior chamber depth of the eye was normally distributed. In the first 13 years of life, anterior chamber depth appears to increase. It was also observed that this increment was accompanied by thinning of the lens, so that the distance from the cornea to the posterior pole crystalline lens remained relatively constant. Between 20 to 70 years of age, the anterior chamber depth decreases from approximately 4.0mm to around 3.5mm because of age-related increase in the lens thickness.

Fiona *et al.,* (2001) have confirmed that during the first year of life, growth is not a simple scaling process in which the relative dimensions of all ocular components change equally. Growth in axial length is better described by a second-order function of age, while increases in both the anterior chamber depth and linear lens thickness are constant.

1.6.4 Vitreous chamber depth

In a study by Helen *et al.* (2008) which studied the ocular biometry in preterm infants and its implications in estimating retinal illuminance**,** it was shown that eye size in the subjects increased rapidly between 30 and 55 weeks of gestation and this increase in eye size was comparable to that seen in term infants. However, the ratio of dilated pupil area to vitreous chamber depth was highly variable. In this study retinal illuminance of the infant was estimated using both stimulus luminance and troland values and it was compared with that of the adult eye. It was seen that the retinal straylight appeared to be dependent on ocular biometry. Furthermore, it was demonstrated that retinal straylight not only increased with age, but increased with axial length as well. Further studies are needed to identify the cause of this dependency (Jos *et al.,* 2009).

A study by Tien *et al.,* (2001) aimed to determine and describe the variations in ocular biometry in adult Chinese individuals in Singapore They reported that ocular dimensions varied with age and gender in these adult Chinese subjects. This variation in

noncycloplegic refraction in people age 40 years or more may be explained by differences in axial lengths (principally vitreous chamber depths) between younger and older individuals. Moreover, in individuals aged 60 years and more, the variation in non-cyclopegic refraction can be additionally attributed to differences in lens nuclear opacification**.**

1.6.5 Optic nerve head

The optic disc or optic nerve head is the intraocular portion of the optic nerve (2^{nd} cranial nerve). It may be round or slightly oval in shape. This structure is situated about 3 mm medial to the fovea, roughly 1mm above the posterior pole of the eye (Figure 1.1). Its diameter is 1.86 ± 0.21mm vertically and about 1.75 ± 0.19mm horizontally.

The optic nerve is formed by the second order neurons of the retinal ganglion cells. It extends up to the optic chiasma, where the two optic nerves meet. Then it proceeds posteriorly towards the lateral geniculate body.

On examination of the fundus, the optic disc is pale pink in colour and much paler than the surrounding retina. The central pallor of the disc is due to the absence of axons, leading to exposure of the underlying lamina cribrosa. It is slightly depressed at its center, where the central retinal vessels enter and leave the eye. The edge of the optic disc is slightly raised (Snell and Lemp, 1998). The neuroretinal rim is the tissue