NEURODEVELOPMENTAL OUTCOMES OF VERY LOW BIRTH WEIGHT INFANTS IN A TERTIARY HEALTH CARE CENTRE

THESIS SUBMITTED TO

THE TAMIL NADU DR. MGR MEDICAL UNIVERSITY, CHENNAI

FOR THE AWARD OF DEGREE OF DOCTOR OF PHILOSOPHY

by

Dr. SAMUEL P. OOMMEN

DEPARTMENT OF PEDIATRICS

CHRISTIAN MEDICAL COLLEGE, VELLORE

JANUARY 2015

CONTENTS

ABBREVIATIONS USED IN THE THESIS

AAP	American Academy of Pediatrics
ABC	Adaptive Behavior Composite of VABS
AC	Assisted Conception
AEDF	Absent End Diastolic Uterine artery Flow
AGA	Appropriate for gestational age
AIIMS	All India Institute of Medical Sciences
AKI	Acute Kidney Injury
ART	Assisted Reproductive technology
ATNA	Amiel-Tison Neurologic Assessment
BAER	Brainstem auditory evoked response
BAPM	British Association of Perinatal Medicine
BPD	Bronchopulmonary Dysplasia
BSID-3	Bayley Scales of Infant Development - 3rd edition
BW	Birth weight
CBCL	Childhood Behavior Check List (Achenbach)
CI	Confidence Interval
CLD	Chronic Lung Disease
CMV	Cytomegalovirus
CP	Cerebral Palsy
CPAP	Continuous Positive Airway Pressure
CS	Cesarean Section
CSF	Cerebro-spinal fluid
DASII	Development Assessment Scales for Indian Infants
DDST - 2	Denver Development Screening Test - Second edition
DM	Diabetes Mellitus
ELBW	Extremely Low Birth weight
ELGAN	Extremely Low Gestational Age Newborn
EOS	Early Onset Sepsis
FMQ	Fine Motor Quotient of PDMS
g	Grams
GA	Gestational age
GDM	Gestational diabetes mellitus
GMDS	Griffith's Mental Developmental Scales
GMFCS	Gross Motor Functional Classification System
GMQ	Gross Motor Quotient of PDMS
GQ	General Quotient of GMDS
HC	Head circumference
HR	Hazard Ratio
HRIC	High Risk Infant Clinic

IDM	Infants of diabetic mothers
IUGR	Intrauterine growth retardation
IVH	Intraventricular hemorrhage
LGA	Large for gestational age
LOS	Late Onset Sepsis
LR	Logistic Regression
M-CHAT	Modified Checklist for Autism in Toddlers,
MDG	Millennium Development Goal
MDI	Mental Developmental Index of BSID-3
NDI	Neurodevelopmental impairment
NEC	Necrotizing Enterocolitis
NICHHD	National Institute of Child Health and Human Development
NICU	Neonatal Intensive Care Unit
NNF	National Neonatology Federation
NNPD	National Neonatal-Perinatal Database
NRN	Neonatal Research Network (of the NICHHD)
NSG	Neurosonogram (Cranial ultrasound)
OAE	Oto-acoustic emission
OR	Odds Ratio
PDA	Patent Ductus Arteriosus
PDI	Psychomotor Developmental Index of BSID-3
PDMS	Peabody Developmental Motor Scales
PHH	Post hemorrhagic hydrocephalus
PIH	Pregnancy Induced Hypertension
PMA	Postmenstrual age
pre-OLs	Precursors to the oligodendrocytes
PT-AGA	Preterm Appropriate for gestational age
PT-SGA	Preterm small for gestational age
PVL	Periventricular leukomalacia
QOL	Quality of Life
RDS	Respiratory Distress Syndrome
REDF	Reversed End Diastolic Uterine artery Flow
ROP	Retinopathy of Prematurity
RR	Relative risk
SCPE	Surveillance of Cerebral palsy in Europe
SD	Standard deviation
SGA	Small for gestational age
SLE	Systemic Lupus Erythematosus
SQ-EH	Sub-quotient of Eye-hand subscale of GMDS
SQ-H&L	Sub-quotient of Hearing and language subscale of GMDS
SQ-Loco	Sub-quotient of Locomotor subscale of GMDS

SQ-Pf	Sub-quotient of Performance subscale of GMDS
SQ-PR	Sub-quotient of Practical-reasoning subscale of GMDS
SQ-PS	Sub-quotient of Personal-social subscale of GMDS
TDSC	Trivandrum Developmental Screening Chart
TMQ	Total Motor Quotient (of PDMS)
UN	United Nations
UNICEF	United Nations Children's Fund
US	Ultrasound scan or Ultrasonography
UTI	Urinary tract infection
VABS	Vineland Adaptive Behavior Scales
VHW	Village heath Worker
VLBW	Very low birth weight
VSMS	Vineland Social Maturity Scale
WeeFIM	Functional Independence measure
WHO	World Health Organization

LIST OF THE TABLES

LIST OF FIGURES

PREFACE

This is a brief report of a journey of several years. The quest of this journey was to answer the fundamental question "what happens to the infants born with a birth weight of less than 1500 g in this country?" There are over 500 tertiary care NICUs providing state of the art care and the survival of Very low birth and extremely low birth infants are comparable to the world's best centers. However unfortunately there is very little data about the long term outcome of these infants. From the published literature over the last 20 years, the total number of VLBW infants followed up for varying periods of time ranging from 1 year to 18 years is less than a thousand in this country!

Developmental follow up requires a team comprising Pediatricians or Neonatologists, Psychologists, therapists (occupational therapists, physical therapists and speech therapists) and requires input from other medical specialists. Developmental assessments using standardized assessment tools are time consuming and demanding on the child who is being assessed, the parents and the assessor. On an average a standardized developmental assessment (if the child is cooperative) requires about one hour of dedicated time. In children with developmental problems or if the child is inattentive for any reason, the demands of time and effort increase considerably. Thus developmental follow up is a time consuming, labour intensive and an expensive intervention. This may be the reason why there is very little follow-up of preterm children. However developmental follow up is of paramount importance.

The very low birth weight infants are probably the largest group with life-long morbidity. Once they survive the life-threatening complications in NICU, many of them develop

neurological, developmental and sensory impairments. They continue to have learning and behavior problems in school.

This institution where this study on the “Neurodevelopmental Outcomes of Very Low Birth Weight Infants born in a Tertiary Health Center” was done has a state of the art Neonatal ICU and a well-staffed Developmental Pediatrics Unit with psychologists, therapists and Developmental Pediatricians. Therefore this was a unique opportunity to do this study. Infants with developmental delay or other complications like cerebral palsy when identified could also be provided appropriate therapy. It is our hope that the information obtained from this study in addition to contributing to the scientific knowledge will improve the health and wellbeing of this very vulnerable and special group of children.

INTRODUCTION

Baby Nathan, 980 grams

Nathan, 3 years old

"Behind every fact is a face;
behind every statistic there is a story"

ABSTRACT

BACKGROUND: The very low birth infants (VLBW) are exposed to multiple risk factors in the antenatal, perinatal and neonatal periods which result in significant short term morbidities and adverse neurodevelopmental outcomes. There is limited data about the survival and the long-term neurodevelopmental outcomes of these infants from India.

OBJECTIVES: The primary objectives of this study were to determine the survival and neurodevelopmental outcomes at 18-24 months corrected gestational age, of a cohort of very low birth weight infants and to identify the perinatal and neonatal factors associated with these outcomes. In addition the study also looked at the growth and development of the small for gestational age infants in comparison to appropriate for gestational age infants and the relationship between the postnatal growth and the neurodevelopmental outcomes of the infants was also explored.

DESIGN, SETTING AND PARTICIPANTS: This was a longitudinal follow-up of the VLBW infants from the time of admission into the NICU of a tertiary level neonatal ICU, till their developmental assessment at 18-24 months corrected gestational age. The first phase of the study was from admission into the NICU till death or discharge from nursery. The second phase was from the time of discharge till the final neurodevelopmental assessment. The Amiel-Tison Neurologic examination and the Griffiths Mental Developmental Scales (GMDS) were used to determine the final neurodevelopmental outcomes.

METHODS: Data regarding the antenatal, perinatal and neonatal periods were collected prospectively. The end points of the study were death, cerebral palsy or the

developmental outcome determined by the General Quotient (GQ) on the GMDS. The growth status at birth was estimated using the third percentile of the Fenton's curves which was used to categorize the study cohort into small or appropriate for gestational age. The Z-scores of weight, length and head circumference were determined using the WHO-ANTRHO software at the time of assessment.

Logistic regression models were used to identify the following: antenatal, perinatal and neonatal risk factors resulting in death in the NICU; risk factors resulting in poor neuro-developmental outcome; risk factors which resulted in poor language outcomes and the risk factors which were associated with being underweight at two years.

A sensitivity analysis was done to decide if the infants who did not come for the study affected the final results of the study

RESULTS: The survival in the first phase of the study was 92.26% (89.4%-94.54%, 95% CI). Septicemia was the major cause of death. Severe intraventricular hemorrhage (IVH-Grades 3 and 4), respiratory distress syndrome (RDS) and ventilation were significantly more in the boys. The factors which were significantly associated with death on the multivariate logistic regression model were birth weight of less than 1200g, perinatal asphyxia, respiratory distress syndrome (RDS), severe necrotizing enterocolitis, patent ductus arteriosus and septicemia.

In the Phase II of the study: 65.6% of the infants completed the neurodevelopmental assessment. The incidence of poor neurodevelopmental outcome [General Quotient (GQ) <2SD] was 11.37% (8.6%-14.9% 95% CI) and incidence of Cerebral palsy in this study was 1.1 (0.39-2.63). The mean GQ was 93.6 (SD $\pm$ 13.01). There were forty eight

children with poor neurodevelopmental outcomes, which included five children with cerebral palsy. The neurodevelopmental outcomes of the girls were significantly better than that of the boys.

None of the antenatal, perinatal or neonatal risk factors were related to the poor neurodevelopmental outcome (GQ <2SD) on the multivariate logistic regression model, but post--natal growth (particularly Z-score of weight below 2 SD) at the time of assessment was significantly associated with poor neurodevelopmental outcome. Multivariate logistic regression model looking at the reasons for poor language development showed that perinatal asphyxia, post-natal weight restriction (Z-score of weight below 2 SD) and low maternal education level were associated with poor language abilities.

Multivariate logistic regression models which looked at the cause of post-natal growth restriction showed that low maternal education, small for gestational status and neonatal hypoglycemia were significantly associated with remaining underweight (Z-score of weight below 2 SD) at the time of assessment.

There was no difference in the survival and neurodevelopmental outcomes between small for gestational age (SGA) infant and appropriate for gestational age (AGA) babies. However the post-natal growth of SGA babies was significantly worse than that of AGA babies.

Sensitivity analysis using “Best case” and “Worse case scenarios” showed that the exclusion of those who did not come for the final assessment (those who did not give

consent, those who died and those who were lost to follow up) did not affect the final results.

CONCLUSIONS: The survival and neurodevelopmental outcomes of the VLBW infants in this study are the best reported from this country and are comparable to Western data. Poor post-natal growth (resulting in being underweight) was associated with poor neurodevelopmental outcome. There was no difference in the survival and neurodevelopmental outcomes of small for gestational age babies compared to those who were born appropriate for gestational age. Social factors particularly socio-economic status and maternal educational level play an important role in the neurodevelopmental outcomes of the VLBW babies.

1. INTRODUCTION

The birth of a new baby is a time of eager anticipation and excitement. However in about one-third of the pregnancies in this country, the babies are born too small or born too early and the excitement is quickly replaced with trepidation and anxiety. Most parents are not prepared for the weeks and months ahead. Initially the several weeks in NICU mean days of uncertainty when the very survival of their newborn is at stake. They are overwhelmed by the various terrifying procedures and the often incomprehensible medical jargon. It is also the beginning of one of the most expensive treatments. Finally after the weeks of NICU care and the infant surviving the seemingly insurmountable odds he is ready to go home.

Even for parents whose babies are relatively well at discharge, this is the beginning of another exhausting roller-coaster period with months of sleepless nights and anxious days. After the period of extended stay in the NICU where they could depend on the staff for emotional, social and medical support, the parents suddenly feel isolated and alone when they come home. Each day is a tension because the babies are still very vulnerable. There are challenges in feeding, sleeping and combatting infections. For those parents whose infants carry the sequelae of the neonatal complications like intraventricular hemorrhage, chronic lung disease, retinopathy of prematurity, this is a seemingly endless journey of pain and uncertainty. Their burden is tremendous. Surviving these ordeals and maintaining some homeostasis in their lives is a daily struggle.

This thesis is a study of this journey of a cohort of babies who were born too small and the overwhelming odds they had to overcome.

1.1 DEFINITIONS

Low Birth Weight (LBW), which comprises a special group of children in terms of mortality, morbidity and long term developmental outcomes has been defined by the World Health Organization as weight at birth, of less than 2500 g.[1,2] Very Low Birth Weight (VLBW) infants have a birth weight of less than 1500 g and Extremely Low Birth Weight (ELBW) infants have a birth weight of less than 1000 g. Premature birth has been defined as delivery before 37 weeks of gestation. A baby's low weight at birth is either the result of preterm birth or due to restricted intrauterine growth.[3] Small for gestational age (SGA) traditionally has been defined as a weight below the 10th percentile of birth weight-for-gestational age for a specific reference population.[4,5] Though often not synonymous, SGA is quite commonly used as proxy for intra uterine growth restriction.[6]

1.2 LOW BIRTH WEIGHT INFANTS

The World Health Organization (WHO) estimates that about 20 million LBW infants are born every year and 96.5% of them are born in developing countries. These babies comprise about 15.5% of all the births.[7] But of the estimated, 4 million babies who die in the neonatal period every year, low birth weight contributes to 60–80% of all the neonatal deaths and so LBW is an important contributor of neonatal mortality.[2,8,9] In countries where the prevalence of LBW is very high, it is known that most LBW infants are growth restricted rather than preterm.[10,11] In addition to being a predictor for the baby's development low birth weight has long been used as a surrogate indicator of maternal malnutrition and poor pregnancy health care.[11]

1.2.1 BURDEN IN INDIA

India, because of its population, has the dubious reputation of being the largest contributor to the global burden of low birth weight infants and neonatal mortality. The table below gives the current dismal reality of the newborns in the country -

Live births:	There are 27 million live births every year in India[5]
Low birth weight Babies:	30% of the babies born in India are low birth weight, which amount to about 7.5 million low birth weight babies every year.[5,12] About 60% of the LBW babies in India have intrauterine growth restriction while the remaining 40% are born preterm.[13]
Preterm babies:	Every year 3.5 million preterm babies are born in India and this contributes to 23.6% of the global burden of preterm births.[8]
Small for gestational age:	46.9% of all babies born in the country are small for gestational age. (There are babies who weigh more than 2500 g, but are still considered growth retarded). Most of the SGA babies are born at term and they account for almost 94% of the total number of SGA babies born in the country.[5]
Neonatal deaths:	About 7.6 lakh neonates die every year in India, the highest for any country in the world.[12] Community based studies indicate that LBW infants are 11 to 13 more at risk of dying than normal birth weight infants and more than 80% of all neonatal deaths occur among LBW and preterm infants.[14]

The National Neonatal Perinatal Database (NNPD),[13] recorded data of over 1.5 lakh infants born in 18 perinatal centers all over the country in 2002-03. Of these 31.3% of all live births were low birth weight, 3.4% of infants were born with birth weight less than 1500 g (VLBW), 0.7% of the infants were extremely low birth weight and 14.5% of infants were preterm. This is in contrast to the data of the same period in the United States were 7.9% of the live born infants were born low birth weight, 1.45% were born very low birth weight and 12.3% of infants were preterm.[15] However the statistics of the NNPD presented above are likely to be inaccurate, since in India, many infants are born at home and therefore not weighed at birth. Thus the estimates of low birth weight obtained from most developing countries which are usually compiled from health centers are likely to be biased.[16]

1.2.2 MILLENNIUM DEVELOPMENT GOAL-4

At the United Nations Millennium Summit in September 2000, the world leaders committed themselves and their nations to achieve the time-bound and quantified targets of the Millennium Development Goals (MDG).[17] The fourth MDG (MDG-4) is to reduce the under-5 mortality rate (U5MR) and neonatal mortality by two thirds by 2015. India is a signatory to the UN declaration of the MDG and is obliged to decrease the childhood mortality by two-third by 2015. Although India has made has made significant progress and the neonatal mortality rate has significantly decreased from 52 (per 1000 live births) in 1990 to 29 (per 1000 live births) in 2012, it is still unlikely to achieve its MDG-4 target.[18,19]

Two-thirds of the neonatal deaths occur in the first two weeks and deaths in the first week account for 45% of the total under-five deaths in the country.[12] The three major causes

of neonatal deaths in India (which account for about 78% of all neonatal deaths) are prematurity and low birth weight, neonatal infections and birth asphyxia and birth trauma.[20,21]

1.2.3 ETIOLOGY AND OUTCOMES OF LOW BIRTH WEIGHT BABIES

From an etiologic perspective the two different types of LBW (IUGR and Preterm birth) are quite heterogeneous in their etiologies and in their long term outcomes.[3] The most important determinants of IUGR and preterm birth in developing countries are listed below [22,23] -

IUGR	PRETERM BIRTH
• Low energy intake/gestational weight gain	• Genitourinary infection
• Low pre-pregnancy body mass index	• Multiple births
• Short stature	• Pregnancy induced hypertension
• Malaria (in endemic countries)	• Low pre-pregnancy body mass index
• Cigarette smoking	• Incompetent cervix
• Primiparity	• Prior preterm birth
• Pregnancy induced hypertension	• Abruptio placentae
• Congenital anomalies	• Strenuous work
• Other genetic factors	• Cigarette smoking

IUGR and preterm birth also have important differences with respect to prognosis. Preterm infants are at increased risk of infant death, neonatal morbidities and long term complications in their growth and development. The immediate neonatal complications include respiratory distress syndrome (RDS), patent ductus arteriosus (PDA), intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) and retinopathy of prematurity (ROP) while long term complications include psychomotor delay and

cerebral palsy.[24] Preterm birth also generates high health care costs, particularly for neonatal intensive care, which is required for several weeks.[25,26]

Severely growth restricted infants are at an increased risk of neonatal death and of significant short term morbidity from hypoglycemia, hypothermia, hypocalcaemia and polycythemia.[27,28] Over the longer term they tend to have permanent deficits in growth and neurocognitive outcomes.[29] Epidemiologic studies by Barker and colleagues have suggested that such infants may be at increased risk for type 2 diabetes, hypertension and coronary artery disease when they reach middle age many decades later.[30,31] Furthermore follow-up of a large longitudinal cohort from India has shown that infants who are small and thin at birth, but started becoming obese from childhood are likely to have impaired glucose tolerance or diabetes during adulthood.[32]

1.3 THE VERY LOW BIRTH WEIGHT INFANTS

The field of Neonatology has witnessed unprecedented advances in the last three decades. Currently in developed countries even extremely premature babies of 22-25 weeks gestational ages and birth weights of 500-750 grams routinely survive because of improved perinatal management, prenatal administration of corticosteroids, surfactant replacement therapy, sophisticated fluid and parenteral nutrition delivery systems, advances in neuroimaging and innovations in ventilation like the high frequency ventilators. Even in India it is now routinely possible to save the lives of the extremely small and premature VLBW and ELBW infants. The limits of viability are being challenged almost every day. Nevertheless in preterm and low birth weight infants, mortality rates and neonatal morbidities increase substantially with the decreasing

gestational age and decreasing birth weight.[33]

1.3.1 NEONATAL COMPLICATIONS OF VERY LOW BIRTH WEIGHT

Despite all the advancements of neonatal care, the early days of the VLBW infants are fraught with potentially life threatening complications. Because of the immaturity of the organs, the preterm and VLBW infants are vulnerable to many neonatal complications and have a higher rate of mortality compared to normal term infants.

In a report from the National Institute of Child Health and Human Development (NICHHD) Neonatal Research Network the following neonatal complications were seen in 8515 VLBW and ELBW infants weighing between 400 g to 1500 g [34] -

- Respiratory distress 93%
- Retinopathy of Prematurity 59%
- Patent ductus arteriosus 46%
- Bronchopulmonary dysplasia 42%
- Late onset sepsis 36%
- Necrotizing enterocolitis 11%
- Grade III and Grade IV intraventricular hemorrhage 7% and 9%
- Periventricular leukomalacia 3%

Survival rates: The rates of survival to discharge in the above ELBW cohort ranged from 6% for babies born at 22 weeks to 92% to babies born at 28 weeks.

According to the data from the National Neonatal-Perinatal database 2002-3, the survival rate for ELBW infants was 45%, for infants between 1000 to 1500 g the survival rate was 73.4% and for infants above 3000 g the survival rate was 99.2%.[13]

1.3.2 LONG TERM COMPLICATIONS OF VLBW INFANTS

Follow-up of VLBW infants have shown they are at increased risk for impaired neurodevelopmental outcome compared to term babies with normal birth weight. The neurologic, developmental, sensory and functional morbidities increase with decreasing birth weight.[35] It is well known now that the VLBW infants also have a higher mortality and are more likely to have higher rates of cerebral palsy[36–39], have greater risk for ophthalmic morbidities like impaired visual acuity, strabismus, visual field defects,[40–43] and hearing problems.[44] VLBW infants are at greater risk for poor academic performance than those born with normal birth weight because of their impaired cognition, neurosensory defects, and behavioral and psychological problems[45–49] They are also likely to have more respiratory illnesses compared to term babies.[50] They have specific psychological and behavioral problems including attention deficit hyperactivity syndrome, general anxiety, and depression.[51,52] In addition to the effects of the very low birth weight, neonatal complications like bronchopulmonary dysplasia,[53] perinatal infections,[54,55] necrotizing enterocolitis[56], retinopathy of prematurity, intraventricular hemorrhage, hypoglycemia and the presence of congenital anomalies are all associated with an increased risk of poor neurodevelopmental outcome. The development of hypertension, insulin resistance, and impaired glucose tolerance in adulthood has also been associated with very low birth weight.[57] The morbidities which often extend to later life, result in an enormous physical, psychological and economic costs for the VLBW survivors.[25,26]

The incidence of cerebral palsy is generally accepted as 2-4 per 1000 in the general population of developed countries.[58] In a meta-analysis of over 100 studies which looked

at the outcomes of the VLBW infants (all studies were done in developed countries) the incidence of cerebral palsy of 7.7% and the incidence of all disabilities was 25%.[59] This study also reported the relative risk for cerebral palsy among surviving the VLBW infants was about 38 times than it is in the general population of these countries. Unfortunately there is no data available in India. The table below summarizes the short-term and long-term complications the VLBW babies[60]

Affected Organ or System	Short-Term Problems	Long-Term Problems
Pulmonary	RDS, BPD, pneumothorax, air leak, apnea of prematurity	Reactive airway disease, asthma
Gastrointestinal or nutritional	Hyperbilirubinemia, feeding intolerance, NEC	Failure to thrive, short-bowel syndrome, cholestasis
Central nervous system	IVH, PVL, hydrocephalus	Cerebral palsy, hydrocephalus, cerebral atrophy, developmental delay, hearing loss
Ophthalmologic	Retinopathy of prematurity	Blindness, retinal detachment, myopia, squint
Cardiovascular	Shock, PDA, pulmonary hypertension	Pulmonary hypertension, hypertension as adults
Renal	Water and electrolyte imbalance, acid–base disturbances	Hypertension in adulthood
Endocrine	Hypoglycemia, transiently low thyroxine levels, cortisol deficiency	Impaired glucose regulation, increased insulin resistance

1.3.3 SMALL FOR GESTATIONAL AGE BABIES AND THEIR COMPLICATIONS

Western studies have shown that being small for gestational age (SGA) at birth confers an additional hazard to survival, growth and neurodevelopmental outcome in preterm infants.[61] Some studies have demonstrated that SGA is a risk factor for mortality in term infants as well. In a systematic review it was shown that a birth weight of less than 1500

grams in term infants is associated with the greatest risk of mortality (odds ratio of 48.6, 95% CI 28.6-82.5).[62] This is very significant because almost half of the babies born in India are small for gestational age and 94% of them are born at term.[5] The outcome of the SGA infant is worse than those born preterms who are AGA.[63–65]

1.4 IMPORTANCE OF NEURODEVELOPMENTAL FOLLOW-UP.

It has been almost universally accepted that neurodevelopmental outcome is the most important measure of neonatal ICU (NICU) success in preterm and VLBW babies.[66] Since the implications of being born premature or born with a low birth weight are lifelong, long term follow-up is required to understand the impact of the risk factors and the efficacy of therapeutic measures on the growth and neurodevelopmental outcome of high risk infants. These babies require periodic assessments of their growth and nutrition, development, neurologic status and their behavior by a dedicated multidisciplinary team.[67] The main objective during these assessments is to identify the deviant developmental trajectories and initiate early intervention. These infants can also have complex medical problems and may require ongoing care from pediatric subspecialists.

There are standardized guidelines laid down by the American Association of Pediatricians and National Neonatal Federation for provision of follow-up services for high risk infants (which include VLBW infants).[68] As the number of survivors increases many clinical and research questions have surfaced that can only be answered by long term follow-up. Since many VLBW infants can have cognitive and psychiatric morbidities even when they are adults, they may require follow-up for many years.[69]

1.4.1 IMPORTANCE OF THIS STUDY

There are many multi-centric studies from Western countries describing the neurodevelopmental outcome of the VLBW infants. There is only study cohort of LBW infants from Pune which has been followed up from birth to adolescence.[70–74] There are a few hospital based studies which have looked at the Neurodevelopmental outcomes of the VLBW infants in India and the longest period of follow-up has been for three years.[75–78]

During the last decade there has been a phenomenal increase in the number of neonatal intensive care units (NICUs) in the country, especially in the corporatized health care sector and to a lesser extent in the public sector health care facilities**.** In addition specialist training programs in Neonatology have been started in many large perinatal centers in the country.[79] But despite the increase in NICUs and the overall improvement in the quality of neonatal care, data is very scarce about the long term outcome of these infants in India. So there are many unanswered questions like - What happens to VLBW babies after their discharge? How many of them survive? How many have disabilities? What are the antenatal, maternal or neonatal risk factors that lead to poor neurodevelopmental outcome?

It is almost certain that the outcomes of VLBW infants in this country are different from their counterparts in Western countries. In India unlike in developed countries, it is likely that, intrauterine growth restriction and therefore being small for gestational age, neonatal infections, birth asphyxia and neonatal hyperbilirubinemia contribute significantly to cerebral palsy and poor neurodevelopmental outcomes Therefore as Escobar *et al* notes, "It is critical to define rigorously the outcome of VLBW survivors… Regionally and nationally it is important to monitor the overall outcome of such infants so that plans for

future services can be made; this is particularly important as care of VLBW infant is one of the most expensive items in pediatrics".[59]

Despite having the largest population of VLBW infants and thus the possibly the largest cohort of the VLBW survivors, there is only little information about them from this country. The follow-up of these infants also requires significant infrastructure in terms of personnel and requires a multidisciplinary team of neonatologists, developmental pediatricians, child psychologists, therapists (physical therapists, occupational therapists, speech therapists) dieticians, pediatric subspecialists (ophthalmologists, ENT specialist, pediatric neurologist, radiologists) and social workers.[80]

This study was a prospective follow-up of the VLBW infants (birth weight $\leq$1500 g) admitted in a tertiary institute. The VLBW infants were then followed up from the time they were discharged from the Neonatal ICU, till at least 18 months corrected gestational age. The institution where this study was conducted had the infrastructure and the multidisciplinary team required for the undertaking.

The incidence of developmental delay from Indian studies range from 10-17%,[71,76,81] and that of cerebral palsy from 3-5%.[76,82–84] This is less than the incidence of 7.8% for CP and 25% for developmental delay obtained from the meta-analysis of the outcomes of VLBW from over 100 studies, done by Escobar and associates.[59] Since the VLBW in this country are different from that of Western cohorts we therefore decided to test the hypothesis, that the occurrence of CP and developmental delay would be different from that of Western countries. We also hypothesized that risk factors in the perinatal and neonatal period would affect the developmental outcome at 18 months corrected gestational age.

Thus the study was done to ascertain the factors in the perinatal and neonatal period which adversely affected the survival and the developmental outcomes in a cohort of VLBW infants.

Thus…

"*As Sean's parents, we faced the demands of (Sean's) second year often feeling drained and depleted. We were surprised how slowly we recovered from the tension and anxiety of the long hospitalization and stressful months that followed. We increasingly turned to Sean's early intervention program team for support and encouragement…"*

" … the neonatal roller coaster did not stop with Sean's discharge. The ride just got lonelier. At the critical point of discharge, we did not have the time, energy and often, the inclination to find out way through the maze of follow-up…"

(parents of Sean, premature LBW infant who had multiple neonatal complications and continued to have significant neurodevelopmental and sensory impairment). [85]

AIMS AND OBJECTIVES

Dhanushika (800 g) and Dhanushree (850 g)
2 years old

2. AIMS AND OBJECTIVES

Aim of the study

To determine the survival and neurodevelopmental outcomes of Very low birth weight infants (≤1500 grams at birth) admitted into a tertiary level Neonatal Intensive Care Unit (NICU), and were followed up till the infants reached a minimum corrected gestational age of 18 months.

The study ***had two phases*** -

Phase 1: The first phase was from the time of ***admission of the VLBW infants into the NICU till the time of death or discharge*** from the NICU.

Phase 2: The second phase was the follow-up phase which started after ***discharge of the survivors from the NICU till their final neurodevelopmental assessment.***

Main objectives

Phase 1:

To determine the ***relationship between the antenatal, perinatal and neonatal factors which lead to the mortality in the NICU.***

Phase 2:

Objective 1: To estimate the ***incidence of poor neurodevelopmental outcome*** in the survivors who were discharged from the NICU

Objective 2: To determine the ***relationship between perinatal and neonatal risk factors which lead to poor neurodevelopmental outcomes.***

Other objectives

- To determine the differences in the survival and neurodevelopmental outcomes of the Small for gestational age babies (SGA) as compared to the Appropriate for gestational age (AGA) babies.
- To monitor the growth profile of the babies in the cohort and to explore the relationship between post-natal growth estimated at the time of the assessment and the developmental outcome.

Poor neurodevelopmental outcome was defined as -

1. Presence of neurologic abnormalities particularly cerebral palsy
2. The developmental assessment used in this study is the Griffiths Mental Developmental Scale and poor neurodevelopmental outcome was estimated as the General Quotient (GQ) less than 2 Standard deviations (<2SD) below the mean for the age.
3. Presence of blindness or hearing impairment

LITERATURE REVIEW

Baby Nathan at term gestational age

3. LITERATURE REVIEW

The Literature review is organized in the following manner.

Section 1 (3.1): ***Outcomes of VLBW babies in the neonatal period*** from India and other countries is discussed in this sub-section

Section 2 (3.2): The importance of ***Neurodevelopmental follow-up and assessment***

Section 3 (3.3): ***The Neurodevelopmental outcome***s of VLBW babies from India and other countries

Section 4 (3.4): ***Neonatal complications and their effects on the neurodevelopmental outcome***

3.1: SECTION 1 - OUTCOMES VERY LOW BIRTH INFANTS IN THE NEONATAL PERIOD

This section **(3.1)** is arranged in the following manner -

3.1.1: Summary of the Indian ***studies on the outcomes of VLBW infants***

3.1.2: Summary of some important ***studies from other countries*** which have looked at the outcomes of VLBW.

3.1.3: ***Limitations of the Indian studies***

3.1.4: ***An alternative to care of the VLBW in tertiary neonatal centers – a community intervention program*** for the VLBW infants is presented in this sub-section.

Survival rates for the VLBW and the ELBW infants have consistently improved during the 1980s and the 1990s. Although most early follow-up studies reported the outcomes of low birth weight infants weighing less than 2500 g, currently the improvement in survival has shifted the focus to the VLBW infants weighing less than 1500 g, the ELBW infants weighing less than 1000 g and micro-preemies weighing less than 750 g.[66] As the methodology for assessing the gestational age has improved, there has been increasing number of reports evaluating the effects of prematurity rather than that of low birth weight. Preterm delivery is defined as birth before 37 weeks of gestation, very preterm is less than 32 weeks and extremely preterm is less than 28 weeks.[86]

3.1.1. STUDIES ON THE OUTCOMES OF VLBW FROM INDIA

Summarized below are the studies done in India on the outcomes of the VLBW and the ELBW infants. Of a total of 415 Indian articles on LBW babies from the PubMed database, I chose studies pertaining to the survival of the VLBW or the ELBW infants. These have been included and summarized. The studies are arranged in a reverse chronologic order, from the latest to earlier studies.

- **Ashtekar (2014)**[87]

Out of the 134 premature babies in the study, 80% were <1600 g in weight. Their survival was inversely related to the birth weight. None of the babies less than 800 g survived.

Survival improved with increasing gestational age - 17% of the babies 800-1000 g, 48% of the babies 1000 to 1200 g and 64% of the babies 1200 -1400 g survived.

Mortality: The main causes of death were RDS and sepsis

- **Mukhopadhyay (2013)**[88]

This is the largest Indian study involving ELBW infants. In this study 78 of the 149 (52%) babies survived and 57 (39%) survivors had major morbidities.

Major morbidities: In this study the major morbidities were bronchopulmonary dysplasia in 33% of the infants, severe IVH (Grades III & IV) in 68%, severe NEC in 7% of the infants. Among the infants with ROP, 3% required laser therapy.

Causes of Mortality: Death resulted predominantly from septicemia in 46% of the infants, perinatal asphyxia in 20% and pulmonary hemorrhage in19% of the infants.

- **Tagare (2013)**[89]

This is another major Indian study on ELBW infants and in this study, 47 of the 87 ELBW infants (56.1%) survived. Mortality rate was higher in the <750 g group.

Mortality: Pulmonary hemorrhage (25%), RDS (22.5%), IVH (22.5%) and sepsis (20%) were the major causes of death.

- **Thakur (2013)**[90]

This was retrospective study done over 10 years. The survival rate was 61.3% (173/283). Only 7.6% of babies with <700 g, 50% of babies with 700-900 g and 75% of babies with 900 to1000 g survived. **Causes of Mortality:** RDS, Sepsis, IVH and pulmonary hemorrhage and asphyxia were the major causes of death

- **Basu (2008)**[91]

In this study 63.8% of 260 VLBW babies survived. The survival was inversely related to the birth weight. None of babies <700 g survived, 22% of babies with 700-800 g, 45% of 800-1000 g, 55% of 1000 to 1200 and 74% of 1200 -1500 g survived.

Mortality: The mains cause of death was RDS in the less than 1000 g and asphyxia in the over 1000 g categories.

- **Roy (2006)**[92]

Out of the 106 (<1500 g) infants in this study, 70 were VLBW and 36 were ELBW. The main morbidities were neonatal jaundice (47.2% in ELBW and 24.2% in VLBW babies), RDS (38.8% in ELBW and 17.1% in VLBW). ROP (33.3% in ELBW vs. 15.7% in VLBW) and sepsis (25.5% in ELBW vs. 14.2% in VLBW)

Mortality: The survival was inversely related to the birth weight. None of babies who were less than 700 g survived. 58.4% of the babies who were 700-800 g, 70% of babies who were 800-1000 g, 83.4% of babies 1000 to 1200 g and 86% of babies 1200 -1500 g survived. The mortality rate was related to the gestational age (which was highest in infants less than 30 weeks), birth weight (highest in less than 800 g) and male sex.

- **Narayan (2003)**[93]

Sixty seven (49%) ELBW infants survived to discharge in this study. Mortality was greater in <750 g infants, gestational age <28 weeks infants and in male infants

Morbidities: Hyperbilirubinemia (65%), RDS (65%), sepsis (52%), IVH (29%), pneumonia (25%) and ROP (24%). **Mortality causes:** Sepsis (41%) extreme prematurity (24%) were the main causes of death

- **Sehgal** (2003)[94]

This cohort had 52 ELBW babies of which 30 (57%) survived.

Mortality: The contributors to the mortality of the infants were HMD in 63%, pulmonary hemorrhage which occurred in 18%, septicemia in 32% and NEC which occurred in 9% of the infants.

3.1.2 SUMMARY OF STUDIES ON NEONATAL OUTCOMES FROM OTHER COUNTRIES

A. Studies from United States (NICHHD cohorts and Vermont Oxford Network)

- **Hack (1991)**[95]

This study from the NICHHD network looked at the neonatal outcomes of more than 1700 VLBW infants delivered in 1987-88 at seven participating centers.

Survival rates: Survival was dependent on the birth weight and 34% of <751 grams birth weight infants, 66% of infants between 751 and 1000 grams, 87% of infants between 1001 and 1250 grams., and 93% of infants between 1251 and 1500 grams survived.

Morbidities: RDS (67%), symptomatic PDS (25%), NEC (6%), septicemia (17%), meningitis (2%), urinary tract infection (4%), and Grades III & IV intraventricular hemorrhage (18%) were the main morbidities. Morbidity increased with decreasing birth weight.

- **Lemons (2001)**[96]

The perinatal data was collected prospectively from January 1995 through December 1996 by the NICHHD. In this cohort 84% of the infants survived, compared to the survival of 80% in the 1991 cohort and the 74% survival of the 1988 cohorts.

Survival: For infants 401 g-500 g survival rate was 11%, 501 to 750 g birth-weight survival rate was 52%, 751 to 1000 g survival rate was 86%, for 1001 to 1250 g survival rate was 94% and for those 1251 to 1500 g survival rate was 97%.

Morbidities: There was no change in the incidence of CLD, IVH and NEC compared to the previous study. There was marked improvement in survival after RDS due to surfactant use

- **Fanaroff (2007)**[97]

This study showed an increase by one percent in the survival of the VLBW babies (from 84% to 85%) in the NICHHD cohort during the period 1997-2002 when compared with that of the previously mentioned cohort (1995-96). Among the infants who were between 501-750 g, 55% survived; 88% of the 751-1000 g infants survived; 94% of the 1001-1250 g infants survived and 96% of the 1251–1500 g infants survived. This study showed that mortality increased for every decrease of 100 g in the birth weight. Although there was some improvement in the survival the major morbidities remained the same.

- **Horbar (2012)**[98]

This study from the Vermont Oxford Network of 355,806 North American VLBW infants looked at the mortality trends between 2000 and 2009. There was a decreasing trend in the mortality for infants between 500 g and 1500 g. The mortality of 500-750 g babies decreased from 41.7% in 2000 to 36.6% in 2009, in the 751-1000 g infants from 13% to 11.7%, in the 1001-1250 g infants from 6.5%-5.7% and in the 1251-1500 g infants, it remained the same at 3.5%. The study also showed a mild decrease in some of the neonatal morbidities – late onset sepsis decreased from 21% in 2000 to 15% in 2009, ROP from 10.5% to 6.8%. and CLD from 27.1% to 26%. Other morbidities – NEC, IVH and PVL remained almost the same between 2000 and 2009.

- **Stoll (2010)**[34]

This NICHHD study reported outcomes on the basis of the gestational age rather than the birth weights and reported the outcomes of infants between 22 weeks and 28 weeks. This study reported the survival of infants born at 22 weeks. The rates of survival to discharge increased with increasing GA, from 6% at 22 weeks to 92% at 28 weeks (72% overall). The infants who were less than 24 weeks had three times higher mortality rate than those who were 28 weeks of age. The main morbidities were RDS (93%), PDA (46%), severe IVH (16%), NEC (11%) and late onset sepsis (36%). Morbidities increased with decreasing gestational age.

B. United Kingdom (EPICure 1 and EPICure 2 studies)[99]

Improved survival rates of increase from 40% to 53%, was also noted in a population-based British study of extremely premature infants (defined as gestational age between 22 and 26 weeks) born in two time periods – in 1995 and in 2006. Survival increased from 1995 to 2006 with each week of gestation (9.5%, 12%, and 16% for 23 weeks, 24 weeks, and 25 weeks gestation respectively). The median age of death also increased from two days in 1995 to seven days in 2006, which reflected, in part, a shift in the cause of death from early respiratory failure to later complications of prematurity including infection and necrotizing enterocolitis.

C. France (EPIPAGE study)[100]

In France in a cohort of over 4000 babies between 22 and 32 weeks, survival was directly correlated with gestational age; the survival was 97% at 32 weeks of gestation compared

to 31% at 24 weeks and 78% at 28 weeks. The mortality rates were high among the SGA babies, male infants and those born of multifetal gestations.

In summary, review of the world literature has shown that survival rates for the VLBW varied between perinatal centers and between different regions. The survival at 23 weeks gestation was less than 30%, while at 24 weeks gestation, the survival rates were between 17 and 62%; at 25 weeks gestation survival rates was between 35% and 72% and at 26 weeks it ranges from 14% to 76%.[101,102] Since 2000 the survival rates have stabilized at approximately 85% for the VLBW infants and 70% for ELBW infants in most Western cohorts.[103,104]

3.1.3 COMPARING THE SURVIVAL OF VLBW INFANTS IN INDIA TO THAT OF WESTERN COHORTS

From what has been said about the neonatal survival of Indian babies as compared to those from Western cohorts the following observations can be summarized:

- There is limited data on the NICU survival of VLBW and ELBW babies in India. All studies are from few tertiary care centers and therefore not representative of the situation around the country. It is also obvious, that the survival patterns are different in the various centers.

- The Indian data is from individual centers but the Western data is obtained from many collaborating perinatal centers. For example the Vermont Oxford Network maintains a database of the VLBW based on the collaboration of over 300 tertiary level centers.[105]

- There is only study from a premier perinatal center which has looked at the trends in survival between the ELBW infants of different periods (2001-2 and 2009-10).[106] The study showed that survival had improved for ELBW who were 28-30 weeks gestation, but not for those who were born earlier. The authors opine that the improvement in survival between the two periods was probably due to surfactant therapy, non-invasive ventilation and high frequency ventilation.[106] However, the authors also conclude that although the survival rate is improving it is far below that off developed countries.

- The predominant cause of mortality in Indian studies was septicemia, while in most Western studies the main morbidities are RDS, IVH and PDA. This may be due to the differences between the Indian and Western cohorts. The Indian cohorts are more likely to have SGA children, who have a lesser incidence of morbidities like IVH, RDS and PDA.

- There is no information about the survival of less than 500 g infants in this country.

- In India, there are tertiary perinatal centers with state of the art technology and highly specialized doctors and there are secondary level special care newborn units (SCNU) in about 300 districts.[79] So the survival rates of these vulnerable infants are going to vary depending upon the expertise and the infrastructure of the treating centers. Western studies have shown that the survival of the VLBW and the ELBW infants is dependent on the expertise and resources of the centers looking after these babies.[107] A recent study from UK which looked at the survival of the ELBW infants born in level 3 nurseries and those born in level 2 nurseries showed that

survival was better for those born in level 3 nurseries, but there was no change in the morbidities of those who survived.[108] Substandard neonatal care is associated with increased mortality as shown in a study which looked at the causes of neonatal deaths in infants born at 27 to 28 weeks gestation in Great Britain, during a two year period (1998 to 2000).[109]

- Another reason in the difference in survival reported from the various Indian studies could be the inclusion criteria. Some studies have only looked at the survival of in-born babies, while others have also included out-born babies who are transferred after birth from peripheral centers. Survival rate of the ELBW babies and the VLBW babies in Indian NICUs depend not only on the quality of intensive care after reaching the NICU but also on the manner and quality of transportation of these sick babies to the NICU.[110]

3.1.4 ALTERNATE MODELS TO IMPROVE SURVIVAL OF LOW-BIRTH WEIGHT INFANTS

It is very unlikely that highly specialized neonatal care will be available for all the low birth weight babies born in this country. The above Indian studies and the available data on the LBW infants is just the tip of the iceberg. There are definitely many more LBW infants born in the many villages and towns in the country who cannot access neonatal care and there is no information about their outcomes. Therefore we have to look for alternative models of neonatal care.

Furthermore a review by Kramer showed that, in the long run, most interventions including food and micronutrient supplementation of pregnant mothers have had very

little effect in preventing low birth weight and premature babies.[111] This was confirmed by a study done at Kanyambadi village in South India which looked at the low birth weight and preterm birth rates in 1990 and 2005 and found that there was no decrease between the two periods. However the perinatal mortality and neonatal mortality had decreased substantially (by 26%) between the two time periods because of improvements in the antenatal and neonatal care.[112] The authors have concluded that improving infrastructure and training people to look after the consequences of low birth weight may be a more effective option than trying to prevent low birth weights.

Thus despite various interventions the birth rates of LBW babies does not seem to be coming down, so improving infrastructure to look after these babies may be a better option. But in a country with limited resources, is there an alternative, to specialized newborn centers, which can meet the enormous task of improving the survival of low birth weight infants?

THE GADCHIROLI MODEL FOR IMPROVING THE LBW SURVIVAL

In Gadchiroli a village in Maharashtra, Bang and associates demonstrated that most low birth infants can survive in home settings with simple and low cost interventions delivered by community health care workers. They also discovered that only a small percentage may require intensive care.[92,113–115] In the seven years of interventions in the field trial in rural Gadchiroli, more than five thousand newborns (including over two thousand low birth weight infants and more than five hundred premature infants) were managed at home. The resident Village Health Worker (VHW) in each village was trained to assess the neonates at birth, to identify the LBW and premature babies and manage them at home. The VHW and the mothers were trained in early initiation of

respiration and feeding, providing warmth, protection from infections and preventing other comorbidities

Although there was no change in the incidence of preterm births and only a small reduction in the incidence of LBW babies, with these simple measures at home the mortality rates decreased by more than 60% among the low birth weight and premature babies. This proved that a majority of the LBW infants could be effectively managed at home and only a small proportion required referral to a larger health center.

Three factors contributed to the survival of the infants.

- The simple but efficient care provided by the mothers and the VHWs resulted in a marked decrease in sepsis, asphyxia, hypothermia and feeding problems.
- Prompt treatment of suspected sepsis with antibiotics
- Supportive care provided by frequent home visits to encourage breast feeding and ensuring thermal care.

The authors were successfully able to prove their hypothesis that even though the incidence of LBW and preterm births could not be prevented, survival could still be improved by prevention and management of comorbidities, especially infections.[115,116]

So in conclusion, the outcomes of VLBW who are looked after in level 3 NICUs are improving in India, although the survival rates are far behind that of Western countries. Septicemia remains the main cause of mortality in developing countries. But in a country where 30-40% of births occur at home, it is important to look for alternate forms of neonatal care. Models which promote universal access to antenatal care, trained birth attendance and effective post-natal care are likely to result in sustained reductions in neonatal mortality.[112] The Gadchiroli model has shown that promoting optimal neonatal

care by training health workers and mothers and home-based management of neonatal infections can significantly reduce the LBW mortality and morbidity.[116] Other simple measures like maternal education during the antenatal period about the importance of breastfeeding, rooming-in of the baby after birth and kangaroo mother care could also go a long way in reducing neonatal mortality.[118] Meta-analysis and systemic reviews have supported the usefulness of community based intervention models in the improving the survival among low birth weights.[119,120]

Thus investing in state of the art neonatal ICUs may not help the babies in born in villages. It would be more prudent therefore, as envisioned in the National Health rural mission (NHRM), to have a stratified approach to newborn care. At the most specialized level there can be regional perinatal centers which provide state of the art care for the very sick neonates. Preceding that, there should be specialized care newborn units (SCNU) at district level, newborn stabilization units (NBSU) at first referral units, newborn care corners (NCC) at all active delivery points in a district and trained community health workers to provide home based care.[79] This would ensure, accessible and affordable health care at the community level, identify high risk mothers who are likely to have sick babies and early referral to the appropriate level of care. This stepwise care can be the way forward in improving survival of low birth and preterm infants in this country.

3.2: SECTION 2 - NEURODEVELOPMENTAL FOLLOW-UP AND ASSESSMENT: THE WHY, WHO, WHEN AND WHAT TO ASSESS

This section briefly reviews the neurodevelopmental follow-up of VLBW & ELBW infants after their discharge from the NICU. In this section I have addressed the following questions about neurodevelopmental assessments and developmental follow-up.

3.2.1: What is the prevalence of neurodevelopmental disabilities among VLBW infants?

3.2.2: ***Why*** do the VLBW children require formal neurodevelopmental assessments and regular follow-up?

3.2.3: ***Who*** are the children who require neurodevelopmental assessments?

3.2.4: ***When*** should the children undergo neurodevelopmental assessments?

3.2.5: ***Which*** domains require assessment?

3.2.6: ***What*** are the tools required for developmental ***assessment?***

3.2.7: ***What is the predictive value*** of developmental assessments?

3.2.8: ***Neurologic assessment*** of VLBW infants

3.2.9: The advantages and disadvantages of using ***birth-weight or gestational age*** as inclusion criteria for VLBW infants

3.2.1 WHAT IS THE PREVALENCE OF NEURODEVELOPMENTAL DISABILITIES AMONG VLBW INFANTS?

There has been a marked improvement in the perinatal care during the last two decades in India which has resulted in the survival of 89% of the preterm babies and 70% of the VLBW babies.[13] This has become possible because of collaboration between the Neonatal specialists and obstetricians, successful implementation of the Neonatal Advance Life Support (NALS), technologic advances in neonatal care, better understanding and management of neonatal problems and the emphasis of intact survival of newborn babies.[121] However the improved survival of these infants has resulted in an increased number of VLBW survivors with long-term neurodevelopmental sequelae.[122] Blindness following Retinopathy of prematurity (ROP), deafness, severe developmental delay and cerebral palsy are the major neurodevelopmental sequelae of VLBW infants. All these disabilities increase with decreasing birth weights and gestational age. In the United States, survivors of premature birth account for approximately 45% of the children with cerebral palsy, 35% of the children with vision impairment and 25% of the children with hearing impairment.[123]

In Western populations the incidence of cerebral palsy is 15% to 20% for children with birth weights of less than 1,000 grams,[124,125] 14% to 17% for children with birth weights of 1,000 to 1,500 grams and 6% to 8% for children with birth weights of 1,500 to 2,499 grams.[126] Western studies have shown that the prevalence of blindness is 5% to 6% and that of deafness is 2% to 3% among the VLBW population.[126–128]

In India about 20-30% of the VLBW infants have ROP.[129,130] Although most cases of ROP resolve and only few lead to permanent blindness, in view of the large number of

VLBW survivors, ROP must be one of leading causes of blindness in the country.[131] The incidence of cerebral palsy, obtained from ***hospital based*** studies among VLBW infants in India, is about 3-4%, [75,81] and that of significant developmental delay is about 8-10%.[76,78,132] ***Population based studies*** in this country have shown that the incidence of cerebral palsy is about 2.8 per 1000.[133,134] Cross sectional studies on two cohorts of children with cerebral palsy from North India, about 10 years apart, have shown a change in the etiology of cerebral palsy. The more recent cohort showed a rise in the proportion of CP associated with prematurity (from 13.2% to 24.3%) and low birth weight (from 20.4% to 37.87%).[135,136]

Studies from the NICHHD[137] and EPICure cohorts[138] which have compared neurodevelopmental outcomes of ELBW infants at 18 to 22 months corrected age, during two epochs, have shown a better survival rate in the later cohorts but the rates of cerebral palsy and severe developmental disability have remained almost the same between the two time epochs. Thus the improvement in survival is at the expense of long-term developmental disabilities.

"High prevalence- low severity" dysfunctions among the non-disabled survivors.

Majority of the survivors of VLBW are "non-disabled" and do not have any of the major neurodevelopmental disabilities mentioned above. But as the "non-disabled" VLBW or ELBW children join school, many of them are detected to have learning disabilities, borderline mental retardation, attention deficit hyperactivity disorders and behavioral problems.[139] These children are also at increased risk for anxiety, depression, social difficulties and conduct disorders.[140] Although these are low-severity dysfunctions

compared to CP or blindness, their prevalence is much higher and they result in a lasting impact on the child and the family.[141]

3.2.2 WHY DO THE VLBW CHILDREN REQUIRE FORMAL NEURODEVELOPMENTAL ASSESSMENTS AND REGULAR FOLLOW- UP?

Since the sequelae of being born with a very low birth weight can affect the child for many years, it is vital that these complications are identified early and the interventions started as soon as possible. Therefore the primary responsibilities of the follow-up program are[68] -

a. **Surveillance:** Monitoring the growth and development of the VLBW and ELBW infants after discharge from the NICU and facilitating the continuity of clinical care. Follow-up programs also provide parental support, anticipatory guidance and expedite referrals to the early intervention programs.

b. **Information:** Follow-up programs are also helpful for the NICUs to audit their interventions and provide the information about treatment outcomes. Collecting information from individual NICUs is useful in compiling regional and national databases which are valuable in guiding national health care planners. The information obtained from these databases also help in the anticipatory guidance of parents based on actual local scenario, rather than relying on information obtained other parts of the globe.[142]

c. **Research** is an important component of follow-up programs. Short term outcomes of survival are not sufficient to assess efficacy and safety of therapies. Follow-up of these infants enrolled in well-designed cohort studies

or clinical trials is essential to evaluate the long term impact of the risk factors and interventions in the perinatal period and determine how they influence growth and development.[68,80,121] A case in point is that of post-natal corticosteroids in bronchopulmonary dysplasia. Although initial short-term studies showed that corticosteroids were useful in treating the respiratory complications, only long term follow-up showed that corticosteroids adversely affected neurodevelopmental outcomes.[143]

3.2.3 WHO ARE THE CHILDREN WHO REQUIRE NEURODEVELOPMENTAL ASSESSMENTS?

A rigorous follow-up of all the neonates discharged from the NICU would not be practical or feasible. Therefore it is important to select infants who are at high risk of developing adverse neurodevelopmental outcomes.[80] There are guidelines laid down by the NNF and the American Association of Pediatrics (AAP) for risk stratification of all "at risk" infants into "high risk", "moderate risk" and "mild risk" for developing neurodevelopmental disorders. The guidelines for subsequent follow-up of these neonates are also laid down.[68,121,144] The VLBW and ELBW babies are in the "high risk" category for developing adverse neurodevelopmental outcomes.

3.2.4 WHEN SHOULD THE CHILDREN UNDERGO NEURODEVELOPMENTAL ASSESSMENTS?

The age of assessment depends on the purpose of assessment. Long-term assessments (in children older than 5 years) are better, and their results are more predictive of the child's future development.[68] However, because of the huge costs involved and the difficulties in tracking the infants, most studies on the effects of perinatal risk factors or clinical trials

involving interventions in ELBW/VLBW infants are limited to 24 months.[145] The British Association of Perinatal Medicine Working Group and the NICHHD consider that the age of two years (corrected for weeks of prematurity), as optimal for the assessment of neurodevelopmental outcomes.[146] By 24 months of age, at least 90% of preterm infants with cerebral palsy, sensory deficits and significant developmental impairment can be identified.[147] Diagnosis of CP at 24 months is no longer confounded by transient neurological syndromes of prematurity.[148] Although five-year evaluations provide valuable information about school outcomes and behavior disorders, because of the huge expenses involved in long term tracking and the need for interim assessments, most follow-up studies are limited to 24-36 months. Furthermore since long term assessments can be affected by socio-economic and familial influences, the neurodevelopmental outcomes may not be due to the perinatal risk factors or NICU interventions.[149]

The definitions of neurodevelopmental disability as defined by the British Association of Perinatal Medicine (2008) are shown in **table 1.**[146] The severity of the disability is decided based on a standardized developmental test score, the presence of severe visual impairment, severe hearing loss and cerebral palsy.

Table 1: British Association of Perinatal Medicine definitions for recommended outcome categories

Domain	Severe neurodevelopmental disability	Moderate neurodevelopmental disability
Motor	Cerebral Palsy with GMFCS level ≥ level 3	Cerebral Palsy with GMFCS level 2 and less
Cognitive	Score less than 3 SD below norm	Score -2SD to -3SD below norm
Hearing	More than 90dB (no useful hearing even with aids)	Hearing loss corrected with aids (up to 70dB)
Speech & Language	No meaningful words or signs	Some but fewer than 5 words or signs
Vision	Blind or perceives light	Moderately reduced vision

Recent change in date of assessment by NICHHD: Recently the NICHHD has decided to do the assessments at 22-26 months corrected age, rather than 18-22 months because the predictive value of the neurologic examination and developmental assessments are better when the child is two years of age despite the increased costs and difficulties in long-term tracking of the infants.[150]

CORRECTING FOR PREMATURITY

Application of corrected age (age of the child estimated from the expected date of delivery, rather than from the date of birth)[151] is controversial but is generally accepted and is currently practiced in most studies on preterm infants.[68]

Studies in favor of full correction

Barrera compared two groups of preterm babies (VLBW group <1500 g and the other higher birth weight (HBW) group of babies 1500-2000 g) with full term babies by assessing their development periodically using the Bayley's scales. It was found that when unadjusted for prematurity the VLBW infants were significantly delayed. However there was no significant difference when the groups were adjusted for prematurity.[152] Lems *et al* from their studies, has suggested that, that correction in motor and mental scores be used till the end of the first year.[153]

Studies which do not advocate correction

Siegal found that in the first year of life, corrected scores were more highly correlated with three and five year test scores. From 12 months of age on, uncorrected scores were more highly correlated. Based on these findings Siegel suggested that use of corrected scores is probably most appropriate during the first months of life when development is

strongly influenced by biologic factors. As the child matures and environmental factors become more important, it is appropriate then to use uncorrected scores.[154]

The concept of correcting or not correcting for prematurity, is based on two different theoretical viewpoints.[155] Those who advocate correcting for gestational age, believe that early development is dependent on the time since conception. Therefore premature infants lag behind term infants during early childhood temporarily. This is based on the idea that development depends on the maturation of central nervous system (CNS) and is independent of environment influences. The premature infants would catch up after complete maturation of their central nervous system. The preference for chronological age (no correction for prematurity) reflects an environmental perspective.[155] Those who advocate this viewpoint believe that external factors are more important than biologic factors like CNS maturity and play a more important role in premature infants. They have purported that parental interaction and developmental stimulation are more predictive of better developmental outcomes.[155] However the relative importance on biologic factors and environmental factors is still unclear. Currently there is no consensus about correction for prematurity.

Although short-term conclusions about the outcome of VLBW and ELBW infants will differ, depending on whether corrected or uncorrected scores are used, long term outcomes are not affected by correction.[139] Most clinicians support adjusting for prematurity in order to reduce parental anxiety and to prevent over referrals to early intervention services. However continued adjustment can lead to delayed diagnosis of developmental problems and late referrals.[155] In clinical practice it is more important to show that the child's development is progressing by periodic assessments than to make

conclusions based on a one-time score on the test. In NICHHD cohorts premature infants are corrected till 24-30 months although others recommend correction to 36 months.[156]

ASSESSMENTS AFTER 36 MONTHS

Many studies have shown that the complications of premature birth continue till adulthood. So there are now many large cohorts which have been followed into school age, adolescence and adulthood. The Pune cohort (**table 3B**) is the only example of dedicated long-term follow-up into adulthood from this country.[71,73,74]

Assessments at 36 months to 5 years: Assessments at this age can measure language skills, evaluate school readiness and identify behavioral disorders. Intelligence testing to obtain the intelligence quotient (IQ) using standardized tests is also possible. Beyond 18 months to 24 months, environmental factors start influencing the child's development as well, so many studies include measures to evaluate home environments, socio-economic status parents and measures of daily functioning.[157]

6-8 years: In addition to IQ, assessment of learning and attention can be done. Specific learning deficits start manifesting at this age. Behavior assessments can be done at this age. After 8 years, the usual evaluations include those for IQ, specific learning disorders, and neuropsychological assessments like testing for executive functions.[158]

3.2.5 WHICH DOMAINS REQUIRE ASSESSMENT?

Assessments for VLBW infants are done in the following categories - neurologic assessment (usually Amiel-Tison neurologic assessment), development and intelligence testing (using standardized developmental assessments and IQ tests), vision and visual motor integration, speech and language assessments, gross motor and fine motor

assessments, assessment of functional skills of daily living, school readiness and assessment of behavior.[159] The AAP[68] and the AIIMS (based on NNF guidelines)[80,121] have laid down protocols for assessment of these children at various ages. In addition neurologic and developmental assessment and monitoring of growth, VLBW infants should be screened for Retinopathy of Prematurity and a detailed assessment of the hearing must be done. If hearing loss is suspected the child should have Brainstem auditory evoked response or Oto-acoustic emissions to confirm the results. **Table 2** compares the assessments recommended by AAP and the NNF at 24-36 months.

Table 2: AAP and the NNF - AIIMS protocols for assessment

Area of assessment	American Association of Pediatrics (AAP) Protocol	NNF & All India Institute of Medical Sciences (AIIMS) Protocol
Growth	Weight, Length, Head circumference	Weight, Length, Head circumference
Nutrition	Body Mass Index, skin folds, Caloric/protein fat intake; energy expenditure	Mid arm circumference, Triceps skin fold thickness, Weight for length ratio, Growth velocity, Energy intake and energy expenditure, Bone density
Neurologic assessment	Standard for age; Amiel-Tison neurologic examination	Standard for age; Amiel-Tison neurologic examination, Hammersmith neonatal neurological examination
Neuroimaging	Conventional	As required (Ultrasonograms, CT or MRI)
Development	Psychomotor Development Index (PDI) and Mental Development Index (MDI) on Bayley's Scale of Infant development (BSID)	1. Development Observation Card (DOC) with CDC grading 2. Trivandrum Developmental Screening Chart (TDSC) 3. Denver Development Screening Test (DDST) / Denver II 4. Development Assessment scale for Indian Infants (DASII)
Language	Parent check list, Usually limited at this age	Language Evaluation Scale Trivandrum (0-3, Usually limited at this age
Functional behavior	Functional Independence measure (WeeFIM) , Vineland scales, CBCL	Vineland Social Maturity Scales, CBCL, Screening for autism

3.2.6 WHAT ARE THE TOOLS REQUIRED FOR DEVELOPMENTAL ASSESSMENT?

The gold standard for developmental assessment at 18-24 is the administration of a well-standardized developmental test which covers motor, language, social and cognitive domains.[145] The commonly used infant development scales are the Bayley Scales [currently the Bayley Scales for Infant and Toddler Development- 3rd edition (BSID-3)],[160] Griffith's Mental Developmental Scales (GMDS),[161,162] and the Developmental Assessment Scales for Indian Infants - 2nd edition (DASII).[163] In all these scales the composite of the various abilities are computed to give the developmental quotient(s). In the GMDS this is termed as the General Quotient. The BSID and DASII have two components to the developmental quotient - the motor quotient [known as Psychomotor developmental quotient (PDI) in the BSID or Motor Developmental Quotient (MoDQ) in the DASII] and a mental quotient [called Mental developmental Index (MDI) in BSID or Mental developmental quotient (MoDQ) in the DASII]. The composite developmental quotient(s) can be compared to that of a normative sample consisting of other children of the same age. The results obtained about the developmental abilities should be an accurate reflection of the child's capabilities and predictive of the child's future development.[164]

For many years the Griffiths scales were used as the standard "developmental test". This has been now overtaken by the Bayley scales as the developmental assessment tool in many parts of the world. Most of the major longitudinal cohort studies (of the NICHHD in USA, EPICure in UK, and EPIPAGE in France and Victorian Collaboration in Australia) have used the Bayley Scales of Infant Development. However the Griffiths scales continues to be used in many of European and Asian countries for assessment of

infants and young children. Many studies involving ELBW and VLBW have used the GMDS for developmental assessment.[165–171]

Developmental tests undergo extensive testing for validity, reliability, and accuracy and are standardized using children and families who represent the cultural, linguistic, and economic diversity of the intended population in order to be as accurate as possible.[172] In India the most popular developmental assessment test is the Developmental Assessment Scale for Indian Infants.[163] Although the DASII is referred to as the "gold standard" for assessment of Indian infants, it was standardized on a Marathi speaking population in Baroda. In view of the immense heterogeneity of the socio-cultural milieu and because of the numerous languages and dialects spoken in different parts of the country, it is likely that the ***current version of the DASII*** may not be culturally sensitive and appropriate for the population of the entire country. Sadly there is no other developmental assessment tool in this country. There are studies using the DASII in VLBW, ELBW infants (although the sample sizes are small) and in developmentally challenged children or from disadvantaged environments.[76,173–178]

3.2.7 WHAT IS THE PREDICTIVE VALUE OF DEVELOPMENTAL ASSESSMENTS?

It has been known for some time developmental assessments using the standardized developmental scales for infants (BSID and the GMDS) are not sensitive to predict the IQ of older children. This is mainly because, the decreased verbal skills in the toddlers compared to the older children, limits the comparability of the developmental assessments with IQ tests. Sutcliffe and colleagues[179] found that the GQ obtained from the Griffiths' scales at one and half year could predict the full scale IQ and the

performance IQ obtained from the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R) intelligence test to some extent, but the GQ could not predict the verbal IQ of the WPPSI-R.[179] This is because at 18 months the verbal and language skills are only emerging and therefore, developmental assessments at this age will not accurately predict the verbal capabilities when the child is older. So the Griffiths measure is more likely to be useful as a general indicator of subsequent development, but not a test for predicting language abilities.

Hack and colleagues found that Mental Development Index (MDI) on the BSID –II at 20 months corrected age, was not predictive of cognitive functioning at 8 years in their cohort of 330 ELBW children. Although mean MDI at 20 months was 76, mean cognitive score at 8 years was 88. The positive predictive value of having a low cognitive score of <70 at 8 years given a low cognitive score (<70) at 20 months was only 0.37.[180] Ment and colleagues had similar findings in a cohort of VLBW infants. Expressive language abilities were measured serially using the Peabody Picture vocabulary tests- revised (PPVT-R). They found that the scores seemed to improve with age. The median score was 88 at 3 years and 97 at 8 years.[181]

Bowen and colleagues looked at the relationship between the Griffiths Mental Development Scales at 1 and 3 years and the Stanford-Binet Intelligence Scale. They found that the GQ at 3 years on the GMDS correlated with IQ score of the Stanford Binet IQ test, however the 1 year GQ had poor predictive value.[182]

Although these results are encouraging, these findings do not mean that VLBW children with early delays routinely have later normal cognitive function. Furthermore in children without major neuro-disabilities, low score during infancy could be a marker for

subsequent risk of learning and behavior disorders at later school age.[183] Therefore it is important the child is on regular developmental monitoring and early interventions should be provided in case there is a developmental delay detected at the time of the developmental assessment.

3.2.8 NEUROLOGIC ASSESSMENT OF VLBW CHILDREN

Severe neurodevelopmental impairments in the VLBW and ELBW survivors are usually due to neurologic and sensory (vision and hearing) impairments. Neurologic examination is thus an integral part of the neurodevelopmental follow-up. In infants, unlike older children and adults much can be learned by observation of posture, movement, and quality of movement and examination of passive and active tone.[184,185] So neurological examination techniques like the Amiel-Tison Neurologic examination or the Hammersmith neurologic examination technique are of immense value. Neurologic abnormalities become obvious while doing the motor components of developmental assessments, (like the Peabody Developmental Motor scales, Bayley's, Griffiths or DASII) because the gross motor and fine motor skills will be affected if there are any abnormalities of tone and power.[184] Infants with mild tonal abnormality usually improve with time unlike children with severe neurologic abnormality who are likely to develop neurodevelopmental disabilities.[68]

The Amiel-Tison neurologic assessment is mainly based on the study of tone - active tone, passive tone and resting posture and is widely used for assessment of infants in India and all over the world.[186,187] This is the usual neurologic examination done in the NICHHD studies. An Indian study showed that the assessment at three months by this

method is a good predictor of outcome at 12 months.[185] Since this is a neuro-motor assessment, the mental abilities cannot be ascertained from this test and this requires a formal developmental assessment.[184]

Transient dystonia which occurs in preterm and VLBW infants can confound the diagnosis of CP during the first year of life.[185] This was first described by Drillien and manifests as increased tone of the trunk and lower limbs with persistent primitive reflexes leading to extensor posturing, scissoring, head lag and delayed supportive responses.[188] Although in the majority of preterms, the dystonia disappears, some infants go on to develop cerebral palsy as was shown in a recent study. The study was done on a cohort of children less than 2000 g and showed that in sixty five infants who had dystonia in the first year only eight infants were finally diagnosed to have CP at three years of age.[189] Another study from India showed that in a cohort of high risk infants who had increased tone, by the end of the first year, the tone had become normal in 87% and only 13% went on to have cerebral palsy.[190] However presence of transient dystonia can increase the risk of cognitive and motor problems and it is not possible to make a confident differentiation between transient dystonia and cerebral palsy at 6–8 months of age.[191] So meticulous follow-up of the child is necessary, for confirmation, till the end of the second year.

Amiel-Tison Neurologic Assessment (ATNA) was initially developed for the neurologic examination of term and preterm infants. However Amiel-Tison and Gosselin have further developed this tool, so that with the same examination protocol and the same system of scoring, the clinician can detect neurologic abnormalities at term gestational age and continue to use the same instrument for follow-up of the child till six years of

age[187,192] A study showed that infants who had abnormal neurologic signs on the ATNA at term gestational age were significantly worse on the Psychomotor and mental developmental indices of the Bayley scales at one year, and in another study showed infants who had neurologic deficits detected by the ATNA had a lower general quotient (GQ) on the Griffiths' mental developmental scales at 3 years and 8 month.[187]

3.2.9 THE ADVANTAGES AND DISADVANTAGES OF USING BIRTH-WEIGHT OR GESTATIONAL AGE AS INCLUSION CRITERIA FOR VLBW INFANTS

Prior to the 1990s infants were primarily grouped by birth weight rather than gestational age because of the uncertainty of the obstetric estimation of gestational age. However, advances in fetal ultrasonography have improved gestational age estimation.[193] Since gestational age is a stronger determinant of organ maturation and viability than is birth weight,[194] most Western studies report their outcomes according to the gestational age. Nevertheless reporting birth weights is also important in India, since 60% of the LBW babies have intrauterine growth restriction while the remaining 40% are born preterm.[13] So reporting only gestational age will miss the population of late preterm and term growth retarded infants. Additionally in most developing countries, because of the lack of adequate prenatal care, many women do not have early ultrasonograms which are needed for gestational age estimation. Therefore both birth weight and gestational age should be considered in outcomes studies.[195]

To summarize this section, despite the costs involved in the follow-up of VLBW, this is an integral part of the continuum of care which starts at admission into the NICU. Long term outcomes determine the success of the interventions in the NICU and detect can

unanticipated complications. Although developmental assessments have questionable predictive value in predicting intelligence or scholastic performance, there is still much usefulness in these assessments. Developmental assessments provide an accurate measure of the child's level of functioning in the pre-school age group, help in identifying children who require developmental remediation, and are an effective way of communicating with parents about their child's developmental strengths and weaknesses.[176] However follow-up should not end with pre-school age and meticulous monitoring is required to identify children who will have learning difficulties, attention problems and behavior disorders.

3.3: SECTION 3 - NEURODEVELOPMENTAL OUTCOMES IN INFANCY

This section discusses briefly about the important studies which have reported on the neurodevelopmental outcomes of the VLBW infants in India and around the world. The section is arranged as follows -

3.3.1: Findings of all the important studies which looked at the ***neurodevelopmental outcomes of VLBW*** babies in India other developing countries have been included.

3.3.2: Important ***studies from the developed countries***.

3.3.3: Comparison of ***the Indian studies with that of the developed countries***.

The NICHHD defines "**neurodevelopmental impairment**" as – (a) Presence of Psychomotor developmental Index (PDI) of less than 70 and Mental developmental index (MDI) of less than 70 on the Bayley Scales of Infant development (BSID-3rd edition) (b) presence of visual impairment of less than 20/200 (c) hearing impairment requiring bilateral amplification (d) cerebral palsy.[196] Since BSID-3rd edition is the most popular developmental assessment tool this definition is used in most Western studies.

3.2.10 NEURODEVELOPMENTAL FOLLOW- UP OF INDIAN CHILDREN

There are a few studies done in India which have followed up Very low birth weight infants from birth to a corrected age of two or three years. These are summarized in **tables 3A and 3B.** To maintain continuity **table 3B** summarizes the studies done on the Pune Low birth weight cohort. This is the only cohort which has been followed up till adolescence.

Table 3A: Summary of Indian studies with longitudinal follow-up of Very Low birth infants

Author (date)	Research question	Sample size and Tools used	Main findings
Nair (2014)[174]	To assess effectiveness of TDSC based early intervention in LBW	240 LBW (<2500 g) babies were compared to 260 normal controls TDSC (Trivandrum developmental scales for children) and DASII	No difference in the development of LBW babies and the normal birth weight babies. Rates of CP and developmental delay not mentioned.
Lakshmi (2013)[197]	Compare outcomes of preterm infants with history of absent or reversed end-diastolic umbilical artery Doppler flow (AREDF) vs. infants with forward end-diastolic flow (FEDF).	103 AREDF very low birth weight (<1500 g) (VLBW) infants and 117 FEDF VLBW infants Amiel- Tison Neurologic examination	At 12-18 months corrected age, AREDF group had a trend towards increased risk for cerebral palsy (7% vs. 0.1%, P=0.06) compared to FEDF group.
Modi (2012)[75]	Neurodevelopmental outcome of VLBW at 12 months corrected age.	37 of initial 45 VLBW followed up at 1 year, compared to 35 normal infants DASII	DQ at 12 months was significantly lower in VLBW infants (91.5+7.8) than NBW infants (97.5±5.3)
Sharma (2011)[82]	To determine neurosensory outcomes of VLBW (≤32 weeks ≤1500 g) at corrected age (CA) of 18 months	31 out of initial 64 completed assessment Amiel- Tison neurologic examination and DASII	3 of 31 (10%) had cerebral palsy 3of 31(10%) had developmental delay
Mukhopadhyay (2010)[76]	Neurodevelopmental and behavioral assessment of VLBW (≤34 weeks, ≤1500 g) at corrected age (CA) of 2 years..	71 infants from the initial sample of 132 were assessed at 18 months. 20 infants were ELBW DASII and Preschool behavioral checklist (PBCL) at CA of 2 years.	83% (of the 71 infants) had Mental DQ of ≥70 and 75% had motor DQ of ≥70. No difference between the ELBW and the rest in their mean Mental and motor Developmental quotients. 3% had cerebral palsy
Paul (1998)[81]	Neurodevelopmental outcome of "at risk" NICU graduates. 101 infants were followed till 3 years.	55 of 101 were VLBW. Followed up to 3 years CA. Bayley Scales of Infant Development (BSID) (with Phatak's adaptation for Indian Children)	10.9% of VLBW had Neurodevelopmental impairment

Table 3B: Summary of the longitudinal follow-up of Very Low birth infants & high risk infants from Pune[71,74,83,84,198]

Author (date)	Research question	Sample size and Tools used	Main findings
Chaudhari (2013)[74]	To assess the cognitive development of non-handicapped low birth weight (LBW) infants at 18 years	161 LBW and 73 normal birth weight children Assessment of Cognition was done by Raven's Progressive Matrices	The IQ of the study group was significantly lower than that of controls. Preterm SGA had lowest IQ
Chaudhari (2004)[71]	Assessment of IQ, visuo-motor skills, learning abilities in 12 years old children who were less than 2000 grams at birth	180 children followed up of which 78 were VLBW. IQ test: Wechsler's Intelligence Scale, Visuo-motor: Bender Gestalt test, Draw-a-Person Specific learning disability: Wide Range Achievement Test	12 (15.4%) mentally retarded children in VLBW group as compared to only 3 (3.3%) amongst controls. The number of children with mental retardation (IQ <70) had also risen form 3.5% at 6 years to 13.3%
Chaudhari (2000)[198]	Study the mortality and morbidity in high risk infants	• 286 high risk infants assessed. Of these 92 were VLBW • Stanford Binet IQ test at 6 years	Mortality was greater (22%) in the VLBW group. 16.3% of VLBW were 'slow learners' compared to 5.6% of children birth wt. >2000g
Chaudhari (1996)[84]	Determine neurologic sequelae in high risk infant	• 336 High risk vs. 70 normal controls followed up for 3 years. 109 (32.4%) were VLBW. • Amiel-Tison Method, BSID and Raval's Scale for social maturity were used	Totally 16 (4.8%) had cerebral palsy. Six (5.5%) of VLBW had CP. Sensorineural hearing loss was present in 5 (1.5%) children while 1 subject had cortical blindness. Seizure disorders in 3.9%.
Chaudhari (1991)[83]	Determine the development of preterm babies. Followed up to 24 months	• 171 preterm babies, (of these, 75 or 43.7% were VLBW). 110 assessed at 18 months and 81 at 24 months • BSID -2	7 of 171 (4%) had cerebral palsy 4 of 171 (2.3%) had gross developmental delay. Morbidities in the VLBW subgroup not specified.

Neurodevelopmental follow-up from other developing countries

Thailand: A study from Thailand which looked at the outcome of 30 VLBW infants at 18-22 months. Of these five children (16.67%) had visual defect, one child (3.33%) had moderately severe hearing loss, one child (3.33%) had cerebral palsy and seven children (23.33%) had delayed development.[199]

South Africa: In this study the 106 of a total of 143 (74%) VLBW infants were evaluated using the BSID at 16.48 months (mean age). The mean cognitive subscale was 88.6 (85.69 - 91.59 95% CI), nine children (8.5%) had developmental delay and cerebral palsy was diagnosed in 4 (3.7%) of babies.[200]

Bangladesh: This was a study on a cohort of preterm newborn infant survivors (<33 weeks).. 85 of the initial 159 infants (53.5%) were assessed using the BSID-II at a mean of 31 months. Of these 36% of the infants had developmental delay, 12% of the infants had CP, 18% of the infants had blindness and 6% of the infants had deafness.[201]

3.2.11 NEURODEVELOPMENTAL FOLLOW- UP FROM OTHER COUNTRIES

Table 4 summarizes the details of the recent studies from Western countries which have looked at the neurodevelopmental outcomes. Since the 1990s most developed countries have stopped looking at the outcomes of VLBW (1000-1500 g) and most of the recent studies only discuss the outcomes of ELBW (less than 1000 g or 750 g) or extreme preterms (less than 28 weeks). However I have included a few studies from the 1990s which have looked at the neurodevelopmental outcomes of VLBW infants (<1500 g).

Table 4: Summary of the Studies which have looked at the neurodevelopmental outcomes of VLBW and ELBW infants

Author (year) Country	Inclusion criteria (GA/Birth weight)	Age of assessment & test	Neurodevelopmental Impairment	Other characteristics
Serenius (2013)[202] **(EXPRESS study, Sweden)**	All infants born alive or stillborn in Sweden before 27 weeks gestation between 2004 and 2007. Compared with age and sex matched controls. 456 of 491 (94%) children were evaluated	2.5 years BSID -III	94% of survivors were followed up. 44.5% had delay on BSID (20% moderate to severe) CP: 7% (1.3% severe) Visual impairment: 3.7% (0.9% blind) Hearing impaired: 0.9% (0.2% deaf)	Incidence of disability was inversely related to the gestational age. (60% at 22 weeks; 51% at 23 weeks, 34% at 24 weeks,27% at 25 weeks,; and 17% at 26 weeks).
Ishii (2013)[203] **Japanese Neonatal research network**	ELBWs born between 22 and 25 weeks.	36-42 months. Kyoto Scale of Psychological Development	562 of 782 (71.9%) were followed up 13.7% of survivors had CP 8.2% had hearing impairment 1.7% had visual impairment 35.4% had cognitive delay	Study with largest number of survivors at 22 -23 weeks. 45.5% of 22 weeks survivors, 32.8% of 23 week, 36.6% of 24 weeks and 33.1% of 25 weeks had DQ <70.
Hintz (2011)[204] **NCHHD-NRN USA**	Extremely low birth weights at an estimated gestational age of <25 weeks during 2 periods: 1999–2001 (epoch 1) and 2002–2004 (epoch 2).	18-22 months BSID-II	Infant survival was similar between epochs (35.4%, vs. 32.3%) Moderate-to-severe CP: 11.1% (epoch 1) vs. 14.9% (epoch 2) MDI was <70 in 44.9% in epoch 1 and 51% in epoch 2 Neurodevelopmental impairment was diagnosed in 50.1% v. 58.7%	Early-childhood outcomes for infants born at <25 weeks' estimated gestational age were unchanged between the 2 periods.
Schlapbach (2012)[205] **Switzerland**	Extremely premature infants live born between 24 and 27 weeks from 1/1/2000-31/12/08	18-24 months BSID-II	684/844 (81%) were followed up. 64% showed good outcome, 24% had moderate and 11% severe neurodevelopmental impairment.	

Gargus (2009)[206] **NICHHD-NRN (USA)**	To look for unimpaired ELBW survivors in the NICHHD cohorts 1998-2001. (Unimpaired PDI and MDI in BSID within 1 SD of the mean, normal neurologic exam, vision, hearing swallowing were normal	18-24 m BSID II	Outcomes of 5250 (84%) infants were known at 18 m. 16% were unimpaired 22% had mild impairments, 22% had moderate/severe neurodevelopmental impairments (Bailey <70, CP, Bilateral blind or deaf)	Less than 1% of live-born infants of 500 g survive free of impairment at 18 months, this increases to almost 24% for infants of 901 to 1000 g. Female gender, singleton birth, higher birth weight, absence of neonatal morbidities, are related to better unimpaired outcomes
Doyle (2010)[207] **Victorian Infant Collaborative Study Group, Australia**	All live born infants 22-27 weeks GA were included and survivors (n=172) was assessed	2 years BSID-III	94.8% were followed up 9.8% had CP 2.5% deaf. None were blind Dev. Delay in 47.9% (16% moderate to severe delay)	Compared to cohorts in 1991-2 and 97-98 from the same region survival rates for infants born at 22-27 seems to be the same but the neurosensory outcomes in survivors appear to have improved
Bodeau-Livinec (2008)[208] **EPIPAGE (France) and British Isles (EPICure)**	EPICure and EPIPAGE are 2 population-based studies, from the British Isles and France, respectively, that included extremely preterm infants (<28 weeks)	2 years BSID Kaufman Assessment Battery for Children (K-ABC) at 5-6 years	90% (280 infants) followed up. CP at 24 to 30 months was 20% in the EPICure study versus 16% in the EPIPAGE study, whereas the risk Dev. Delay :<70 (-2SD) at 5 to 6 years was 10% vs. 14%, respectively	Outcomes between the two studies were not significantly different.
Sommer (2007)[209] **Austria**	48/53 (91%) of infants <27 weeks GA were assessed	2 years GMDS	CP in 6% (4% non-ambulant &, 2% ambulant) Development: 40% were normal, 6% had mild delay, 35% (moderate delay) and 19% severe delay (DQ<-3 SD)	Profound growth failure in weight in 39% and head circumference<3rd in 19% of the infants at 2 years
Gianni (2007)[210] **Italy**	141 ELBW infants assessed Compared MRI at term conceptional age, neurofunctional exam at 1 year and assessment at 36 m	36 months GMDS	CP: Not mentioned Developmental delay (GQ≤70): 14.2%	Abnormal MRI at term conceptional age, and poor Neurofunctional assessment at 1 year can predict poor cognitive outcome at 36 months

Hoekstra (2004)[211] **Minnesota (USA)**	Retrospective review of 778 infants between 23-26 weeks	BSID – II At 36 m 3-6 y: DDST , ELMS, ZPAT	87% were followed up at mean of 47.5 months. CP: Not mentioned 17% had moderate impairment and 20% severe impairment	Proportion of severe impairment decreased with increasing age. 34%, 21%, 20%, 17% for 23, 24, 25, 26 weeks gestation respectively
Wood (2000)[125] **EPICure study (UK)**	Prospective longitudinal cohort. 283 survivors of 20-25 completed weeks gestation	BSID-II At 30 months	92% follow-up. CP: 50/280 (18%) Blind: 7 (0.03%) Deaf : 5 (0.02%) had profound deafness Many others had less severe degree hearing and visual impairments	At 30 months almost 50% of the survivors had disabilities in mental and psychomotor development, neuromotor function, or sensory and communication function. About 25% of them had severe disability.
Vohr (2000)[212] **NICHHD-NRN (USA)**	Cohort of 1765 VLBW (<1500 g) infants in the NICHHD network	BSID-II at 8-22 months corrected gestational age	78% were followed up 17% had CP 37% MDI <70, 29% PDI <70, vision impairment: 9% hearing impairment: 11%.	CP, developmental delay increased with decreasing birth weight.
Ment (1996)[213] **NICHHD-NRN (USA**)	Randomized, trial for preventing IVH with low dose indomethacin in <1250 g infants. Study group got indomethacin and control group got saline	Stanford-Binet IQ test at 36 month	343 (89%) children were examined at 8% each in both groups had CP No difference in mean IQ between the two groups	Low dose indomethacin was shown not have any neurodevelopmental consequence and was found to improve survival at 36 months
Veelken (1991)[214] **Germany**	Prospective cohort of VLBW Babies	GMDS at 18-20 m	CP: 14.8% 8% without neurological abnormalities was moderately retarded 5% were severely retarded 1.5% were blind due to ROP.	

ELMS: Early Language Milestone Scale; ZPAT: Zimmerman Preschool Articulation Test.

3.2.12 COMPARING THE NEURODEVELOPMENTAL OUTCOMES OF VLBW INFANTS IN INDIA WITH THAT OF THE DEVELOPED COUNTRIES.

Let me first summarize the findings of outcomes from the cohorts from the developed countries.

1. **Survival has improved and the limits of viability are changing**

In developed countries advances in the last two decades in perinatal and neonatal management have resulted in the survival of extremely premature infants who are born at the limits of viability (22–25 weeks). The use of prenatal corticosteroids for fetal lung maturity, surfactant in respiratory distress syndrome, prophylactic indomethacin for prevention of intraventricular hemorrhage, improved nutritional management and ventilatory techniques have all contributed to the improved survival.[215–217] A 2012 NICHD study of infants <1000 g and <28 weeks gestation born between 2002 and 2008 reported a survival rate of 39% for infants less than 24 weeks compared with 81% for infants between 25 and 27 weeks gestation.[218] There are studies from Japan which have reported infants who were born at the limits of viability (22 weeks) and survived.[203] Currently the survival rates are approximately 85% for VLBW and 70% for ELBW infants in developed countries.[219]

2. **Neurodevelopmental outcomes have not improved much**

As mentioned earlier, improved survival has not resulted in improved neurodevelopmental outcomes. There is an inverse relationship between birth weight or gestational age and the risk for developmental impairment. There is an increase in the level of neurodevelopmental impairment as birth-weight or gestational age (especially in

the less than 25 weeks) decreases and this is seen all the studies cited. Although there has been some evidence of improvement in neurodevelopmental impairment rates since the 1990s, rates are high particularly in the between 22 and 25 weeks gestational age infants.[220]

3. Differences in survival

There are significant differences in rates of survival and neurodevelopmental impairment by geographic region and neonatal network related to multiple factors including population characteristics, perinatal and neonatal management and the follow-up protocols

However it must be emphasized that these studies summarized in the **table 4** were done in countries where there is relatively easy access to perinatal care, there are regional centers specialized in looking after ELBW babies, provision of life support at delivery and near universal admission for infants who are micro-preemies (less than 26 weeks gestation). This is not possible in a resource stretched country like India, where the enormous costs for perinatal care is borne by the parents and where most people are poor.

Summarizing the data from Indian studies

Unfortunately there is a paucity of data. **Tables 3A and 3B** present the data of all studies in India which have looked at the outcome of VLBW infants in the last two decades. Combining all the studies, we have information of less than 600 VLBW infants.

From the available database summarized (**tables 3A and 3B**) the following relevant observations can be made -

1. The sample sizes of the individual studies are very small. In addition some studies have looked at the outcomes of the VLBW infants as part of the developmental follow-up of a heterogeneous group of "high risk infants". In these mixed cohorts the etiologies, risk factors and outcomes are varied and therefore it is difficult to make definite conclusions.[22]

2. All the Indian studies are hospital based studies from tertiary centers which are regional referral centers. Therefore it may not be correct to extrapolate the results of these studies to the entire country. The dropouts are also very large (ranging from 18% to about 50%) and so it is difficult to estimate the true level of incidence of cerebral palsy or other neurosensory impairments. It is important to have information of the all the infants who are recruited since children who dropped out may be more affected than children who are followed up.[145]

3. It is also not clear if the children who were lost to follow-up were the children with good outcomes or the ones with neurodevelopmental impairment. Other studies have shown that children who were more difficult to track are likely to have higher rates of disability.[221,222] Especially among the lower socioeconomic groups, untraced survivors may be more handicapped as those who are evaluated.[223] Even survival of these babies is uncertain.

4. Moreover the outcomes which were reported were not uniform. Most studies have reported cerebral palsy, but not all the studies have reported the incidence of global developmental delay or neurosensory impairments.

Since there is limited data (regionally and nationally) on the incidence of cerebral palsy or developmental delay in the general population, it is difficult to determine the risk of having cerebral palsy in the VLBW as compared to the term infants.[59]

In spite of the limitations the following can be inferred -

1. There are significant neurodevelopmental morbidities among VLBW children which are evident from early childhood. The main morbidities being cerebral palsy, developmental delay, sensory impairments (deafness, blindness) and behavior problems.
2. The incidence of cerebral palsy among the VLBW in all studies ranges between 3% and 5%, which is comparable to data available from Western studies. In Escobar's meta-analysis of the outcomes of VLBW from about 100 Western studies the median incidence of cerebral palsy was 7.7% and the estimated incidence of disabilities among VLBW survivors was 25%.[59]

Thus in order to improve the information about the outcome of VLBW from India, it is imperative that all centers which look after these babies in this country, contribute the data obtained from their developmental follow-up programs into a national database. This information can then be used for counseling parents, for allocation of resources and for making national policy decisions.

3.4: SECTION 4 - NEONATAL COMPLICATIONS AND THEIR EFFECTS ON THE NEURODEVELOPMENTAL OUTCOME

The complications which occur in VLBW infants are predominantly because of the immaturity of their organs to adapt to an extra-uterine environment. The risk of acute neonatal illness increases with decreasing gestational age, reflecting the fragility and immaturity of the brain, lungs, immune system, kidneys, skin, eyes, and gastrointestinal system. These complications which have life-long consequences in terms of the neurodevelopmental outcome, are further influenced by the effects of the social factors which come into play from early childhood.

Usually there are three risk categories which decide the developmental outcome of VLBW/ELBW babies.[68,164]

- **Biologic risks:** These are perinatal complications which include lower birth weight, prematurity, IVH, PVL, NEC, congenital anomalies, CLD, septicemia, meningitis etc.
- **Risks of therapeutic interventions:** These are adverse effects which occur due to treatment modalities like ventilation, parenteral nutrition, oxygen therapy, post-natal administration of corticosteroids etc.
- **Effects of the social and environmental characteristics:** The social and/or environmental characteristics of families become more increasingly important as the child matures and some of these include socio-economic status (SES), maternal education, marital status, income, mother's age and environmental stress.

This section refers to some of the important risk factors in the neonatal period and interventions which have been shown to affect the neurodevelopmental and cognitive outcomes of preterm and low birth weight infants. Since most of the studies have used Bayley's Scales of Infant Development for developmental assessment, developmental outcomes are expressed in terms of the Psychomotor developmental index (PDI) and Mental developmental index (MDI). Neurodevelopmental impairment is defined as <70 on the PDI and <70 on the MDI or presence of cerebral palsy, blindness or hearing impairment.

It is important to realize that neonatal morbidities associated with the adverse outcomes and interventions in the NICU do not occur in isolation. A study which looked at the influence of multiple morbidities showed that the rate of neurodevelopmental impairment (NDI) increases with every added morbidity.[224] The morbidities analyzed in this study were bronchopulmonary dysplasia, severe brain injury and severe Retinopathy of prematurity. For the entire cohort the NDI was 35%. However the rate of NDI was 18% for children with no morbidity, 42% for those with one morbidity, 78% for those with two morbidities and 88% for those with all three morbidities. The NDI rate for children with three neonatal morbidities was almost five times the rate of children with no history of neonatal morbidities. Thus survival in the nursery and later neurodevelopmental outcomes are the cumulative effect of the multiple morbidities and multivariate analyses are required to confirm independent effects of the morbidities.[164]

In this section the influence of the following factors on the neurodevelopmental outcomes of VLBW infants have been reviewed in the following subsections -

Male gender (3.4.1), **extreme prematurity** (3.4.2), **antenatal corticosteroids and RDS** (3.4.3), **bronchopulmonary dysplasia** (3.4.4), **post-natal corticosteroids** (3.4.5), **NEC** (3.4.6), **septicemia** (3.4.7), **PVL** (3.4.10), **IVH** (3.4.11). The outcomes which result in neurodevelopmental impairment like **visual impairment** (3.4.8), **hearing impairment** (3.4.9) and **cerebral palsy** (3.4.12) are also included.

3.4.1 MALE GENDER

Although male gender is not a "risk factor" for poor neurodevelopmental outcome, most studies have demonstrated that male ELBW infants are more likely to have cerebral palsy or severe neurodevelopmental impairments compared to female infants.[225-227]

In a NICHHD cohort of over 7000 VLBW infants, boys had higher rates of BPD, had lower APGAR scores and were less likely to survive.[225] In another study which looked at the neurodevelopmental outcomes of ELBW babies at 18-22 months corrected gestational age, the survival of boys was 58.3% compared to 66.9% in girls, and boys were more likely to have BPD, severe IVH and ROP "plus disease". Boys were more likely to have MDI <70 (41.9% vs. 27.1%) compared to girls. Multivariate analyses confirmed the independent effect of male sex on the outcomes in this study.[226] The differences in the outcomes seem to persist into school age and adulthood. The clinical trial on "Indomethacin in IVH prevention", showed that at eight years of age, boys in the study were more likely to have difficulties in reading and lower cognitive scores as compared to the girls who took part in the study.[228] Another study showed that at 20 years of age, VLBW males were shorter compared to their normal birth-weight male peers, but VLBW girls had caught up with their normal birth-weight peers.[229] However a recent study from

Australia demonstrated that, although the mortality and neurologic outcomes at 2-3 years were worse in male VLBW infants, these were most pronounced in infants who were less than 27 weeks gestation and gender differences were not significant in infants after 27 weeks gestation.[230]

Fleisher and colleagues looked at four indices of lung profile (lecithin / sphingomyelin ratios, percentage disaturated lecithin, phosphatidyl-glycerol, and phosphatidylinositol) from the amniotic fluids of male and female fetuses. They demonstrated that all four indices revealed a higher degree of lung maturity in female than in male fetuses during the last two months of normal pregnancy.[231] Furthermore, in-vitro studies on male rat fetuses are have revealed that androgens and Mullerian Inhibiting Factor adversely affected surfactant production, which probably contributes to the lung immaturity in premature males.[221,222]

Thus, the lung immaturity probably predisposes the male infants to higher rates of RDS, intubation, BPD and contributes to the higher rates of IVH, all of which can result in higher mortality and adverse neurodevelopmental outcomes. This lung immaturity hypotheses is supported by studies which show that the differences in survival are more apparent in infants who are more premature.[234]

3.4.2 EXTREME PREMATURITY

It is well known that the outcomes of ELBW and extremely premature infants are far worse than infants who are born at later gestational ages. During the second and third trimester there is active brain growth with neuronogenesis, neuronal migration, maturation, apoptosis and synaptogenesis.[235] During this active period of growth, the

immature brain is vulnerable to hypoxia, ischemia, under-nutrition and sepsis which can result in a cascade of events increasing the threat of complications like germinal matrix hemorrhage, periventricular leukomalacia and ventriculomegaly, all of which lead to subsequent neurodevelopmental impairment.[164] Much of the poor cognitive outcomes in extremely premature babies are due to the sequelae of PVL and IVH. The stress of the therapeutic measures during their prolonged NICU stay further increases the vulnerability to injury.

MRI studies have shown that the volumes of grey matter, white matter, basal ganglia and cerebellum are much lesser in children who were born preterm compared to their age-matched peers.[236] Even in premature infants with no evidence of white matter involvement on neonatal cranial ultrasound, diffusion-tensor imaging (DTI) has shown microstructural abnormalities in the neural connectivity of premature children compared to term controls at 12 years of age which has correlated significantly with cognitive outcomes.[237]

Extremely premature infants breathe through their terminal bronchioles, since their alveoli are still underdeveloped and they lack surfactant. By approximately 30 to 32 weeks of gestation, the lungs make surfactant which reduces the alveolar surface tension, thereby facilitating alveolar expansion and reducing the likelihood of alveolar collapse atelectasis.[238] Respiratory distress syndrome (RDS), a common complication of prematurity, is caused primarily by deficiency of pulmonary surfactant in the immature lung.[238] RDS and other pulmonary complications (pneumothorax, hypercapnia, hypoxia) predispose to development of intraventricular hemorrhage.[239] It has been shown that even in children with uncomplicated IVH (no parenchymal involvement or ventriculomegaly)

the cognitive outcomes are worse [240] compared to infants without IVH. Furthermore studies have also shown that uncomplicated IVH is associated with 16% decrease in cortical volume at term gestational age.[241]

Thus the grey matter and white matter structures of preterm survivors are different from their term counterparts and these structural differences manifest as learning and behavior abnormalities later in life.

3.4.3 RESPIRATORY DISTRESS & ADMINISTRATION ANTENATAL CORTICOSTEROIDS

Respiratory distress syndrome is a major cause of morbidity and mortality in preterm infants and its incidence increases with decreasing gestational age. The risk is highest in extremely preterm infants, as illustrated by a study from the NICHHD that found a 93 percent incidence of RDS in a cohort of 9575 extremely preterm infants (gestational age 28 weeks or below) born between 2003 and 2007.[242]

Specific interventions are focused on preventing or decreasing the severity of RDS and include the following[243] -

- Administration of antenatal corticosteroids
- Administration of exogenous surfactant
- Provision of assisted ventilation

The administration of antenatal glucocorticoids reduces the risk of RDS in premature infants because it improves neonatal lung function by enhancing maturational changes in lung architecture and by inducing enzymes that stimulate phospholipid synthesis and release of surfactant.[244]

In addition to its benefits in RDS, antenatal corticosteroid administration has been shown to decrease mortality, and rates of IVH and incidence of chronic lung.[245,246] The Cochrane review on antenatal administration of corticosteroids found that there was reduction in the rate of neonatal death (Relative Risk 0.69), Respiratory distress syndrome (RR 0.66), respiratory support and intensive care admissions (RR0.80), intraventricular hemorrhage (RR 0.54), necrotizing enterocolitis (RR0.46) and early onset sepsis (RR 0.56).[247] Currently all mothers who are at risk of preterm delivery of less than 34 weeks gestation are advised corticosteroids.[248]

In addition to its benefits in reducing mortality and the incidence of IVH, RDS and BPD, antenatal corticosteroids have been shown to significantly improve neurodevelopmental outcomes. A large multi-center trial which looked at the neurodevelopmental outcomes of nearly five thousand ELBW infants at 18-22 months showed, neurodevelopmental impairment (moderate–severe cerebral palsy and psychomotor developmental delay), intraventricular hemorrhage and periventricular leukomalacia and necrotizing enterocolitis were significantly less in the children who were administered antenatal corticosteroids.[249]

3.4.4 BRONCHOPULMONARY DYSPLASIA (BPD) AND NEURO- DEVELOPMENTAL OUTCOMES

Bronchopulmonary dysplasia (BPD) is a serious morbidity among preterm infants and is diagnosed when there is a continued need for supplemental oxygen at 36 weeks postmenstrual age.[250] The incidence of BPD increases with decreasing gestational age (the incidence is 42% for birth weights 501–750 g, 25% for birth weights 751–1000 g,

11% for birth weights 1001–1250 g and 5% when the birth weights are 1251–1500 g).[103] Infants with a birth weight of less than 1250 g account for 97% of all patients with BPD.[103] In another 42% of the infants less than 28 week gestational age had BPD.[242]

Mortality: Infants with severe BPD have a higher risk of mortality than infants with mild disease or unaffected of the same gestational age. Death is usually caused by respiratory failure, unremitting pulmonary hypertension with cor pulmonale, or acquired infection.[25]

Neurodevelopmental impairment

BPD increases the risk of neurodevelopmental impairment in the preterm and the VLBW infants and this is probably as a result of multiple contributing factors like frequent episodes of hypoxia, poor growth, and probably because of use of post-natal corticosteroids.[251] The spectrum of neurodevelopmental impairment seems to correlate well with the severity of BPD and a large cohort study showed that the incidence of cerebral palsy, developmental delay, blindness, hearing impairment and growth outcomes worsened with the severity of BPD.[252] Another study showed that BPD and post-natal corticosteroid treatment for BPD were significant risk factors for neurologic abnormality and neurodevelopmental impairment (MDI and PDI of <70 on the Bayley Scales of Infant Development).[212] The effect of BPD on neurodevelopmental outcomes persists through school age as demonstrated in a study which showed that the VLBW infants who had BPD, when tested at 8 to 10 years of age, scored poorly in their cognitive performance, compared with controls.[253] Another study on the survivors of BPD at 10 years of age, showed that on comparing with unaffected preterm controls, neurological abnormalities, including subtle neurological signs, cerebral palsy, microcephaly, and behavioral difficulties were highly prevalent in the BPD group (71% compared with 19%

in control group, P<0.005).[254] Infants with BPD have poor post-natal growth and this may be due to increased energy expenditure associated with their respiratory disease, difficulty in maintaining full nutrient and mineral intake, and due to diuretic therapy.[255]

The long- term effects of BPD on growth are not certain. Previous studies have indicated that children with BPD are smaller in size than controls.[256] However after taking into account possible confounders, some studies have shown that the poor growth in BPD may be due to the overall effect of prematurity and perinatal complications because of the BPD alone.[257,258]

Long term pulmonary complications of bronchopulmonary dysplasia

Up to 50 percent of children with BPD require re-hospitalization during the first two years of life, usually due to viral respiratory illnesses.[259,260] Recurrent wheezing episodes are very common in children with bronchopulmonary dysplasia, but unlike in asthma they are less likely to respond to bronchodilators.[261,262]. Pulmonary Artery Hypertension (PAH) which occurs in 20–40% of infants with BPD is an important risk factor for mortality.[263] Airway hyper-reactivity, airway obstruction and emphysema are the adulthood consequences of BPD in the neonatal period.[264]

3.4.5 POST-NATAL CORTICOSTEROIDS IN BRONCHOPULMONARY DYSPLASIA AND ITS EFFECT ON NEURODEVELOPMENTAL OUTCOME

Initial reports indicated that there was significant improvement of BPD in infants following the administration of corticosteroids. However Yeh *et al* reported that although dexamethasone had reduced the incidence of BPD, infants exposed to dexamethasone had higher rates of neuromotor dysfunction (39.7% vs. 17.1%) compared

to placebo controls.[265] When these survivors were re-evaluated at 8 years of age, children who had received dexamethasone were found to have lower verbal, performance and full scale IQ in addition to the persistence of poor motor skills. The mean head circumference and height were also lower for the dexamethasone group.[266]

A recent Cochrane review on the effects of administering post-natal corticosteroids has shown that it reduces the risk of developing bronchopulmonary dysplasia and patent ductus arteriosus. However there are short-term adverse effects which include gastrointestinal bleeding, intestinal perforation, hyperglycemia, hypertension, hypertrophic cardiomyopathy and growth failure. The review found that there is an increased risk of abnormal neurological examination and cerebral palsy with post-natal corticosteroid administration.[267]

However the in the latest trial using dexamethasone to prevent chronic lung disease, it was found that the risk of death, NDI and poor growth were similar between the treatment group and the control group. According to the authors this may be because 49% of the placebo group had received corticosteroids for other reasons during their NICU stay.[268] Currently use of post-natal corticosteroids to prevent bronchopulmonary dysplasia is not recommended.[269]

3.4.6 NECROTISING ENTEROCOLITIS AND NEURODEVELOPMENTAL OUTCOMES

The clinical condition of Necrotizing enterocolitis (NEC) is characterized by ischemic necrosis of the intestinal mucosa and affects about 10-15% of the VLBW infants.[270,242] The severity of NEC depends on the staging initially proposed by Bell and modified by

Walsh and Kliegman[271,272]. Although most cases resolve with conservative management, advanced NEC which can result in bowel perforation would require surgery.

Nursery outcomes

Advances in the neonatal intensive care, earlier diagnosis, and aggressive treatment have improved the outcome of infants with necrotizing enterocolitis. As a result, approximately 70 to 80 percent of infants who have NEC survive.

Survival following NEC depends on the severity of the condition. In a large Western study of about 18,000 infants with NEC there was an overall mortality of 28%, and the mortality was higher (35%) among those who required surgery.[273] Other studies have also shown that mortality is more likely in those who undergo surgical intervention than in infants who undergo conservative treatment.[274]

The mortality decreases with increasing birth weight. This is evident from the data from the Vermont Oxford Network [275] on over 70,000 premature infants which showed that the risk of decreased with increasing birth weight (BW) as follows -

- Birth weight 501 to 750 g – 12 percent risk, 42 percent mortality with NEC
- Birth weight 751 to 1000 g – 9 percent risk, 29 percent mortality with NEC
- Birth weight 1001 to 1250 g – 6 percent risk, 21 percent mortality with NEC
- Birth weight 1251 to 1500 g – 3 percent risk, 16 percent mortality with NEC

Neurodevelopmental Outcomes: Hintz *et al* compared neurodevelopmental and growth outcomes of ELBW infants with surgically treated NEC and medically treated NEC, with infants without NEC in a retrospective study of over 2500 infants from the NICHHD registry. At 18-22 months corrected gestational age, 24% of infants who had surgically managed NEC developed CP, and 37% of those children had cognitive disabilities (MDI

<70, PDI <70) compared to those who did not have NEC. Regression analysis confirmed that surgical NEC was an independent risk factor for neurodevelopmental impairment.[276] Chacko and colleagues[277] demonstrated that the ELBW infants who underwent laparotomy (majority of which was for NEC) had a poor developmental outcome as compared to controls. They speculated that occurrence of NEC and bowel perforations are frequently associated with cardiorespiratory failure and sepsis resulting in metabolic acidosis and hypotension which are in turn associated with poor neurodevelopmental outcomes. Other studies have also confirmed that children with NEC who undergo surgery have a poorer developmental outcomes.[278,279]

A meta-analysis showed that 45% of children who had neonatal NEC had a higher risk of cerebral palsy, visual, cognitive and psychomotor impairment. The infants who have Bell's stage III and those who required surgery had more than twice the risk of neurodevelopmental impairment compared to infants who did not require surgery.[56,280]

NEC especially those which require surgical intervention is associated with neurodevelopmental impairment and so the impact of NEC reaches beyond the gastrointestinal system affecting both neuromotor and cognitive outcomes.[281] The strong association of surgically treated NEC with poor outcome may reflect the fact that the sickest infants are the ones who need surgical intervention and therefore are likely to have post-operative complications which may independently affect neurodevelopmental outcome.[270]

3.4.7 NEONATAL SEPSIS, MENINGITIS AND NEURODEVELOPMENTAL OUTCOMES

Septicemia is one of the most important causes of mortality and morbidity of infants in the NICU.[101,103,242,282,283] The VLBW infants are at risk for both early onset (within 72 hours of birth) and late onset (after 72 hours) sepsis. Rates of infection increase with decreasing birth weight and gestational age.[283] Neonatal sepsis is a bigger problem in Indian NICUs compared to the Western NICUs. Indian studies have shown that sepsis affects 30-50% of preterm or low birth weight infants admitted in the nursery.[89,92,94,106,284,285] In addition to the immediate mortality and morbidity in the NICU, sepsis and its complications result in definite neurodevelopmental sequelae.

Mortality

Neonatal sepsis continues to be one of the primary causes of mortality in neonatal ICUs and particularly among very low birth weight infants. Mortality is almost 25% in early-onset sepsis (EOS) and 18% percent in late-onset sepsis (LOS).[282,286] The Indian studies on ELBW infants have shown a mortality of up to 51%[88,106] Early-onset sepsis is more uncommon than LOS but is a potentially lethal problem among very-low-birth-weight infants. The Western studies have noted that the pathogens have changed from gram positive Group B streptococcus to predominantly gram-negative organisms.[287,288] Mortality due to gram-negative infections is higher than that due to gram-positive infections at all ages of onset of sepsis. Late-onset sepsis that is fulminant (lethal within 48 hours) is more likely to be caused by gram-negative organisms.[289,290] In infants with late onset sepsis, intubation, administration of pressor therapy, hypoglycemia, thrombocytopenia, and development of necrotizing enterocolitis were independent risk factors for sepsis-related death.[289]

Morbidity

Preterm infants with sepsis are at risk for both short-term and long-term complications.

Short-term complications: The experience from the NICHHD suggests that sepsis worsens the risk of PDA, NEC, BPD and increases the duration of ventilation.[291] The mean duration of hospital stay and mortality was higher in infants who had late onset sepsis compared to the uninfected infants.[292]

Neurodevelopmental Sequelae

Sepsis is a risk factor for long-term neurodevelopmental impairment either by direct infection of the central nervous system or indirectly due to inflammation. Infection results in the release of inflammatory cytokines.[55] Cytokines can damage the periventricular white matter directly, or they can destroy the myelin producing cells, or they can provoke the onset of preterm labour or they can damage the germinal matrix leading to intraventricular hemorrhage.[293] So there are multiple ways sepsis can lead to brain damage in the premature infant and consequently leading to poor developmental outcome.[294] Neonatal sepsis is shown to affect the post-natal head circumference in 62% of the infants, thus further contributing to the risk of neurodevelopmental impairment.[295]

In a meta-analysis which pooled the data on 13,755 very preterm and VLBW infants, infants with perinatal infections had poorer mental development ($P < 0.001$) and motor development ($p<0.001$) compared to the very preterm and VLBW infants without infections.[55] Follow-up studies of the EPIPAGE cohort showed that, 9% of the infants who had sepsis, developed cerebral palsy and 12% had cognitive impairment when assessed at five years of age. The risk of developing cerebral palsy after early onset and

late onset sepsis was almost the same (odds ratio of 1.7), however the risk was higher in combined early and late onset sepsis (OR= 2.33).[296]

Another meta-analysis showed that Sepsis in VLBW infants was associated with an increased risk of one or more long-term neurodevelopmental impairments (odds ratio (OR) 2.09).[54]

In a prospective study from the Neonatal Research Network of the NICHHD of over six thousand ELBW infants, survivors who had sepsis as neonates were more likely to have an adverse neurodevelopmental outcome at 18 to 22 months of corrected gestational age. This included higher rates of cerebral palsy, lower Bayley scales Infant Development II scores, and increased vision impairment compared with uninfected infants. In multivariate analyses after adjusting for confounders, children with infection remained at increased risk of MDI <70, PDI <70, CP and NDI.[295]

There is overwhelming evidence that sepsis in newborns particularly in the VLBW/ELBW infants is associated with a high risk of neurodevelopmental impairment and cerebral palsy. The most effective way of avoiding sepsis is to prevent them to the extent possible. The WHO and AAP have recommended measures to reduce infections in the ICU, many of which are simple and cost effective.[297-299] So measures like hand hygiene, judicious use of antibiotics, maintaining sterility while doing invasive procedures, early initiation of breast feeding, kangaroo mother care, surveillance of nosocomial infections and avoiding overcrowding can go a long way in preventing cerebral palsy and neurodevelopmental impairment.

3.4.8 VISION IMPAIRMENT, RETINOPATHY OF PREMATURITY & NEURODEVELOPMENTAL OUTCOME

Retinopathy of prematurity (ROP) is due to the proliferation of aberrant retinal vessels in response to the interruption of normal neuronal and vascular development in preterm infants.[300]

ROP affects a substantial number of premature infants worldwide and its incidence and severity is inversely related to the gestational age.[301] In a population-based cohort study from New Zealand and Australia the overall incidence of severe ROP among infants born at less than 32 weeks' gestation was 10 percent. Severe ROP increased from 3 to 34 percent as gestational age decreased from 27 to 24 weeks, respectively.[301] Multivariate analyses from Western studies have shown decreasing gestational age and birth-weight, prolonged ventilation, surfactant use for RDS and hyperglycemia requiring insulin are strongly associated with ROP.[302–304]

However there is enough epidemiologic evidence which shows that the mean birth weight and the mean gestational age of infants with severe ROP is greater in developing countries compared to that of developed countries.[305–308] A multi-centered study showed that the mean gestational age of infants from developed countries who developed severe ROP was less than 800 grams and that of infants from developing countries was more than 1000 g, suggesting that the risk factors of ROP in developing countries are different from that of developed countries.[307]

The incidence of ROP in India is about 11-44%, the incidence of severe ROP is 8-12%, and the mean birth weight age of Indian babies with ROP is around 1500 g.[131,305,308–310]

The National Neonatology Forum therefore, recommends screening of all preterm

neonates who are less than 34 weeks at birth and have a birth weight of less than 1750 g; as well as babies 34–36 weeks of gestation or 1,750–2,000 g birth weight if they have risk factors for ROP.[311] Multivariate analysis from an Indian study has revealed the following risk factors having an independent effect on ROP - respiratory distress syndrome (adjusted OR=8.1), PDA requiring medical or surgical management (adjusted OR=3.2), and meningitis.[308]

Neurodevelopmental Outcomes

ROP is strongly associated with neurodevelopmental impairment and cerebral palsy.[281] In the multicenter Cryosurgery for Retinopathy of Prematurity Study, a longitudinal cohort of children with ROP was followed up and was assessed at 5½ years of age. Rates of severe disability increased from 3.7% for those children with no ROP to 19.7% for those with threshold ROP.[312] The subgroup of children with threshold ROP in the cohort was reassessed at 8 years. The assessments revealed that children with unfavorable vision had more developmental disability (57% vs. 22%), required special education services (63% vs. 27%), had lower academic levels (39% vs. 15.8%) and cerebral palsy (84% vs. 48%) compared to children with a favorable visual outcome[313] In a study by Schmidt *et al* on ELBW infants with severe ROP (unilateral or bilateral stages 4 or 5), who were assessed at 18 months 10% children had died, 24% children had cerebral palsy, 49% children had MDI <70 and 3.8% children were deaf and 15% were blind.[224]

There are no Indian studies which have looked at the neurodevelopmental outcomes of children with ROP.

3.4.9 HEARING IMPAIRMENT AND NEURODEVELOPMENTAL OUTCOMES

About 1-3% of the infants admitted into the NICU are likely to develop hearing impairment.[314] In a nested case-control Norwegian study, children with birth weights less than 1500 g had a six-fold greater risk for hearing loss compared with children with birth weights 3500 and 3999 g.[315] In Kochi, a community based hearing screening of all infants showed that the incidence of hearing loss among the high risk children was about 1%.[316] Newborn infants with hearing impairment who are not rehabilitated early, will steadily worsen in their language skills, cognitive abilities, and their social skills.[317]

The use of drugs like aminoglycosides & loop diuretics, exposure to the constant background noise generated by life support systems, hyperbilirubinemia, cytomegalovirus (CMV) infection and hypoxia are the main causes of hearing loss in VLBW infants.[44] Hearing loss requiring amplification is more likely to occur in the presence of other neonatal morbidities like sepsis, NEC, brain injury and ROP.[164]

Early detection and rehabilitation of hearing impairment by 6 months of age has a definite advantage for acquiring normal language compared to detection of hearing impairment after 6 months of age. It has also been shown that universal hearing screening in the NICUs in USA has led to earlier diagnosis and intervention and improved language and learning abilities.[318]

3.4.10 PERIVENTRICULAR LEUKOMALACIA

Periventricular leukomalacia is a unique white matter injury which occurs predominantly in the premature infants and subsequently results in cerebral palsy, cognitive impairment and visual disturbances.[319] PVL is more common in premature than in term infants.[320]

The injury of PVL comprises has a focal component which may be cystic or non-cystic and a more diffuse component. The focal component results in localized necrosis of all cellular elements in the deep white matter resulting in cyst formation. If the cysts are visible on conventional MRI or cranial ultrasound it is termed "cystic PVL" and if the cysts are not visible, it is termed "non-cystic PVL". The diffuse component is more cell-specific and involves injury to the pre-oligodendrocytes cells which results in astrocytosis and microgliosis.[321,322]

PVL is a consequence of the unique vascular anatomy of the immature brain, its diminished capacity of autoregulation and the inadequate response to free radical damage. The pathogenesis of Periventricular leukomalacia involves the following processes[323] -

- **Ischemia[322]:** The white matter in the premature infant in supplied by two sets of arteries – short penetrating (which penetrate the subcortical white matter) and long penetrating arteries (that supply the deep white matter). In the premature infants the distal fields of these vessels which supply the periventricular white matter are not well developed. So the regions around the ventricles are vulnerable to reduced blood flow because of the diminished vascularization. A decrease in the cerebral blood flow predisposes these areas in severe ischemia.[322] In addition Positron emission tomography (PET) studies have confirmed that the cerebral white matter blood flow in the preterm brain is much less than that of mature infants or adults.[324] So there is a minimal level margin of safety for blood flow to cerebral white matter in premature infants.

- **Impaired cerebral autoregulation**[321]**:** In mature infants and adults, cerebral blood pressure is maintained despite blood pressure variation due to cerebral autoregulation. However this is not well developed in preterms and so there is reduced perfusion of the brain in times of systemic hypotension. Impaired autoregulation is worsened by perinatal asphyxia, hypotension, hypocarbia and hypoxemia which further aggravate the ischemic damage in preterm brains.
- **Damage of Pre-oligodendrocytes**[325,326]**:** The pre-oligodendrocyte cells (pre-OLs) mature to form the oligodendrocytes - the myelin producing cells of the White matter. Ischemia (due to the impaired vascular autoregulation and the anatomic factors mentioned above), inflammation and asphyxia result in release of cytokines. The pre-OLs are selectively destroyed by the cytokines through free radical mediated mechanisms. Thus loss of the pre-OLs prevents formation of myelin which results in. reduction of white matter volume causing ventriculomegaly.
- **Role of Maternal/fetal infections, inflammation and cytokines:** Chorioamnionitis leads to cytokine production, particularly Tumor Necrosis Factor (TNF-α), which can access the fetal brain and directly damage the pre-OLs of the white matter, or activate microglia and lead to production of oxygen free radicals which also contribute to white matter injury.[293,327] Numerous studies on maternal chorioamnionitis has proven this fact, since chorioamnionitis is very strongly associated with periventricular leukomalacia and cerebral palsy.[328,329]

Neurodevelopmental impairment – Cerebral palsy and cognitive deficits secondary to PVL

Periventricular leukomalacia is strongly associated with cerebral palsy,[330,331] visual insufficiency[332] and cognitive impairments. Studies have shown that the stage of cystic PVL graded according to the de Vries staging, corresponds to the extent of the neuromotor deficit and visual insufficiency, and almost all stage III PVL infants develop CP.[333] The spasticity which characterizes cerebral palsy is due to the necrosis of the periventricular long tracts. The extent of the periventricular white matter loss corresponds to the topography of CP. Children with only posterior periventricular white matter involvement are likely have spastic diplegic type of CP with communicative abilities, while those with periventricular white matter loss extending till the anterior periventricular region are likely to be severely disabled with quadriplegia, visual insufficiency and seizures.[334]

Cognitive impairment in PVL

The periventricular white matter damage explains the spasticity present in cerebral palsy but is not sufficient to explain the existence of grey matter (GM) disease which manifests as cognitive and behavioral deficits.

Cognitive deficits in PVL are related to injury to the thalamus, thalamocortical pathway and cortical grey matter. Pathologic studies have shown that there is greater neuronal loss in the thalamus (38%) as compared to the cerebral cortex in the children who have PVL.[335] It has also been shown that thalamic reduction correlates with the deficits in working memory and intelligence in school going children with PVL.[336]

In addition to thalamic volume loss, cognition is also dependent on the extent of the grey matter involvement which occurs concomitantly with the white matter injury. Grey matter loss in the frontal and temporal regions correlates with decreased verbal IQ and grey matter volume loss in temporal and occipital regions corresponds to decreased diminished performance IQ.[337] In addition to cognitive impairment, thalamic injury also contributes to spasticity since damage to the thalamocortical pathway is hypothesized to alter the connections between the sensory and motor cortex and the cortico-spinal tracts. Cortico-spinal tract injury leads to spasticity.[338] During the third trimester, when PVL is most likely to occur, the thalamocortical system is also developing, thus thalamic and cortical injury during this critical period could explain the cognitive deficits in the children with PVL.[320]

3.4.11 INTRVENTRICULAR HEMORRHAGE

Intraventricular hemorrhage is a life-threatening complication of premature infants. In a large cohort of the NICHHD, 16% of the babies less than 1500 g had severe IVH. The incidence of IVH increases as the gestational age decreases and the incidence was 38% in infants of 22 weeks compared to 7% in infants of 28 weeks.[34] In a study in South America using a multiple logistic regression model the following risk factors were found to be predictive of severe IVH – decreasing gestational age, mechanical ventilation, non-administration of antenatal corticosteroid, male gender and presence of respiratory distress syndrome.[339]

The pathogenesis of IVH in preterm infants is because of two main factors – the fragility of the germinal matrix system and disturbances in the cerebral blood flow (lack of autoregulation).

- **Fragility of germinal matrix**[340,341]**:** IVH usually starts in the sub-ependymal germinal matrix which is located between the caudate and thalamus. This highly vascular region contains glial and neuronal precursor cells. Unlike the other blood vessels in the brain the capillaries of the germinal matrix are very fragile and thin walled, because they lack pericytes, have poorly developed basal lamina, have deficient endothelial tight junctions and lack astrocyte end-feet ensheathing.[239] These fragile capillaries drain into the venous system. When the cerebral blood flow increases in response to hypoxia, hypercapnia or when there is a venous stasis due to hypotension, the fragile germinal matrix capillaries rupture. When there is a large bleed the ventricles fill with blood.
- **Lack of autoregulation**[323,325]**:** Unlike term infants, preterms lack the capacity of cerebral autoregulation and therefore are vulnerable to changes in the systemic blood pressure. So increase or decrease in systemic blood pressure can injure the capillaries in the germinal matrix causing bleeding into the ventricles. IVH is thus a progression of germinal matrix hemorrhage

The **short term complications** of IVH are post hemorrhagic hydrocephalus (PHH), periventricular leukomalacia and death. PHH occurs because the small blood clots caused by the IVH block CSF reabsorption.[342] About 5% of infants with Grade 1 and 2 IVH die and PHH develops in about 7%; in contrast severe IVH has a mortality of 20% and PHH develops in about 75% of the infants.[343] Intraventricular hemorrhage releases large

amount of iron moieties which generate free oxygen radicals which can cause injury to the pre-oligodendrocytes.[322] and IVH also results in ischemia. Both these can lead to periventricular leukomalacia.[327]

Long term complications: Intraventricular hemorrhage is an important cause of neurodevelopmental impairment. More than 75% of children who have severe IVH have cognitive impairments and cerebral palsy.[327] Studies have also shown that the odds ratio of developing cerebral palsy after surviving severe IVH is about 15.9 and that of mental retardation is between 9.97 and 19.[344,345] Although it is seen among the more premature infants, IVH is a stronger predictor of poor long term neurodevelopmental outcomes than gestational age.[346] Another large cohort study which looked at the cognition of children at 8 years found that, the adverse outcomes depended on the type of the intracranial lesion (PVL or IVH) rather than on the gestational age,[347]again highlighting that the neurodevelopmental outcomes depend more on the presence of IVH or PVL rather than the gestational age.

3.4.12 CEREBRAL PALSY

Cerebral palsy is a group of heterogeneous, non-progressive disorders of tone and posture due to injury to the developing brain. The Executive Committee for the Definition of Cerebral palsy in 2005 defined CP as "*group of disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behavior and/or by a seizure disorder*".[348]

Epidemiology

- **Europe:** According to information obtained from a large database comprising more than 6000 children with CP, obtained from 13 different regions of Europe, the overall prevalence of CP was 2.08/1000 between 1980 and 1990.[349]
- **USA:** A population-based American study reported that the prevalence of CP at eight years of age was 3.6 per 1000 children.[350]
- **Surveillance of Cerebral Palsy in Europe** (SCPE) which is an European collaborative network of cerebral palsy registers reported a prevalence of 72.6 per 1000 infants (who were alive at one month) among VLBW infants, compared to 1.2 per 1000 among infants of birth weights more than 2500 g.[351]
- **India:** There is only one population based study from India and the prevalence of CP in less than 10 years of age is believed to be about 2.27/1000.[134]

Etiology of cerebral palsy

The etiology of cerebral palsy (CP) is multifactorial. The known causes account for only a small proportion of cases.[352] Prenatal, perinatal and post-natal etiologies are known to result in the clinical syndrome of CP. Prematurity is a common association in Western countries. In developing countries the most common causes are perinatal asphyxia, perinatal and neonatal infections, kernicterus and prematurity.

Table 5 shows the multifactorial etiology from a study of 213 children diagnosed to have CP in Australia, compared to the two studies from India by P. Singhi *et al* in 2002 and 2013. Some of the children had more than one associated pathology. There is an increase in the prevalence of CP due to VLBW and prematurity in the later (2013) cohort.

Table 5: Etiology of Cerebral Palsy in India compared to Australia

	Strijbis EM *et al* [353]	P.Singhi *et al* [135]	P. Singhi *et al* [136]
No. of cases	**213**	**1000**	**1212**
Prematurity	78%	13.2%	24.3%
Multiple pregnancy	20%	1.2%	3.4%
IUGR	34%	Not mentioned	Not mentioned
Intrauterine infection	28%	Not mentioned	Not mentioned
Antepartum hemorrhage	27%	Not mentioned	Not mentioned
Severe placental pathology	21%	Not mentioned	Not mentioned
Kernicterus	0%	21.6%	35.1%
Neonatal seizure	Not mentioned	25.2%	26.9%
Neonatal sepsis	Not mentioned	14.6%	30.6%
Low birth wt.	Not mentioned	20.4%	37.8%
Asphyxia	2%	45.3%	51.98%

Cerebral Palsy in the VLBW infants

Cerebral palsy in the VLBW infants is due to brain damage which occurs due to antenatal factors, or complications of prematurity or probably a combination of both.[36]

A study which compared the VLBW children with CP to VLBW children without CP the following factors were associated with CP [354] -

- Place of delivery: Odds ratio of developing CP was 6.3 in children born in primary care (level 1 neonatal center) compared to a specialized level 3 neonatal center
- Pre-eclampsia and exposure to Magnesium sulphate was associated with a reduced risk of developing CP (OR 0.08)

- Maternal chorioamnionitis and neonatal seizures were strongly associated with CP.
- Notably asphyxia was not associated with CP in this study,
- Other factors which showed significant associations with the presence of CP were short inter-birth intervals and antepartum hemorrhage

Germinal matrix/ intraventricular hemorrhage and its sequelae and periventricular leukomalacia are the most common pathologies associated with CP in the very low birth weight infants and white matter damage is the most important antecedent of cerebral palsy.[355,356]

The rate of CP is much higher in preterm than term infants and this is illustrated by the following studies -

1. In a population-based study from Sweden of 216 children with CP born between 1987 and 1990, the gestational-age specific prevalences were 80/1000 for extremely preterm, 54/1000 for very preterm, 8/1000 for moderately preterms and 1.4/1000 for term infants. Birth weight-specific prevalences from the same study were 57/1000 for birth weights <1000 g, 68/1000 for 1000-1499 g, 14/1000 for 1500-2499 g and 1.4/1000 for ≥2500 g.[357]
2. Multiple studies from various large cohorts have shown that the incidence of CP is 18-23% in extremely premature infants[125,358-360] and the incidence increases as the gestational age decreases. Very low birth weight infants are hundred times more likely to develop cerebral palsy compared to infants whose birth weight are more than 3000 g.[361]

However in India it is likely that perinatal factors like perinatal asphyxia and neonatal factors like meningitis and kernicterus also contribute substantially to CP in VLBW infants.[136] A much smaller contribution may be because of prenatal factors like cerebral dysgenesis and possibly chromosomal factors Although VLBW infants only contribute to 3.4% of the total births[13] in India, with the improving survival rate among the VLBW, it is probably one of the largest causes of cerebral palsy and disability.

This concludes the Literature review. In the above four sections – the ***first*** section was about the survival and the ***third*** section was about the neurodevelopmental outcomes of VLBW infants from India and other countries. The Indian studies were compared to Western countries. There is limited data from India about the survival and neurodevelopment of very low birth weight infants. The ***second*** section reviewed the need and the components of a dedicated follow-up program. Finally in the ***fourth*** section, some of the important complications in the neonatal period which affect the survival and the neurodevelopmental outcomes of VLBW infants were highlighted. With this information we went ahead to do the study to look at the incidence of death and poor neurodevelopmental outcomes of our cohort of VLBW infants and to see if the aforementioned neonatal factors influenced their survival and long term outcomes.

PATIENTS AND METHODS

Ms. Hima (Occupational therapist) checking the “Eye-Hand Coordination”

4 PATIENTS AND METHODS

(The information presented in this section is as per the **STrengthening the Reporting of OBservational studies in Epidemiology (STROBE)** guidelines**.**[362,363]**)**

4.1 STUDY DESIGN

This study was ***an observational study - the longitudinal follow-up of a cohort of very low birth infants*** who were admitted into Neonatal Intensive Care Unit (NICU) of the Christian Medical College (CMC) hospital, a tertiary level referral hospital.

4.2 PARTICIPANTS

There were 776 VLBW infants in the study with birth weights ***equal and less than 1500 g.*** (Although by definition, VLBW infants are less than 1500 g, those who were equal to 1500 g were also included since most major studies include babies weighing 1500 g in their cohorts)

4.3 SETTINGS

The recruitment of the study cohort was done between the time period September 1, 2010 and 31st March 2012 and the follow-up phase concluded in November 2014. The study was conducted using the facilities of the Neonatal ICU (Nursery), the High Risk Infant Clinic and the Developmental Pediatrics Unit of the Christian Medical College, Vellore.

4.4 FOLLOW-UP PROTOCOL and OUTCOMES

The infants were recruited after consent from the parents. They were followed up until the final neurodevelopmental assessment.

The study ***had two phases*** -

Phase 1: The first phase was from the time of ***admission to the NICU till the time of death or discharge*** from the NICU.

Phase 2: The second phase was the follow-up phase which started after ***discharge from the NICU till their final neurodevelopmental assessment.***

For the first phase ***death in the NICU*** was the outcome. For the second phase the neurodevelopmental outcome gauged by the ***General quotient (GQ)*** obtained on the neurodevelopmental assessment scale – Griffith's Mental Developmental Scales (GMDS) was the outcome.

4.5 INCLUSION & EXCLUSION CRITERIA

The inclusion and exclusion criteria for Phases 1 and 2 are presented below:

	INCLUSION CRITERIA	EXCLUSION CRITERIA
Phase 1	1. All live VLBW infants born at the Christian Medical College 2. Out – born infants who were referred for the NICU care within 24 hours of birth, with birth weight ≤1500	VLBW infants who were born with significant anomalies which were incompatible with survival beyond few hours
Phase 2	Infants who were discharged from the neonatal ICU after phase 1, whose parents were willing to bring them, for regular follow-up till the period of final assessment	Infants whose parents were not willing to come for subsequent follow-up.

4.6 PLAN OF THE STUDY

4.6.1 Phase 1: NICU PHASE

During their stay in the NICU the following details of the infants were recorded.

Details of the mother and her antenatal period: The demographic details of the mother, her prior pregnancies, previous medical and obstetric complications, details of the antenatal period were collected by interviewing the mother and from the Obstetric records

Details of the perinatal period – Details pertaining to the infant's birth, resuscitation, APGAR score, progress in the NICU and the neonatal complications were obtained by reviewing the Neonatal records. The treatment and interventions during the period of stay in the neonatal ICU were as per the existing treatment protocols of the Neonatal ICU.

Gestational age estimation: Gestational age was estimated from the early ultrasound scans or in the absence of ultrasonography was calculated from the mother's last menstrual period. In exceptional cases when both of the above were unavailable or unreliable, the gestational age was estimated post-natally using the Dubowitz examination technique.

Small for gestational age was defined as weight less than the 3rd percentile of gestational age using the fetal growth curves of Fenton *et al*.[364]

Definitions: The definitions of the antenatal factors, perinatal, neonatal and other variables used in the study are presented in the **Appendix section**.

Screening of the eyes for the evidence of retinopathy of prematurity was done by the same ophthalmologist. The screening and subsequent follow-up were done according to the protocols of the Pediatric Ophthalmology department and the National guidelines.[311]

The Hearing screening was done as part of the neonatal hearing screening that exists in the Institution. All infants admitted in the NICU were screened for their hearing at 35 dB on both sides, using Neonatal automated Auditory Brainstem Response (ABR). In infants who failed the first screening, a second screening was done after two weeks. If the infant failed the second assessment then a detailed hearing assessment which involved Brainstem Auditory Evoked Response (BAER) and Oto-acoustic Emissions (OAE) was done.

Serial Cranial ultrasound examinations (Neurosonogram) were done in all the very low birth infants to look for any evidence of intra-ventricular hemorrhage, periventricular leukomalacia and ventricular enlargement, as per the usual protocol practiced for all the VLBW babies. The existing practice of the NICU was that two serial scans are done, the first scan within 72 hours of birth and the second between days 7 and 10. A third scan was done 4-8 weeks after birth.

Counseling the parents for consent to participate in the follow-up phase of the study

During the hospital stay, the parents were counseled about the need for careful follow-up of the infants after discharge and signed consent was obtained from the either of the parents. Although what was done during the period of the study was the standard of care in this institution, informed consent for participation was obtained prior to discharge from

the NICU from one of the parents. By institutional policy most infants are discharged only after they had attained a weight of 1800 grams.

4.6.2 Phase 2: CONDUCT OF THE FOLLOW-UP PHASE

The infants were recruited into the study during their stay in the Nursery. Parents who had given their signed consent could withdraw from the study at any point. The usual practice of the institution is that all high risk infants (which include the VLBW infants) are followed up regularly at the High risk infant clinic (HRIC) run by the Neonatology department until they reach one year of age. At any point if they are detected to have developmental delay and they require developmental stimulation or early intervention, they are then referred to the Developmental Pediatrics Unit. Infants who were recruited into the study were seen by me (the Principal Investigator) on a regular basis in the High risk infant clinic during their follow-up visits.

During the High risk Infant Follow-up visit

- The anthropometric measurements was recorded, and the neurologic examination was done as described by Amiel-Tison[187,365] during every visit.
- Weight was measured using electronic weighing machines which were regularly calibrated. Supine length was measured using an Infantometer and the head circumference was measured using a non-stretchable tape.
- The neurological examination was performed as described by Amiel-Tison[187,192] and this included evaluation of the muscle tone, power, Amiel-Tison angles and posture. The infants were considered neurologically normal if there was no abnormality on the examination. The diagnosis of cerebral palsy was made based

on the definition of Bax and associates.[348] A child was considered to have CP if there was abnormal muscle tone (spasticity, dystonia) at least in one limb and if there was abnormal control of movement and posture.

- Children with CP were classified as per the Surveillance of Cerebral Palsy in Europe (SCPE) algorithm.[366] Functional classification was done according the Gross Motor Functional Classification System (GMFCS) described by Palisano *et al.*[367]
- At any point during the follow-up, if there was any indication of developmental or cognitive delay, early intervention was commenced by the psychologists and the therapists of the Developmental Pediatrics Unit.
- Children were referred to other Pediatric specialists for further evaluation as and when required.

4.7 NEURO-DEVELOPMENTAL ASSESSMENTS

A. Amiel-Tison Neurological Assessment

Amiel-Tison Neurological assessment (ATNA) is a simple and time-tested neurological assessment method which can be performed as part of the routine examination of an infant.[186,192,365] The assessment includes assessment of the head growth, neurosensory function and spontaneous motor activity, the passive muscle tone, the primitive reflexes, assessment of the baby's adaptation to manipulation during examination and feeding autonomy. The Amiel-Tison neurologic examination is the standard examination technique in many of the studies on the neurodevelopmental outcomes of high risk infants (which include VLBW babies). The great advantage of this neurologic

examination is that the same procedures can be used for examination from term gestational age till the school going age. Therefore the child can be followed up with the same protocol.[192]

Depending on the child's abilities in the various functions, the child is scored from 0 to 2. A score of "0" indicates that the function is judged to be optimal. A score of "1", indicates a minor to moderate grade of neurologic abnormality and a score of "2" indicates a severe grade of neurologic abnormality.

For a child between 10-24 months the table below, defines normal and mild, moderate deficit and severe deficit.

Table below was taken from, Amiel-Tison C and Gosselin J "Neurologic development from Birth to Six years"[192].

SECTIONS (or FUNCTIONS)	SCORE
. **1. Head growth** (Head circumference, palpable sutures) **2. Social interactions** (alertness & attention, visual tracking and excitability) **3. Passive muscle tone** (limbs and trunk) • Trunk imbalance • Stretch Reflex in limbs Hypotonia of rigidity **4. Involuntary movements** **5. Parachute reflex** (scored according to age of acquisition) **6. Gross motor skills** (scored according to age of acquisition) • Head control • Sitting position **7.Independent walking**	
Scoring **Severe deficit:** Score of 2 in at least six of seven sections; **Moderate deficit:** Score of 1 in five of seven sections; Normal or Mild deficit if the scores are mainly 0	

B. Peabody developmental Motor Scales[368]

At one year corrected age, the infants recruited for the study were assessed using the Peabody Developmental Motor Scales (PDMS) by the Occupational therapist involved with the study.

The Peabody Developmental Motor Scales - Second Edition (PDMS-2) is a standardized and norm-referenced test of the gross motor and fine motor skills for American children. The PDMS is composed of six subtests that measure the fine and gross motor abilities of children from birth through five years. The six sub-tests are -

Reflexes sub-test: measures the appropriateness of the primitive reflexes in infants less than one year.

Stationary sub-test: checks the ability of the infant to maintain equilibrium.

Locomotor sub-test: Looks at the development of ambulation – crawling, creeping, walking and running

Grasping sub-test: Looks at the development of grasp from the primitive palmar grasp to the development of complex action with the fingers (like buttoning etc.)

Object manipulation sub-test: this scale checks the ability of infants to handle objects appropriate for their developmental age.

Visual-Motor Integration sub-test: this scale measures the ability of the children to use their hands and their eyes in activities like building blocks, catching and the hand-eye co-ordination.

Based on the performance in the above six sub-tests ***a gross motor quotient (GMQ), a fine motor quotient (FMQ) and a total motor quotient (TMQ) can be estimated. The TMQ is a composite of the overall motor abilities of the child.***

Although PDMS is not validated in the Indian population, it has been used in India. A study showed that there were differences in the performance of Indian children compared to the American norms but the differences were within 0.5 SD.[369] According to the administration manual less than 1 SD (TMQ of <90) on the American norms is considered abnormal.

In our study the TMQ which is a continuous variable was collapsed to a categorical variable and TMQ of >90 was considered normal and TMQ of less than 90 was considered abnormal. We used the PDMS for the interim assessment of the motor development of the study cohort at one year of corrected gestational age. The Occupational Therapist who was involved with the administration of the PDMS has several years of experience in assessment of newborns and infants.

C. The Griffiths Mental Development Scales[161]

The Griffiths Mental Developmental Scales (GMDS) are used to measure the developmental abilities of children from birth to 8 years of age. Currently there are two sets of Scales - for the age group 0-2 years (Griffiths Mental Developmental Scales, 0-2 years) and for the ages 2-8 years (Griffiths Mental Developmental Scales Extended Revised).[162,370]

In the first scale (the Griffiths Mental Developmental Scales 0-2 years), an overall developmental profile is obtained from the five subscales examining the Locomotor abilities, Personal-Social abilities, Language abilities, Eye-and-Hand Coordination abilities and Performance abilities. In the 2-8 year Scales (Griffiths Mental

Developmental Scales Extended Revised), in addition to the above mention five sub-scales, the profile is expanded to add a Practical Reasoning Subscale.

A brief description of the Subscales

Sub-scale A - Locomotor: This sub-scale assesses skills in the gross motor domain. The scale tests the ability to balance, coordinate and control movements, walk upright and tests the motor tasks which increase in complexity as the child grows (like running, jumping, skipping etc.).

Sub-scale B - Personal-Social: Initially assesses the interaction with the mother, object permanence and as the child becomes older it assesses the competence in activities of daily living and interaction with caregivers and other children.

Sub-scale C - Language: This scale assesses the Receptive and expressive language. Initially this includes the child's response to familiar and unfamiliar sounds, later ability to vocalize, listen to instructions and stories, use of words, phrases and sentences and social use of language.

Sub-scale D - Eye and Hand Co-ordination: This scale assesses the fine motor skills, initially grasping and manipulating objects. Later complex activities of manual dexterity and those which require visual-motor coordination (like writing and drawing shapes) are assessed.

Sub-scale E - Performance: This scale assesses the speed of working, spatial concepts and precision in new situations.

Sub-scale F - Practical Reasoning: This scale is scored only for children over two years of age and checks the ability to solve practical problems

The ***sub-quotient*** for each of the above sub-scales can be obtained using the appropriate Analysis manual. ***The General quotient (GQ) which is the composite of all the sub-quotients is then estimated. The GQ is used as an indicator of the child's overall developmental abilities.***

The GMDS scales can only be used by Pediatricians and Psychologists who are certified after completing the training course accredited by the Association for Research in Infant and Child Development (A.R.I.C.D), UK.

The GMDS is not standardized for the Indian population. So the children were compared to the standards of the norms given in the Analysis manuals.[162,370,371] The mean sub-quotients and their standard deviations are different for the various subscales are shown in **table 6**. Sub quotients which are more than 2 standard deviations below the mean indicate significant developmental delay in that particular sub-scale. General quotient of more than 2 standard deviations below the mean indicates global developmental delay.

Table 6: Means and Standard Deviations of the Sub-quotients and General Quotient of the GMDS

SUB-SCALES (DOMAINS) IN THE GMDS	0-2 YEARS			2-8 YEARS		
	Mean	SD	<2SD	Mean	SD	<2SD
LOCOMOTOR-Sub-quotient	100.2	15.9	**<68**	100.41	16.32	**<67**
PERSONAL SOCIAL Sub-quotient	101.1	16.3	**<67**	100.26	16.20	**<67**
HEARING & SPEECH Sub-quotient	100.6	16	**<68**	99.78	17.75	**<64**
EYE-HAND COORDINATION Sub-quotient	100.2	15.9	**<68**	100.46	15.58	**<68**
PERFORMANCE Sub-quotient	100.4	16	**<68**	99.87	17.21	**<64**
PRACTICAL REASONING Sub-quotient	-	-	**-**	99.79	17.43	**<64**
GENERAL QUOTIENT	100.5	11.8	**<76**	100.18	12.76	**<74**

The Griffiths Mental Development Scales (GMDS) was selected as the assessment tool for this study because it has been used very widely in the assessment of infants and

children for over 30 years.[145] The GMDS was administered by Psychologists of the Developmental Pediatrics Unit who along with the Principal Investigator are certified to use the GMDS and have over seven years of experience in administering it to infants and children. Although the GMDS is not standardized in India this was preferred over the Developmental Assessment Scale for Indian Infants (DASII)[163] predominantly because of our experience and competence in using the GMDS. The GMDS has been extensively used in infants including in the assessment of ELBW and VLBW infants.[372–374] The DASII, based on Bayley Scale of Infant Development (BSID) has been standardized only on a small population of children from Western India.[76,375]

Blinding was not possible because developmental follow of high risk infants is part of the regular standard of care. So, the principal investigator, the neonatologists, psychologists, occupational therapists and the other clinical specialists were familiar with most children.

Categorization of General Quotient: The General quotient (GQ) and the sub-quotients of the sub-scales are continuous variables. For the purpose of analysis, the GQ was considered a categorical variable with 2 categories

- ***Good Neurodevelopmental outcome*** **(GQ ≥2SD or GQ ≥76)**
- ***Poor Neurodevelopmental outcome*** **(GQ <2SD or GQ <76)**

These were the final outcomes of the second phase of the study. We chose less than 2SD as the cut-off to decide between good neurodevelopmental outcome and poor neurodevelopmental outcomes since 2SD is accepted as the cut-off level for developmental delay in most psychometric tests.

Children detected to have developmental delay: If any infant was detected to have developmental delay, appropriate therapy was started and the child was asked to come for regular developmental monitoring to the Developmental Pediatrics Unit. Although this was not part of the study protocol, these children were regularly seen by the members of the team and the appropriate intervention was provided.

Correction for gestational age: Although correcting for prematurity is controversial, in our study all infants were corrected for prematurity till 36 months of age as advised by Maureen Hack[156] There were four infants who were more than 36 months at the time of assessment. The oldest infant was 42 months of age. For the sake of uniformity, correction of gestational age was done for them as well. There was two to four points difference in the General quotient when correction was applied and when correction was not applied. The correction did not affect the categorization of three of the four children (who had good neurodevelopmental outcome even without the correction for prematurity). However for one child if correction had not been applied he would have moved to the poor neurodevelopmental outcome group.

Monitoring of anthropometric measures: Weight, length and head circumference were recorded during every visit. The measurements of these parameters obtained at the time of the final assessment were expressed as Z scores with reference to the WHO multicenter growth reference study (MGRS) using the WHO "ANTHRO" software.[376]

The study for was considered as "completed" when the Griffith's Mental Developmental Scales (GMDS) assessment was over.

4.8 OPERATIONAL DEFINITIONS OF OUTCOME MEASURES

Normal development: Developmental quotient of within 2SD of the mean of the General quotient.

Poor Neurodevelopmental outcome (which indicates significant developmental delay): General Quotient (GQ) 2SD below the mean on the Griffith's Mental Developmental Scales was considered as the definition for 'Poor neurodevelopmental outcome'. Thus ***GQ of <76*** in the children 24 months and less, and ***GQ <74*** in children over 24 months was considered as indicative of Poor neurodevelopmental outcome **(Table 6).**

Neurological abnormality (decided based on the Amiel-Tison Neurological Assessment-ATNA): Using the scoring system described above the child was ***graded as neurologically abnormal if the child had moderate to severe deficits and normal if the child had only mild or no deficits.***

Cerebral Palsy: Non-progressive central nervous disorder characterized by abnormal tone in at least one extremity and abnormal control of movement and posture.

Visual impairment: A vision of less than 6/60 in both eyes with spectacles

Hearing impairment: Bilateral impairment requiring hearing aids or auditory thresholds of above 70 dB in both ears, obtained by using Brainstem auditory evoked response (BAER)

THE STUDY WAS APPROVED BY THE INSTITUTIONAL REVIEW BOARD (ETHICS COMMITTEE) OF THE INSTITUTION.

Table 7: Brief summary of how the study was conducted

Phase 1: Nursery	Data collection (antenatal, perinatal, neonatal stay in NICU) Consent for participation	
Phase 2: High risk clinic and Developmental Pediatrics Unit	**Tests administered**	**Interventions (as required)**
Multiple visits to the HRIC for follow-up depending on the infants' needs.	• Growth monitoring • Neurologic assessment using the Amiel-Tison Neurological assessment (ATNA)	1. Address Parental concerns 2. Developmental screening 3. Treat medical problems 4. Rule out sensory problems 5. Refer to appropriate specialist 6. Developmental assistance by the developmental Psychologist and Occupational Therapist (early intervention) 7. Family counseling and support 8. Anticipatory guidance
At one year (Corrected gestational age)	• Growth monitoring • ATNA • Peabody Developmental Motor assessment	
After 18 months (corrected gestational age)	• ATNA • Neurodevelopmental assessment using GMDS • Z-scores of weight, height and head circumference obtained using the WHO-ANTHRO software	

4.9 STATISTICAL METHODS

4.9.1 CALCULATION OF SAMPLE SIZE

Sample size to determine the incidence of poor neurodevelopmental outcomes:

According to Escobar *et al*'s meta-analysis[59] (looking at the outcome of VLBW infants in over 100 studies), the median incidence of disabilities was 25%.

So Sample size (n) = $\frac{(z_{1-\alpha/2})^2 \times pq}{d^2}$

Where level of significance ($z_{1-\alpha/2}$) is 1.96 (for α of 5%)

P is 25%,

q is (1-p) = 75%

d is the level of precision and is taken as $\pm$ 5%

So sample size was calculated as **288 and when** adjusted for a drop out of 30% then the required sample size was **374**

Sample size to determine the relationship between perinatal and neonatal risk factors which lead to poor neurodevelopmental outcomes:

The sample size for various risk factors is presented in **table 8**. Risk factors which were considered were those known to have a significant association with poor neurodevelopmental outcome. These are (1) cranial ultrasound abnormalities particularly cystic periventricular leukomalacia and intraventricular hemorrhage (Grades III and IV)[330] (2) severe necrotizing (>Grade 2) enterocolitis[279] (3) Maternal chorioamnionitis[328] (4) extremely low birth weight (birth weight of less than 1000 g)[212] (5) Hypoglycemia.[377]

In infants with cranial ultrasound abnormalities, nearly 92% of have significant disabilities.[330] Low birth weight infants in general have disability of about 25%. In order to show that the difference is statistically significant with alpha and beta errors at 5% and 20% respectively, we had to study 10 children in each group. Similarly for children with the risk factors ELBW, NEC Hypoglycemia and Chorioamnionitis, we required to study 86, 30, 30 and 83 children in each group (risk present and absent) respectively (**table 8**). Thus we anticipated that the sample size of 374 (obtained for the Objective 1) which would have nearly 94 infants with poor neurodevelopmental outcome (given that 25% of VLBW have poor outcome) and would be sufficient to meet the sample size of the second objective

Table 8: Sample size calculation for hypotheses testing for risk factors.

Two-proportion hypothesis testing	Abnormal Cranial US	ELBW	Severe NEC	Hypoglycemia	Chorioamnionitis
Proportion in group I	0.25	0.25	0.85	0.75	.5
Proportion in group II	0.92	0.49	0.45	0.25	0.25
Estimated risk difference	-0.67	-0.24	0.4	0.5	0.25
Power (1- beta)%	80	80	80	80	80
Alpha error (%)	5	5	5	5	5
1 or 2 sided	2	2	2	2	2
Required sample size for each arm	7	62	21	14	58
Drop out Adjusted (30%)	10	86	30	20	83

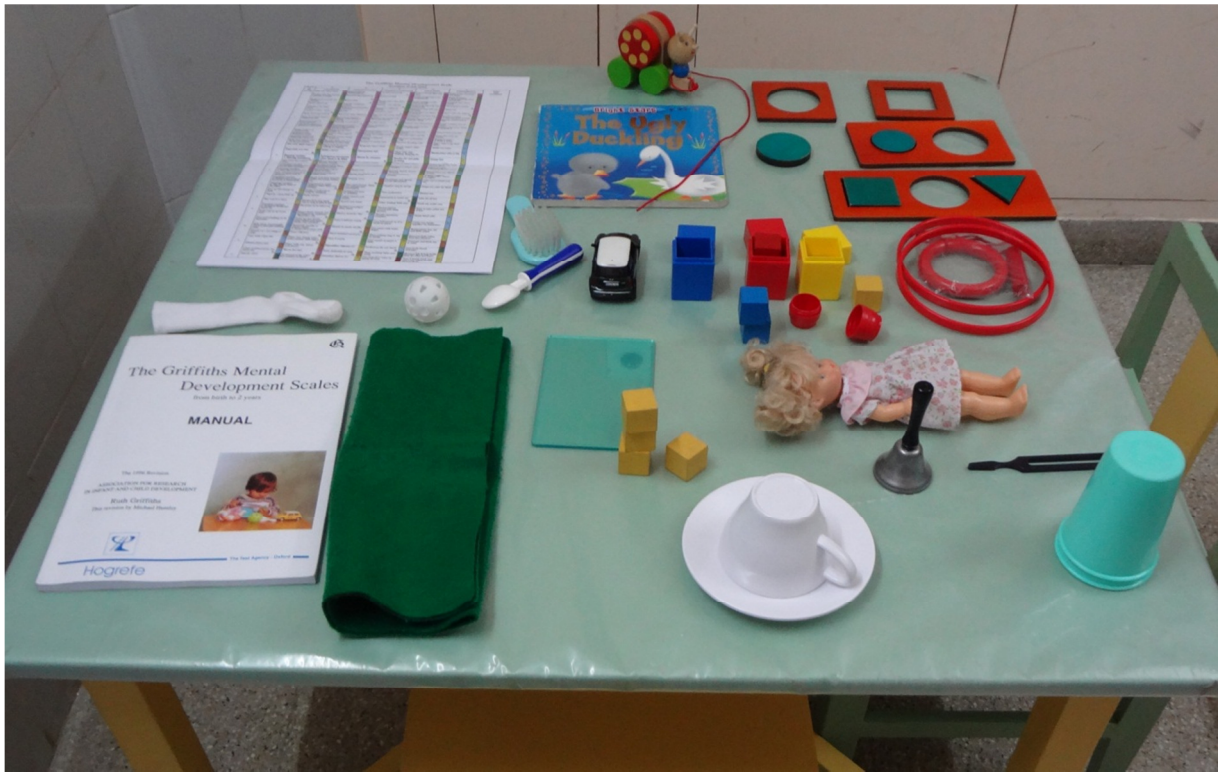
4.9.2 STATISTICAL PROCEDURES USED FOR THE STUDY

- Data was collected on a proforma and the information entered into the EPIDATA database. All the risk factors were defined using standard definitions obtained from renowned textbooks. The operational definitions of each variable are presented in the "Appendix section".

- The incidence of the outcomes (death, developmental delay and CP) are presented with 95% confidence interval.
- Variables are summarized with descriptive statistics (mean, median in cases where the distributions are not normal & standard deviations).
- Continuous variables were checked for normality by visually inspecting the histograms and using the tests for normality (Kolmogorov-Smirnov p-values and Shapiro-Wilk p-values).
- Difference in means between continuous variables were tested using independent sample t-tests or Mann–Whitney U tests (where normality assumptions were violated).
- Kruskall-Wallis test was used to test multiple groups when the distributions were skewed. Outliers were not included in some of the analyses and are mentioned.
- Actual p-values were reported.
- Bi-variate analyses using Chi-square test (or Fisher's exact test) was done to study the significant associations between dichotomous risk factors and outcomes. Relative risks were computed to describe the associations.
- Continuous variables were categorized in certain cases and are mentioned. 95% confidence intervals (95% CI) were used to express the precision of relative risks and odds ratios.
- P-values of <0.05 were considered significant on bivariate analyses and the associations were explored further using step-wise multivariate logistic regression analysis. The final model was one in which the predictors remained in the model if the p-value was <0.05.

- Model assumptions and fit were evaluated using Hosmer and Lemeshow Goodness of Fit statistics and p-value of >0.05 was considered as good fit. The best model is presented with adjusted Odds ratios and 95% CI.
- Kaplan–Meier analysis was used to estimate the survival of the infants in NICU. Risk of death was compared between groups with the risk factor and the group without the risk factor. Risk of death was compared between the groups using the Log-rank test. P-value of <0.05 was considered significant risk.
- Cox proportional hazard analysis was used to estimate the relation of specific risk factors with the time to death. Cox regression was done after checking proportionality of the hazards using the log-log plots. The best model is presented with adjusted Hazards ratios and 95% confidence intervals.
- The subjects who did not come for the final assessment were compared with the subjects who came for the final assessment to see if there were any significant differences between the groups.
- Sensitivity analysis was done to see if the subjects who did not come for the final assessment would have affected the results using "best case" and "worst case" scenarios. For the "best case" scenario, those who did not come for the assessment were considered as having a good neurodevelopmental outcome. For the "worst case scenario" those who did not come were considered as having a poor neurodevelopmental outcome. For both assumptions relative risks with 95% CI were calculated. The two groups were then compared with the children who came for the final assessment to see if there was any difference between the groups.
- All analyses were done using the SPSS package 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS



Griffiths Mental Developmental Scales

5. RESULTS OF THE STUDY

The Results are arranged in four sections **-**

Section 1 - The Results of Phase 1 (the NICU phase): This section presents the details of the ***maternal characteristics, perinatal risk factors and neonatal complications and the outcome of the infants in the NICU*.** The final outcome of this part of the study was ***death in the NICU.***

Section 2 -The Results of Phase 2 (the follow-up phase): The second section looks at the developmental follow-up of those who were discharged alive from the NICU. ***This section addresses the main objectives of the study – the incidence of CP and poor neurodevelopmental outcome and the factors which are associated with the poor neurodevelopmental outcome.*** The Neurodevelopmental outcome gauged by the ***General Quotient (GQ)*** obtained from the Griffith's Mental Developmental scales (GMDS).

Section 3 – Comparison of SGA versus AGA infants: This section compares the survival and the developmental outcome of children who were born small for gestational age **(SGA)** with those who were appropriate weight for gestational age **(AGA)**. The ***Third percentile of birth weight on the Fenton Charts*** were used to categorize the infants into SGA or AGA.

Section 4 – Analysis of the children who were lost to follow up: This section accounts for children who were lost to follow-up. ***This section explores what difference the inclusion of those who did not come for the assessment would have made to the study results through a sensitivity analysis.***

5.1 SECTION 1: THE RESULTS OF PHASE 1 - THE NICU PHASE

This section discusses the details of the babies during their stay in nursery, from the time of birth till they left the nursery or died. The section is arranged in the following manner -

5.1.1: ***Description of the study cohort*** admitted into the nursery – the sex distribution and the distributions of the gestational ages, the birth-weights and the growth status (whether small or appropriate for gestational age) is presented.

5.1.2: Descriptive data of ***maternal characteristics of the study cohort*** is presented

5.1.3: The ***various neonatal complications in the NICU*** are described.

5.1.4: The ***causes of mortality*** are described.

5.1.5: Presents the ***bivariate analysis of antenatal, perinatal, and neonatal factors***

5.1.6: The ***multivariate logistic regression model for predicting death*** is presented

5.1.7: Presents the ***survival analysis*** – Kaplan Meier graphs and the Cox Proportional Hazards model.

5.1.8: The ***final outcomes*** of the study cohort at the time of discharge from the NICU are presented

5.1.9: The ***survival rate of the cohort*** is estimated.

a

FIGURES 1A & 1B DISTRIBUTION OF BOYS AND GIRLS ACCORDING TO BIRTH WEIGHTS AND GESTATIONAL AGES

Fig. 1a BIRTHWEIGHTS

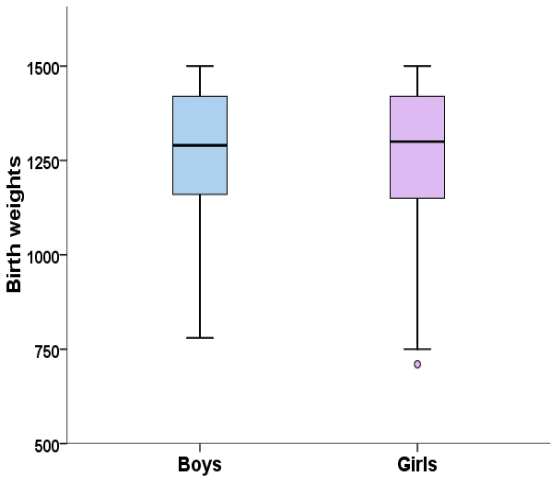


Fig 1 b. GESTATIONAL AGE

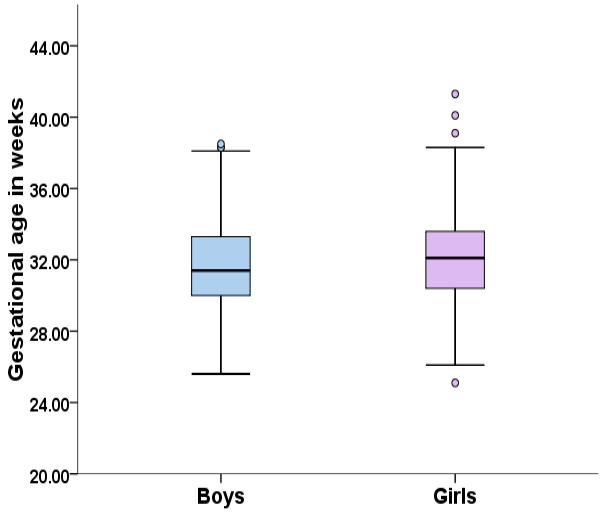


TABLE 9: COMPARISON OF THE GESTATIONAL AGE AND BIRTH WEIGHTS BETWEEN MALE AND FEMALE INFANTS

	Gestational Age (weeks)		Birth weight (grams)	
	Boys	**Girls**	**Boys**	**Girls**
Mean	31.72	32.18	1271.04	1271.86
Median	31.4	32.1	1290.00	1300.00
Std. Deviation	2.61	2.47	170.34	189.24
Range (Min. to Max.)	25 - 38	25 - 41	780 - 1500	710 - 1500
P-value	0.014		0.486	

5.1.1 DESCRIPTION OF THE COHORT ADMITTED INTO NURSERY

There were 776 babies with birth weights ≤ 1500 g admitted to the NICU during the study period of September 2010 and March 2013. The mean birth weight of the cohort was 1270.3g (SD ± 180.4 & range 710 g to 1500 g) and the mean gestational age was 31.9 weeks (SD ± 2.5 & range 25.1 weeks to 41.3 weeks). There were 407 (52.45%) boys and 368 (47.5%) girls in this cohort. In one child (born at 28 weeks), with ambiguous genitalia, the sex could not be confirmed since the child was discharged against medical advice on the second day.

The comparison of boys and girls in terms of the birth weight and gestational age are depicted in **Figures 1a and 1b** and the accompanying table **(table 9).** The male infants in the cohort had a slightly lower gestational age compared to the female infants and this was statistically significant (p=0.014). There was no significant difference in the birth weights (p=0.486).

Table 10 (below) shows the distribution of the male and female infants according to their gestational ages. Nearly 75% of the infants were between 28 and 33 weeks and 4% were term infants.

Table 10: Distribution of the Male and female infants according to their gestational ages.

	<28 weeks (Extreme preterm)	28-31 weeks (Very Preterm)	32-33 weeks (Moderate Preterm)	34-36 Weeks (Late Preterm)	≥ 37 weeks (Term)	Total
Boys (%)	**15** (62.5)	**202** (56.1)	**101** (46.5)	**70** (48.3)	**19** (63.3)	**407** (52.4)
Girls (%)	**9 (**37.5)	**157** (43.9)	**116** (53.5)	**75** (51.7)	**11** (36.7)	**368** (47.6)
Total (%)	**24** (3.1)	**359** (46.4)	**217** (27.9)	**145** (18.7)	**30** (3.9)	**775** (100)

b

FIGURE 2: DISTRIBUTION OF THE VLBW BABIES ACCORDING TO THEIR WEIGHTS

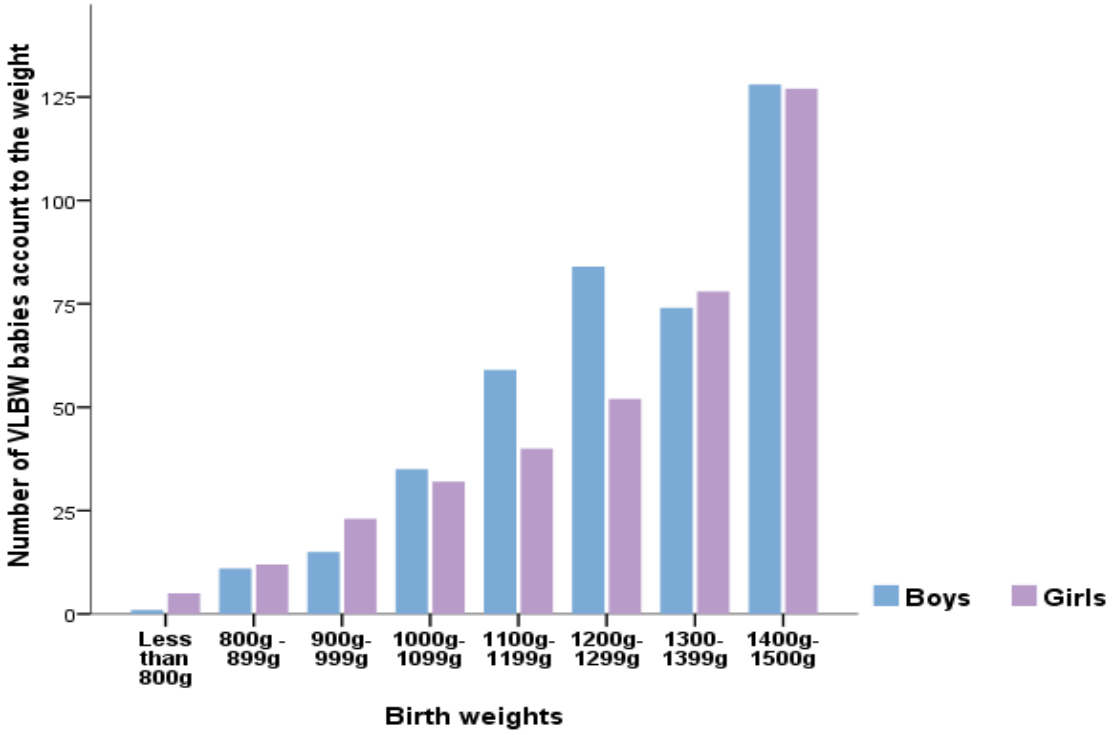


FIGURE 3: DISTRIBUTION OF THE INFANTS DEPENDING UPON THEIR GROWTH STATUS AT BIRTH

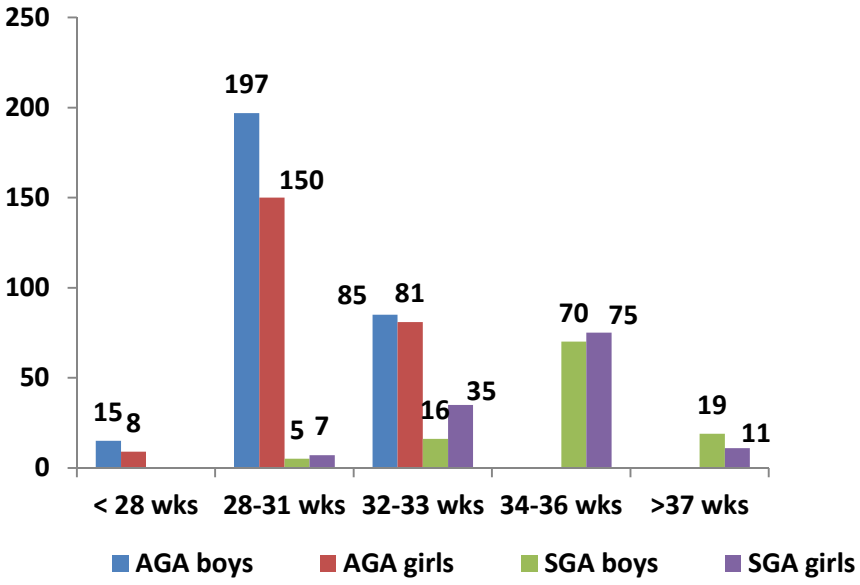


Figure 2 shows the distribution of the weights of the infants in clusters of 100 g. Except for two clusters (1100-1199 & 1200-1299) the birth weights are almost evenly distributed between girls and boys.

Growth status of the babies at the time of birth

Figure 3 depicts the distribution of the babies according to their gestational ages and sex, if they were small for gestational age (SGA) or if they were appropriate for gestational age (AGA). We used the Fenton's charts[364] to decide if the babies were AGA or SGA. Infants whose birth weights were less than the 3rd percentile as per the Fenton charts[364] were considered as small for gestational age. ***The 3rd percentile on the Fenton charts was used because it corresponds to the 10th percentile of two gestational age-specific centile charts for South Indian Infants.***[378,379] There were 239 (30.7%) infants who were small for gestational age (SGA) when the Fenton's third percentile were used. There were more SGA girl babies (53.8%). Majority of the infants (almost 90%) who were <33 weeks of gestation were appropriate for gestational age. All infants, whose gestational age was 34 weeks and more, were small for gestational age, because of the ceiling of 1500 g in the study.

5.1.2 MATERNAL CHARACTERISTICS OF THE STUDY COHORT

Of the total of 776 infants, 561 (72.3%) were singleton babies. Of the remaining, 200 (25.8%) were twins and 15 (1.9%) were triplets. After accounting for the multifetal gestations there were 713 mothers in the study cohort **(table 11)**.

c

TABLE 11: CHARACTERISTICS OF THE MOTHERS OF THE INFANTS IN THE COHORT

Characteristics	Number (%)
Total Mothers (after accounting for multifetal gestations)	713 (100)
Maternal age	
Between 18 to 35	686 (96.2)
Less than 18 (or) More than 35 (only one mother was <18 years)	27 (3.8)
Maternal Education	
Less than Std. 8	86 (12.1)
Between 9th -12th standard	268 (37.5)
Graduate & Post graduate	213 (30)
Consanguineous Marriage*	169 (27.9)
Gravida	
Primi gravida	388 (54.3)
Multi gravida (>3)	56 (7.9)
At least two Antenatal visits	713 (100)
History of Infertility	104 (14.6)
Conceived after treatment (Clomiphene, IUI, IVF)	79 (75.9)
Conceived spontaneously	25 (24.1)
Thyroid illness (Hypothyroidism: 31, Hyperthyroidism: 5)	36 (5)
Diabetes complicating pregnancy (Gestational diabetes: 41, Pre-gestational 9)	50 (7)
Hypertension complicating pregnancy (Pre-eclampsia : 274, Eclampsia:34)	308 (43.2)
Antepartum Hemorrhage	
Abruption	36 (5.0)
Placenta previa & Others	16 (2.3)
Antepartum steroids (611 mothers were less than 34 weeks gestation)	
No steroids at all	141 (23.1)
Steroids given (At least one dose: 217 Two doses given:253)	470 (70.9)
Preterm Premature rupture of membranes (PPROM)	134 (18.8)
Meconium stained amniotic fluid (>Grade 1)	16 (2.3)
Chorioamnionitis	8 (1.1)
Type of Delivery	
Normal	235 (32.9)
Cesarean section	435 (61.1)
Breech and instrumental (Forceps, vacuum extraction)	43 (6)
Place of birth	
Inborn	638 (89.5)
Outborn	75 (10.5)
Obstetric complications prior to this conception & Medical complications	149 (20.9)

Antenatal check-up: It is heartening to note that all mothers had at least two antenatal consultations. Majority (96.2%) of the mothers were between the ages of 18 and 30 years. **Maternal education level:** Most of the mothers (68%) were educated beyond middle school, and about one third had completed graduation.

Preterm premature rupture of membranes occurred in 18.8% of the mothers of the cohort

Pregnancy induced hypertension: The main maternal complication (seen in 43.2%) was pregnancy induced hypertension **(table 11)**. Over one third (36.2%) of the babies born to mothers with PIH were born SGA. Overall there was 7% mortality in these infants and the most common cause of death was septicemia (**table 14**). Although most children who were born to mothers who were pre-eclamptic survived, notably, 20% of children born to mothers with eclampsia died (some of them, due to perinatal asphyxia).

History of infertility: There was history of infertility prior to this pregnancy in 14.6% of the mothers **(table 11)**. Of these majority (75.9%) conceived after treatment, while the rest conceived spontaneously. More than half of the infants (56.7%) who were born after treatment for infertility were born of twin or triplet pregnancies.

Twins and triplets: Among the 200 children born of multifetal gestations, in 55 twin pairs both the twins and in three triplet sets, all the three triplets were part of the study cohort since they had birth weight of $\leq$1500 g **(table 11)**. In the remaining, only one twin or one or two triplets, who were VLBW was included in the study. In our cohort 97.2%

of the multifetal gestational babies were premature and 28% of the babies were small for gestational age (however, this is because of the birth weight ceiling of 1500 g).

Significant past obstetric or medical history: About 11.8% of the mothers had previous history of adverse pregnancy outcomes (multiple abortions, neonatal death, intrauterine death or previous low birth weight infant) and 9.1% of the mothers had medical complications **(table 11)**. The medical complications included anemia, chemotherapy for malignancies, chronic liver disease, chronic renal failure, rheumatologic problems (Systemic Lupus Erythematosus and Rheumatoid Arthritis), hematologic disorders (Paroxysmal Nocturnal Hemoglobinuria, Immune Thrombocytopenic Purpura) congenital and rheumatic heart diseases, cardiomyopathy, malaria, tuberculosis of spine, seizure disorder, HIV sero-positivity (2 patients), Congenital Nemaline Rod Myopathy and psychiatric illness on treatment. The presence of these complications did not affect the survival of the infants [p=0.249, RR 0.926 (0.83-1.030]. The other less common maternal complications were intrapartum hemorrhage (5%), thyroid illness (5%) and chorioamnionitis (1.1%).

Diabetes during pregnancy: There were 50 mothers (7%) with diabetes complicating pregnancy (41 had gestational diabetes and 9 had pre-existing diabetes mellitus), 15% of the infants of diabetic mothers (IDM) were small for gestation and all the infants were preterm **(table 11)**.

Primi gravida: Almost half of the mothers (54.3%) of the mothers were primi-gravidas and about 8% of the mothers had more than 3 previous pregnancies **(table 11)**.

Antenatal corticosteroids: It is heartening to note that at least 70% of the mothers (who delivered at gestational age of 34 weeks or less) had at least one dose of antenatal corticosteroids (betamethasone) **(table 11)**.

Type of delivery: More than half (67%) of the infants were born by Cesarean or instrumental deliveries (assisted breech, forceps or vacuum) **(table 11)**, which is to be expected since many mothers had PIH and other complications. 90% of the babies were born in this institution and the rest were referred from other centers after the baby was born. There was no difference in the outcome between those who were born normally and those born by Cesarean section or instrumental delivery (**table 14**)

Relationship between the maternal characteristics and survival in the NICU

None of the above maternal or antenatal risk factors affected the survival of the babies in the nursery. This is depicted in table 14 which presents the bivariate analysis of these characteristics with death in the NICU.

5.1.3 NEONATAL COMPLICATIONS IN NICU

Table 12 presents the complications of the infants during the period of admission in the NICU. The data are presented according to the gestational age rather than the birth weight since many complications in the VLBW are dependent on the gestational age rather than on the birth weight. The complications in the extremely preterm (<28 weeks), Very preterm (28-31 weeks), moderately preterm (32-33 weeks), late preterm (34-36 weeks) and term babies are compared between boys and girls.

TABLE 12: PERINATAL RISK FACTORS & NEONATAL COMPLICATIONS ACCORDING TO GESTATIONAL AGE

		<28 weeks (Extreme preterm)			28-31 weeks (Very Preterm)			32-33 weeks (Moderate Preterm)			34-36 Weeks (Late Preterm)			≥ 37 weeks (Term)		
S.N	Variable	Boys	Girls	P-value	Boys	Girls	P-value	Boys	Girls	P-value	Boys	Girls	P-value	Boys	Girls	P-value
1	Multifetal gestations (%)	1 (26.7)	3 (33)	0.728	66 (32.7)	44 (27.8)	0.324	27 (26.7)	26 (22)	0.46	18 (25.7)	22 (29)	0.63	5 (26)	1 (9.1)	0.25
2	Diabetes during pregnancy (%)	1 (6.7)	1 (11)	0.703	16 (7.9)	19 (12)	0.192	8 (7.9)	8 (6.9)	0.773	1 (1.4)	3 (4)	0.345	-	-	-
3	PIH (%)	0 (0)	3 (33)	**0.017**	56 (27.7)	64 (40.5)	**0.011**	55 (54)	59 (50.9)	0.597	30 (42.8)	39 (52)	0.271	6 (31.6)	4 (36.4)	0.789
4	Antepartum Hemorrhage (%)	1 (6.7)	0 (0)	0.429	18 (8.9)	18 (11.4)	0.383	4 (3.9)	3 (2.6)	0.568	2 (2.8)	4 (5.3)	0.454	1 (5.3)	1 (9.1)	0.685
5	Antenatal steroids (%)	5 (33)	4 (55)	0.586	46 (22.8)	30 (18.9)	0.383	13 (12.9)	15 (12.9)	0.990	17 (24.3)	22 (29)	0.493	-	-	-
6	PPROM (%)	5 (33)	2 (22)	0.562	60 (29.7)	26 (16)	**0.003**	17 (16.8)	22 (18.9)	0.683	11 (15.7)	5 (6.7)	0.082	0 (0)	1 (9.1)	0.181
7	Cesarean & Instrumental (%)	5 (33)	1 (11)	0.224	113 (55.9)	97 (61)	0.298	74 (73)	85 (73)	0.999	55 (78.5)	63 (84)	0.401	12 (63)	10 (90.9)	0.098
8	Place of birth (%)	3 (20)	0 (0)	0.151	26 (12.9)	17 (10.7)	0.540	8 (7.9)	8 (6.9)	0.773	10 (14)	4 (5.3)	0.068	4 (21)	3 (27)	0.698
9	Perinatal Asphyxia (%)	1 (6.7)	0 (0)	0.429	11 (5.4)	1 (0.63)	**0.012**	4 (4)	10 (8.6)	0.163	4 (5.7)	2 (2.6)	0.357	1 (5.3)	0 (0)	0.439
10	Acute kidney injury (%)	2 (13.3)	1 (11)	1.000	10 (4.9)	4 (2.5)	0.248	2 (1.9)	3 (2.6)	0.758	0 (0)	1 (1.3)	0.288	0 (0)	2 (18.2)	**0.055**
11	NEC- Bell stage ≥ 2 (%)	-	-	-	4 (1.98)	3 (1.89)	0.956	0 (0)	3 (2.58)	0.104	1 (1.42)	1 (1.3)	0.961	-	-	-
12	Apnea (%)	3 (20)	2 (22)	0.897	38 (18.8)	19 (12)	0.084	11 (10.9)	14 (12.1)	0.769	5 (7.14)	2 (2.67)	0.216	1 (5.26)	0 (0)	0.439
13	RDS (%)	11 (73.3)	5 (56)	0.371	83 (41)	53 (33.5)	0.155	10 (9.9)	17 (14.6)	0.279	6 (8.6)	1 (1.3)	0.044	-	-	-
14	BPD (%)	2 (13.3)	0 (0)	0.253	6 (2.9)	2 (1.26)	0.280	1 (0.99)	1 (0.86)	0.926	1 (1.43)	0 (0)	0.302	-	-	-
15	CPAP (%)	10 (67)	6 (67)	1.000	88 (43.6)	54 (34)	0.078	16 (15.8)	21 (18)	0.638	6 (8.6)	1 (1.3)	**0.044**	-	-	-

		<28 weeks (Extreme preterm)			28-31 weeks (Very Preterm)			32-33 weeks (Moderate Preterm)			34-37 Weeks (Late Preterm)			≥ 37 weeks (Term)		
	Variable	Boys	Girls	P-value	Boys	Girls	P-value	Boys	Girls	P-value	Boys	Girls	P-value	Boys	Girls	P-value
16	Ventilation (%)	8 (53)	1 (11)	**0.039**	52 (25.7)	34 (21.5)	0.368	5 (4.9)	14 (12.1)	0.061	3 (4.3)	4 (5.3)	0.755	1 (5.3)	1 (9.1)	0.685
17	Hypotension (%)	11 (73)	2 (22)	**0.015**	56 (28)	43 (27)	0.921	12 (11.8)	16 (13.8)	0.675	9 (12.8)	7 (9.3)	0.499	2 (10.5)	1 (9.1)	0.900
18	Septicemia (%)	2 (13.3)	3 (33)	0.243	37 (18.3)	36 (23)	0.292	16 (15.8)	21 (18)	0.640	11 (15.7)	8 (10.6)	0.385	4 (21)	0 (0)	0.092
19	Hyper-Bilirubinemia (%)	-	-	0.718	8 (3.9)	6 (3.7)	0.622	7 (6.9)	5 (4.3)	0.809	3 (4.3)	1 (1.3)	0.374	3 (15.8)	0 (0)	0.311
21	Hypo-Glycemia (%)	0 (0)	1 (11)	0.187	11 (5.4)	9 (5.7)	0.523	9 (8.9)	12 (10.3)	0.690	6 (8.6)	7 (9.3)	0.853	8 (42)	5 (45)	0.858
22	Poly-Cythemia (%)	-	-	-	6 (2.9)	4 (2.5)	0.796	4 (3.9)	5 (4.3)	0.888	6 (8.6)	6 (8)	0.920	1 (5.3)	3 (27)	0.100
23	Anemia (%)	11 (73)	4 (44)	0.156	72 (35.6)	45 (28)	0.141	13 (12.9)	18 (15.5)	0.563	6 (8.6)	5 (6.7)	0.682	2 (10.5)	1 (9.1)	0.862
24	Thrombo-cytopenia (%)	8 (53)	3 (33)	0.375	78 (38.6)	56 (35)	0.513	42 (41.5)	35 (30)	0.086	32 (45.7)	28 (37)	0.338	8 (42)	5 (45)	0.958
25	Abnormal Calcium (%)	5 (33)	1 (11)	0.235	49 (24.2)	30 (18.9)	0.555	5 (4.9)	13 (11.2)	0.095	1 (1.4)	4 (5.3)	0.128	0 (0)	1 (9.1)	0.227
26	Sodium (%)	6 (40)	4 (44)	0.502	56 (27.7)	44 (27.8)	0.675	12 (11.9)	12 (10)	0.668	10 (14.3)	9 (12)	0.973	5 (26)	5 (45)	0.285
27	Potassium (%)	2 (13)	2 (22)	0.423	31 (15)	24 (15)	0.821	11 (10.9)	8 (6.9)	0.268	5 (7)	4 (5.3)	0.838	1 (5.3)	1 (9.1)	0.693
28	PDA (%)	6 (40)	4 (44)	0.405	36 (17.8)	30 (18.9)	0.772	6 (5.9)	8 (6.9)	0.779	4 (5.7)	5 (6.7)	0.796	1 (5.3)	0 (0)	0.426
29	IVH(>Grade2) (%)	1 (6.7)	1 (11)	0.596	11 (5.4)	0 (0)	**0.003**	3 (2.9)	1 (0.86)	0.276	-	-	-	-	-	-
30	Cholestatic jaundice (%)	-	-	-	9 (4.4)	7 (4.4)	0.972	8 (7.9)	2 (1.7)	**0.029**	2 (2.8)	2 (2.7)	0.943	3 (15.8)	0 (0)	0.153
31	PVL(>Grade2) (%)	-	-	-	-	-	-	0 (0)	1 (0.86)	0.335	-	-	-	-	-	-
32	ROP (%)	2 (13)	1 (11)	0.635	27 (13.4)	31 (19.6)	0.077	5 (4.9)	2 (1.7)	0.268	3 (4.3)	0 (0)	0.092	1 (5.3)	0 (0)	0.640
33	Mortality (%)	6 (40)	1 (11)	0.252	21 (10.4)	18 (11.4)	0.780	3 (2.9)	7 (6)	0.296	3 (4.3)	1 (1.3)	0.310	0 (0)	1 (9.1)	0.149
	Total	**15**	**9**	**24**	**202**	**157**	**359**	**101**	**116**	**217**	**70**	**75**	**145**	**19**	**11**	**30**

A. RESUSCITATION AND PERINATAL ASPHYXIA

Among the 776 infants admitted into the NICU, 108 (13.9%) required some form of resuscitation at birth (bag and mask ventilation, or intubation) **(table 12)**. However in the majority, spontaneous respiration could be established.

Perinatal asphyxia in this cohort was defined by pH ≤ 7.0 or ABE ≥ -12 in Umbilical cord pH or peripheral ABG within one hour or APGAR ≤ 5 at 5 minutes. In 34 infants (4.38%) there was evidence of perinatal asphyxia, (characterized by umbilical artery pH of less than 7.1 and low APGAR (<3) at 5 minutes requiring assisted ventilation and fluid and inotrope support). There were significantly more boys with perinatal asphyxia in the 28-31 weeks (very preterm) group and more girls with asphyxia in the 32-33 weeks (moderate preterm category). However when the entire cohort was analyzed there was no difference in the occurrence of asphyxia between the girls and boys.

B. RESPIRATORY DISTRESS SYNDROME (RDS)

Almost all (96%) the infants with RDS were born before 33 weeks **(table 12)**. Incidence of RDS was maximal in the very preterm group (29-31 weeks). Since most of the children with RDS required respiratory support, majority of the children who received Continuous positive airway pressure (CPAP) or ventilation were also less than 31 weeks of gestation.

As per the Institutional protocol, the first line of treatment for RDS is administration of CPAP. Only if CPAP fails would the infant be intubated and surfactant administered followed by ventilation. Twenty one out of a total of 186 (11.3%) infants received intra-tracheal surfactant. Although it appears that the mortality in the RDS group is high (18%), most children who died were those who had associated septicemia, or grade IV

intraventricular hemorrhage or other conditions. It is likely that these associated morbidities worsened the pulmonary function which resulted in increased ventilatory requirements and death.

C. CONTINUOUS POSITIVE AIRWAY PRESSURE (CPAP)

As mentioned above, CPAP is the first line of management of newborns with RDS in this institution. More than a quarter (26%) of the infants required CPAP. As expected 97% of these infants were less than 34 weeks (**table 12**). In about a third (29.7%) the CPAP was not sufficient and they required ventilator support (using conventional ventilation or High frequency ventilation).

The mean duration of the CPAP for the entire cohort was 46 hours. There were four children who received CPAP for more than one week. The mortality increased with duration of CPAP. Mortality according to the duration of ventilation was as follows - there was 20% mortality among those who were ventilated for less than 24 hours, 11% mortality in those who had CPAP from 1-3 days, 18.5% among those who had CPAP for 4-7 days and 25% in those who had CPAP for more than one week. The higher mortality in those who received CPAP for less than 24 hours was because in these babies these babies were sicker. When CPAP failed, they required ventilator support; however they still succumbed to the illness.

D. VENTILATION

In our cohort 13.4% of the children required ventilation. More than 90% of these were less than 34 weeks **(table 12).** In 20% of the infants who were ventilated, high frequency oscillatory ventilation (HFOV) was required due to failure of conventional ventilation.

The mean duration of ventilation was 59 hours. There were six children who were ventilated for more than one week. The mortality increased with duration of the ventilation. There was 62% mortality among those who were ventilated for less than 24 hours, 32.5% mortality in those who were ventilated for 1-3 days, 56% among those who were ventilated for 4-7 days and 67% in those who were ventilated for more than one week. The higher mortality in those who were ventilated for less than 24 hours was because these were children who were very sick and most of them had multi-organ failure. CPAP and Ventilation were not included in the multivariate logistic regression model, since CPAP or ventilation *per se* were not the cause of death. The, underlying reason for which the child received CPAP or required ventilation was the cause of death and including CPAP or ventilation would therefore confound the model.

E. NECROTIZING ENTEROCOLITIS (NEC)

Thirty infants (3.8%) of the 776 infants developed NEC. Nineteen (63%) of the children with NEC infants had NEC Bell stage 1, nine children (30%) had NEC stage 2 and two children (6.7%) had stage 3 (bowel perforation and required bowel resection). Of the two children with NEC stage 3, one child survived and one succumbed after surgery. The child who survived came back for the assessment at 18 months.

The overall mortality in those who had NEC was 17% (5 of 30 died) and all of them had severe NEC (stage 2 and beyond). The mortality according the 3 stages was - 0% for stage 1, 44% (four out of nine) for stage 2 and 50% (one of two children) for stage 3.

F. BRONCHOPULMONARY DYSLASIA (BPD)

There were 13 children who were diagnosed to have BPD **(table 12)** and who required oxygen therapy for >28 days. Ten of the 13 (77%) were less than 31 weeks gestation; two others were between 32 and 33 weeks. There was one baby who was born at 34 weeks (gestational age calculated from the last menstrual period) who developed BPD. However this child was out-born and the gestational age could not be ascertained accurately. In our cohort BPD and post-natal corticosteroid therapy was not associated with mortality or neurodevelopmental outcomes.

G. ANEMIA AND THROMBOCYTOPENIA

Anemia was a common morbidity **(table 12)**. Anemia can occur due to multiple reasons in VLBW infants who are admitted in the NICU. Although the most important reason is anemia due to prematurity, iatrogenic bloodletting for diagnostic testing is also a major contributor. Anemia was seen predominantly (92.1%) in the infants less than 33 weeks gestational age. Thrombocytopenia was another major hematologic morbidity **(table 12)**, and 50% of the extremely preterm, 37.2% of very preterm, 36% of moderate preterm, 41.2% of late preterm and 44% of term infants had low platelets. There are many causes for thrombocytopenia in the neonate and since thrombocytopenia is regularly present when there are signs of sepsis, it is commonly seen in infants admitted into the NICU.

H. CALCIUM, GLUCOSE, BILIRUBIN AND ELECTROLYTE ABNORMALITIES

Abnormal calcium value was present in 109 infants **(table 12)**. Of these two infants had hypercalcemia and the rest had hypocalcaemia. Calcium was abnormal primarily (94.4%) in infants whose gestational age was less than 33 weeks.

Hypoglycemia was an uncommon complication **(table 12)** and was present in 8.76% of the infants. Both premature babies and intrauterine growth retarded babies are prone to develop hypoglycemia and so it was seen in all the age groups.

Almost 547 (70.4%) infants had bilirubin levels more than 8 g% and required phototherapy. Four infants (0.52%) required exchange transfusion. Hyperbilirubinemia (bilirubin >15 mg%) was seen in 33 (4.4%) infants and was present predominantly in the preterm babies **(table 12)**.

The commonest electrolyte abnormality was hyponatremia followed by hyperkalemia. Among the 163 infants with abnormal sodium values (<130mEq/L and >150 mEq/L), 142 (87.1%) had hyponatremia, 14 (8.6%) had hypernatremia and 7 (4.3%) had both hypo and hypernatremia. Eighty nine infants had abnormal potassium (<3.5 mEq/L and >6 mEq/L). Of these 52 (58.4%) had hyperkalemia, 35 (39.3%) had hypokalemia and two children had both hyper and hypokalemia. Cholestatic jaundice was present in 33 (4.3%) infants and was mainly seen in the very preterm and moderately preterm group **(table 12)**.

I. INTRAVENTRICULAR HEMORRHAGE (IVH)

Overall 111 children (72 boys and 39 girls) had IVH (of any grade). Severe IVH (Grades III and IV) was a major morbidity in the very preterm (29-31 weeks) infants and was seen predominantly in the male infants (15 boys and only 2 girls had severe IVH) **(table 12)**. This is very significant and as mentioned in the Literature review section (**3.4.11**), the male infants were particularly prone to develop severe IVH. Of the 17 infants, only two infants (one male and one female infant) survived and were discharged alive from the

NICU. The rest died or were discharged before completion of treatment in a moribund condition. Periventricular leukomalacia was not a very significant morbidity in this cohort. Of the 51 children (29 boys and 23 girls) who had periventricular leukomalacia, only one girl child had PVL- Grade III **(table 12)**.

J. MALE PREDISPOSITION TO DEVELOPING NEONATAL MORBIDITIES

As discussed earlier (Literature Review **3.4.1**), male babies are at greater risk than female babies in developing neonatal complications. In our study perinatal asphyxia, necrotizing enterocolitis, septicemia, periventricular leukomalacia, PDA and acute kidney injury were similar between boys and girls.

The sex predilection for male babies was observed in the occurrence of certain neonatal morbidities **(table 12)** -

- Boys had a much higher risk of developing severe IVH (Grades III and IV) compared to girls. The overall relative risk (across all gestational age) for male babies was 4.05 (1.1-14.9 95% CI, p=0.003) compared to girls.
- Male infants had a higher risk of developing respiratory distress syndrome compared to female infants. [Relative risk of 1.213 (1.002-1.47 95%CI, p=0.038)].
- Male babies also were more likely to have received CPAP [Relative risk of 1.23 (1.02-1.476 95%CI, p=0.025)] and they also had a slightly higher risk (although not significant) of being ventilated [Relative risk of 1.24 (.957-1.516 95%CI, p=0.094)].

- Preterm premature rupture of membranes resulted in more male babies compared to female babies [22.8% male babies vs. 15.2% female babies, p=0.007; RR of 1.33 (1.06-1.66 95%CI)].
- Interestingly there were more girls born to mothers with PIH as compared to boys [45.6% girls vs. 36.1% boys, p=0.007, RR 1.21 (1.05-1.39 95%CI)].

K. SEPTICEMIA

Septicemia was a major morbidity in the cohort **(figures 5 & 6; tables 12 & 13)**.

- **Total infants with septicemia:** 135 of the total of 776 (17.4%) infants had septicemia.
- **Septicemia and gestational age:** Occurrence of septicemia decreased with increasing gestational age. 20.8% of extremely preterm, 20.3% of very preterm, 17% of moderate preterm, 13.1% of late preterm and 13% of term infants had septicemia.
- **Early and late onset septicemia:** Septicemia of early onset (onset before 72 hours) was present in 47 (34.8%) of the infants, 85 (62.9%) had late onset sepsis (onset after 72 hours) and three infants (2.2%) had early onset sepsis followed by a subsequent episode of late onset sepsis.
- **Organisms causing septicemia**: The main organism causing early onset sepsis was the Burkholderia species and the predominant causes of late onset septicemia were Gram negative organisms like Klebsiella, Acinetobacter and Enterobacter species **(Figure 4).**

Figure 4: EARLY ONSET Vs. LATE ONSET SEPSIS

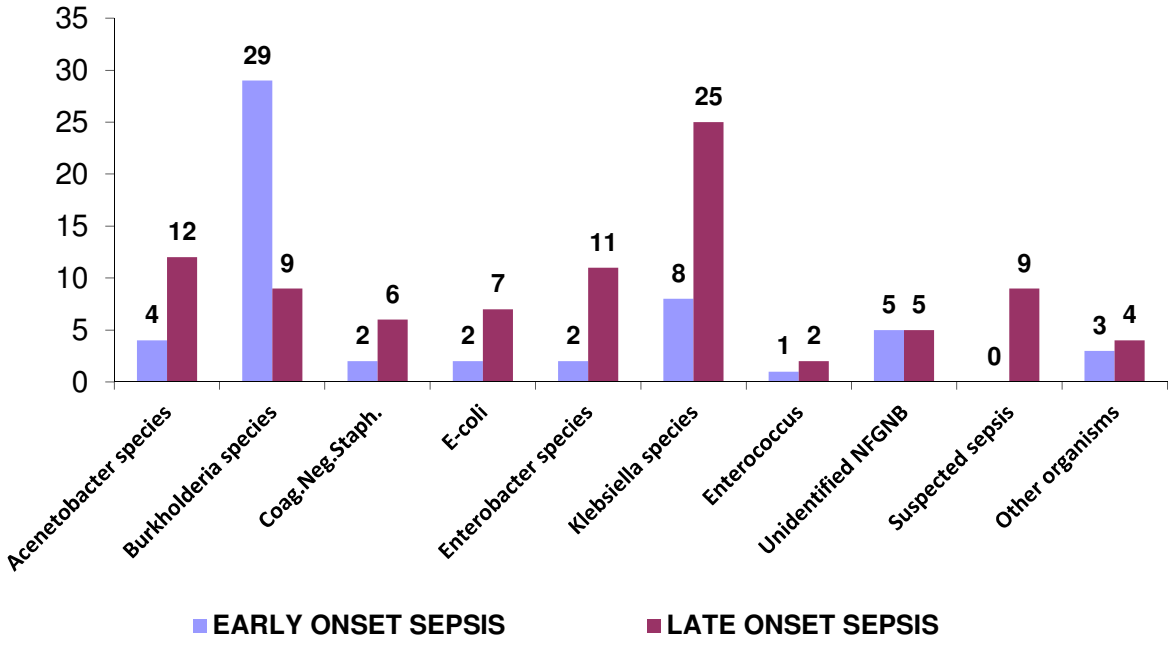


Fig. 5: ORGANISMS CAUSING DEATH DUE TO SEPTICEMIA

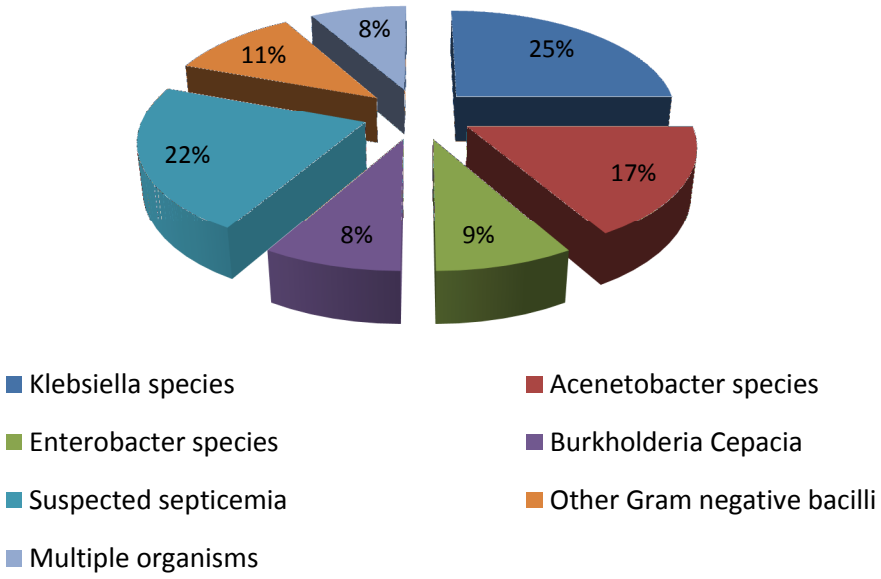


Figure 6: OUTCOMES OF THE VLBW COHORT IN THE NICU

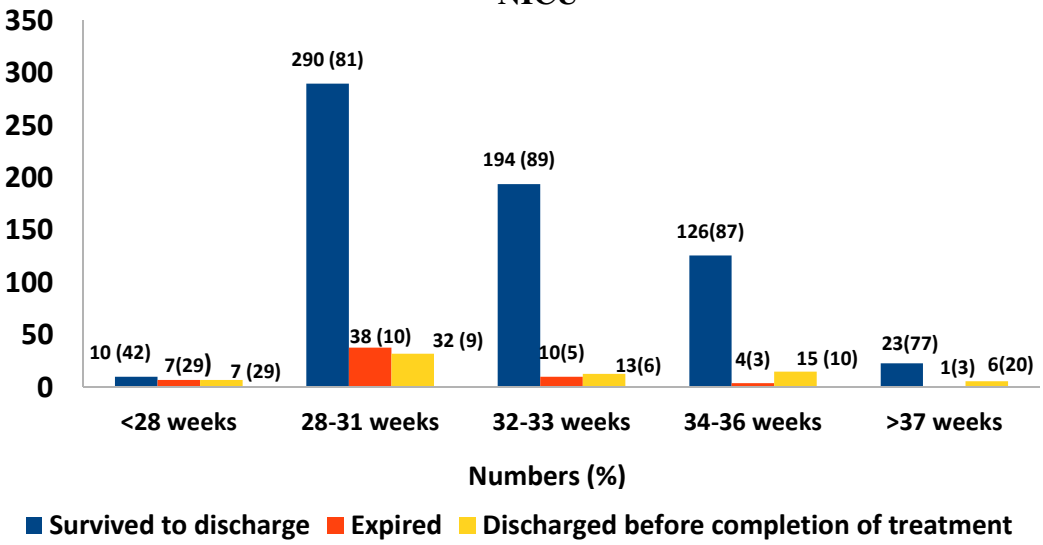


TABLE 13: CAUSES OF DEATH IN THE NICU

	<28 weeks	28-31 weeks	32-33 weeks	34-36 weeks	> 37 weeks	Total
Septicemia	3	25	5	2	0	35
Perinatal asphyxia	0	3	3	2	0	8
Pulmonary hypoplasia	0	1	0	0	0	1
RDS with complications (pulmonary hemorrhage, pneumothorax, PIE)	3	1	0	0	1	5
Intraventricular Hemorrhage (Grades IV)	1	3	1	0	0	5
Cardiac causes (myocardial dysfunction, Tetralogy of Falot)	0	1	1	0	0	2
Necrotizing Enterocolitis (Grade 3)	0	3	0	0	0	3
Extremely low birth weight	0	1	0	0	0	1
Total Mortality (% of the total for the GA)	7 (29.2)	38 (10.6)	10 (4.6)	4 (2.8)	1 (3.3)	60 (7.7)

- **Meningitis:** 26 infants (19.3%) developed meningitis. Twenty one (80.7%) of the 26 infants were discharged alive from the NICU and five children succumbed to meningitis. Four children developed hydrocephalus - two of these underwent ventriculo-peritoneal shunt surgery and improved well. The other two were among the five infants who died of meningitis.
- **Death due to septicemia (Figure 5):** Septicemia was the predominant cause of mortality in this cohort. Thirty five of the sixty (58.3%), of the infants who died, died because of septicemia. Gram negative bacilli septicemia was the leading cause of septicemia related deaths. Although in eight children there was no growth on the blood culture, sepsis leading on to septic shock was strongly suspected in view of the clinical features like sclerema, leukopenia, elevated CRP and thrombocytopenia.

5.1.4 CAUSES OF MORTALITY

Figure 6 and table 13 shows the outcome of the infants after their stay in NICU.

- ***Totally sixty children died in the NICU. Of these 33 (55%) were boys and 27 (45%) were girls. Thus the mortality rate in the NICU was 7.73%. (60/776 infants)***
- Mortality rate was ***8.9% among boys and 8.1% among girls [p= 0.718, RR 0.956 (0.75-1.22, 95%CI)].***
- The survival rate improved with increasing gestation. Mortality was highest in the infants <28 weeks gestation (29.2% of the infants died).. There were 10.6% deaths in the 28-31 weeks, 4.6% deaths in the 32-33 weeks category, 2.8% deaths

in the 34-36 weeks category and only one death (4.3%) in the >37 weeks category (**table 13**).

Although the infants who died had multiple complications, each of which could result in death, the **table 13** depicts the most likely cause of death. For example five children who died of septicemia, had severe IVH. Children who died due to respiratory complications also had features of septic shock. One ELBW child (825g at 28 weeks gestation), the exact cause of death could not be ascertained and the extreme low birth weight is shown as the cause of death.

Like NICUs in other developing countries, unfortunately septicemia was the main cause of death in all gestational ages. Klebsiella was the most common cause of septicemia (figure 5). Other organisms which contributed to mortality included Acinetobacter species, Enterobacter, Burkholderia species and E.coli.

The mortality rate decreased with increasing gestational age. Among the babies who died 58.3% were ≤31 weeks and 91.7% were ≤33 weeks gestational age.

Infants who left before completion of treatment ("Discharged against medical advice")

The percentage of infants who left before completion of treatment are as follows 29.2% in the less than 28 weeks category, 8.9% in the 28-31 weeks category, 6% deaths in 32-33 weeks, 10.3% in the 34-36 weeks and 20% in the >37 weeks categories respectively. Many of them left the NICU in a moribund state

5.1.5 BI-VARIATE ANALYSIS OF ANTENATAL, PERINATAL AND NEONATAL FACTORS AND THE RELATIONSHIP TO MORTALITY

Table 14 shows the bivariate analysis (using Chi-square test) of the various antenatal, perinatal and neonatal risk factors. For this analysis the group of infants "discharged against medical advice" was not considered. The risk factors which were significantly associated ($p < 0.001$) with death in this cohort were - birth-weight, gestational age, PDA, severe IVH, abnormal potassium, sodium and calcium, anemia, septicemia, hypotension, ventilation, CPAP, NEC, acute kidney illness and perinatal asphyxia **(table 14).** Relative risks were also computed.

Relative risks instead of Odds ratios

In cohort studies relative risk is more useful than odds ratios.[380] When the odds ratios were calculated for hypotension, ventilation, severe IVH, NEC, it was very high (the odds ratios for death due to hypotension was 59, the OR for IVH was 69.6 the OR for ventilation was 74.25) The reason the large distortion is because the event (which is death in this case), is especially large in one group (the Expired group) as compared to other group. For example there were 9 deaths out of 11 children in those with severe IVH (which amounts to 82%) compared to 2 survivors (18%) in those with IVH. This happens when hypotension, NEC and ventilation are compared.

Altman says "The odds ratio should ***not*** be interpreted as an approximate relative risk unless the events are rare in both groups (say, less than 20-30%).....In a cohort study Relative Risk (RR) rather than odds ratio (OR) is more relevant…. (However) the odds ratio remains especially useful when researchers need to adjust for other variables, for

TABLE 14: BI-VARIATE ANALYSIS OF RISK FACTORS VS. MORTALITY IN NICU

MATERNAL AND PERINATAL RISK FACTORS

Risk Variables	Discharged alive (%)	Expired (%)	P value	Relative Risk 95% CI
Antepartum H'ge: No APH APH	**602** (92) **41** (89)	**55** (8) **5** (11)	0.581	.028 0.927-1.140
PIH: No Hypertension PIH present	**371** (90) **272** (93)	**41** (10) **19** (7)	0.110	0.963 0.922-1.007
Maternal Diabetes: No Diabetes Diabetes present	**593** (92) **50** (88)	**53** (8) **7** (12)	0.318	1.046 0.947-1.156
Multifetal gestation: Singletons Multifetal Pregnancy	**468** (93) **175** (88)	**37** (7) **23** (12)	0.067	1.049 0.991-1.109
Antenatal Steroid: Received No Steroid received	**520** (92) **123** (90)	**47** (8) **13** (10)	0.634	1.014 0.955-1.077
Type of Delivery: Normal Cesarean	**211** (91) **432** (92)	**21** (9) **39** (8)	0.731	0.992 0.944-1.041
Treated for Infertility: No treatment Conceived after treatment	**559** (91) **84 (**91)	**52** (9) **8** (9)	0.953	1.003 0.90-1.11
Growth (AGA or SGA): AGA SGA	**444** (90) **199** (94)	**47** (10) **13** (6)	0.134	0.963 0.921-1.008
PPROM: No PPROM Present	**515** (92) **128** (91)	**47** (8) **13** (9)	0.745	1.009 0.952-1.070

BIRTH DETAILS AND CHARACTERISTICS OF THE BABIES

Neonatal Characteristics	Discharged alive (%)	Expired (%)	P value	Relative Risk 95% CI
Place of Birth: Inborn Out-born	**575** (92) **68** (89)	**52** (8) **8** (11)	0.511	1.025 0.946-1.111
Baby's Sex: Boy Girl	**338** (91) **305** (92)	**33** (9) **27** (8)	0.718	0.992 0.948-1.037
Birth weight: 1200-1500g* 1000-1099g 500-999g	**473** (95.2**)** **129** (84.8) **44** (77.2)	**24** (4.8) **23 (**15.2) **13** (12.8)	 <0.001 <0.001	
Gestational age: 32-33 weeks***** ≤31 weeks ≥34 weeks	**194** (95.1) **300** (87) **152** (96.8)	**10** (4.9) **45** (13) **5** (3.2)	 0.003 0.421	

Table 14 (contd.) NEONATAL COMPLICATIONS

Risk Variables	Discharged alive (%)	Expired (%)	P value	Relative Risk (95% CI)
Perinatal Asphyxia: absent Asphyxia present	**624** (93) **19** (66)	**50** (7) **10** (34)	<0.001	1.413 1.084-1.842
Septicemia: No Sepsis Confirmed Sepsis	**550** (95) **93** (75)	**29** (5) **31** (25)	<0.001	1.267 1.142-1.404
Hypotension: Absent Hypotension present	**559** (99) **84** (61)	**6** (1) **54** (39)	<0.001	1.625 1.422-1.859
PDA: Absent Present	**571** (94) **72** (80)	**38** (6) **18** (20)	<0.001	1.172 1.055-1.302
IVH: Normal to grade 2 Grade 3 and 4	**619** (94) **2** (18)	**40** (6) **9** (82)	<0.001	5.166 1.475-18.1
Cholestasis: Absent **Present**	**617** (92) **26** (87)	**51** (8) **4** (13)	0.285	1.066 0.925-1.228
Potassium: Normal Abnormal	**533** (95) **68** (79)	**30** (5) **18** (21)	<0.001	1.197 1.072-1.337
Sodium: Normal Abnormal	**479** (95) **124** (84)	**25** (5) **23** (6)	<0.001	1.127 1.048-1.211
Calcium: Normal Abnormal	**467** (94) **82** (86)	**31** (6) **13** (14)	0.011	1.086 1.000-1.181
Thrombocytopenia: Absent Thrombocytopenia present	**420** (97) **223** (83)	**12** (3) **45** (17)	<0.001	1.168 1.105-1.236
Anemia: Absent Anemia present	**498** (94) **145** (84)	**30** (6) **27** (16)	<0.001	1.119 1.045-1.197
Hypoglycemia: Absent Hypoglycemia present	**588** (92) **55** (92)	**52** (8) **5** (8)	1.000	1.002 0.925-1.085
CPAP: No CPAP CPAP used	**487** (94) **156** (84)	**29** (6) **29** (16)	<0.001	1.119 1.048-1.195
RDS: No RDS RDS present	**508** (94) **135** (82)	**30** (6) **30** (18)	<0.001	1.154 1.071-1.244
NEC: No or Bell stage 1 Bell stage 2 & beyond	**637** (92) **6** (55)	**55** (8) **5** (45)	0.001	1.688 0.984-2.896
Acute Kidney injury: No AKI AKI present	**57** 193 **10** (53)	**42** (7) **9** (47)	<0.001	1.770 (1.155-2.713)
Ventilation: No Ventilation Ventilated	**594**(91.9) **52** (8.1)	**8** (13.3) **52** (86.7)	<0.001	1.973 (1.62-2.4)
Hyperbilirubinemia: Bilirubin < 15 Bilirubin > 15	**552** (92) **28** (93)	**45** (8) **2** (7)	0.018	0.885 (0.217-3.586)

which logistic regression is the usual approach".[380] Therefore relative risks rather than Odds ratios are presented in the bivariate analyses (**tables 14 and 23**).

5.1.6 MULTIVARIATE LOGISTIC REGRESSION

The variables identified as significant at P <0.05 in bivariate analyses were entered into a stepwise logistic regression model. Since electrolyte abnormalities, anemia and thrombocytopenia were seen in the setting of septicemia they were not entered into the model. Ventilation and IVH were also not included because of the very high odds ratios. Variables were retained in the adjusted model if they were significant at P <0.05. The goodness of fit of the model was checked with the Hosmer-Lemeshow and a p-value of >0.05 was considered a good fit. The discriminatory ability of the model was assessed with the area under the receiver operating characteristic (ROC) curve.

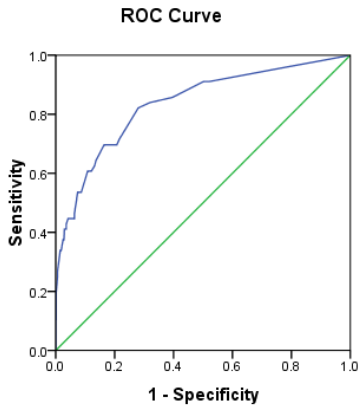
The final model **(table 15)** for predicting death in the cohort of VLBW babies is presented below. The final multivariate analysis indicated that the odds of death was more than 3 times with the birth weight of 500 g-999 g and more than twice when the birth weight was1000- 1199 g. Chances of death was more than twice in the presence of RDS or if the infant had PDA, almost four times in septicemia and five times if the infant had asphyxia or NEC. All variables were significantly associated with a p of <0.05.

Table 15: FINAL MULTIPLE LOGISTIC REGRESSION MODEL FOR PREDICTING DEATH IN THE NURSERY			
Predictor	**B coeff.**	**p-value**	**Adjusted Odds Ratio (95% CI)**
Birth weight 1000-1199 g	0.842	.003	2.321 (1.33-4.05)
Birth weight 500-999 g	1.295	<0.001	3.651 (1.782-7.48)
RDS	0.925	0.003	2.52 (1.5-4.23)
Septicaemia	1.385	<0.001	3.997 (2.4-6.67)
NEC (>Grade 2)	1.72	0.011	5.55 (1.49-20.77)
PDA	0.786	0.009	2.19 (1.22-3.95)
Perinatal asphyxia	1.569	0.001	4.802 (1.953-11.806)
Constant	-3.844	.000	.034

Receiver operator curve: (Figure 7)

The final predictive model (shown above) yielded an area under the ROC curve of 0.836 (0.775-0.897 95% CI; p<0.001) indicating good discrimination, and the Hosmer-Lemeshow statistic indicated a good model fit (p=0.558).

Figure 7: Receiver Operator Characteristics (ROC) Curve for above model predicting death in NICU



5.1.7 SURVIVAL ANALYSIS

A. KAPLAN-MEIR GRAPHS

Kaplan Meier graphs were plotted to look at the survival of the infants with morbidities in the NICU. 643 of the total of 776 (82.9%) were discharged alive from the nursery. Sixty infants (7.73%) had died during their period of nursery stay and 73 (9.4%) infants were discharged prior to completion of treatment against medical advice. The practice in the NICU was to keep babies till they reached 1800 g or until they started breast feeding well. 32 of the 73 infants who were "discharged against medical advice" were relatively stable and left before they reached 1800 g or before breast feeding was well established. Forty one of the 73 infants were "discharged against medical advice" were moribund at the time of discharge.

Censored subjects: The Kaplan- Meier survival analysis estimates the probability of the subjects surviving a certain time duration taking into account "censoring".[381] For this analysis the survival time was chosen as 60 days since almost all patients were discharged within 60 days from the nursery. All infants who were alive at the end of 60 days period and the infants who left the NICU alive before the completion of the time duration (60 days) are considered "censored". In this cohort all 73 infants who left "against medical advice before completion of treatment" should have been included in the "censored" group. However since 41 of the 73 were moribund and death was certain, they are included in the "expired group". The remaining 32 left the NICU in a relatively stable condition are included in the "censored" group.

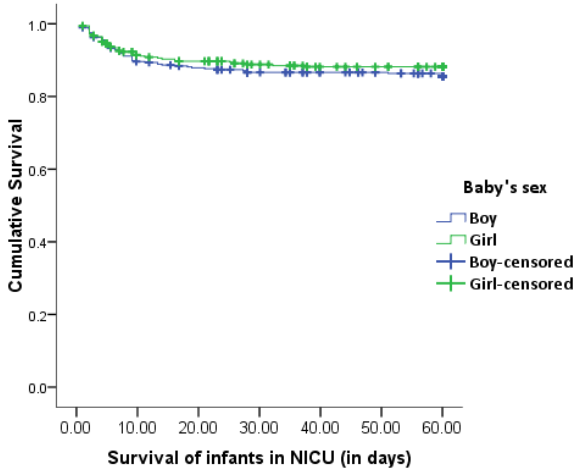
The Kaplan Meier graphs are shown in figures (8 a-h) and compare the group with the morbidities with the group without the morbidity, as presented below.

a. Boys vs. Girls (Figure 8 a)
b. Infants whose gestational age (<28 weeks and 28-31 weeks) compared with those whose gestational age>32 weeks. (Figure 8 b)
c. Infants with birth weight (500 g-999 g) and (1000-1199 g) are compared with those whose birth weight is >1200 g (Figure 8 c)
d. Infants with PDA compared to those without PDA (Figure 8 d)
e. Infants with septicemia compared to those without septicemia (Figure 8 e)
f. Infants with septicemia compared to those without RDS (Figure 8 f)
g. Infants with NEC compared to those without NEC (Figure 8 g)
h. Infants with asphyxia compared to those without asphyxia (Figure 8h)

Chi-square test using Log rank (Mantel-Cox) was done to look for significant difference in survival ($p < 0.01$) between the two groups (those with the morbidity and those without the morbidity). From the graphs and the Log-Rank values it is clear that there was significant difference in the survival rates in infants with the morbidities as compared to the infants without the morbidities. Children with the morbidities (PDS, RDS, NEC grade 2 and above, birth weights below 1200 g, gestational ages below 32 weeks, asphyxia and septicemia) had a poorer survival rates compared to children who did not have these risk factors. There was no significant difference in the survival of boys compared to that of girls.

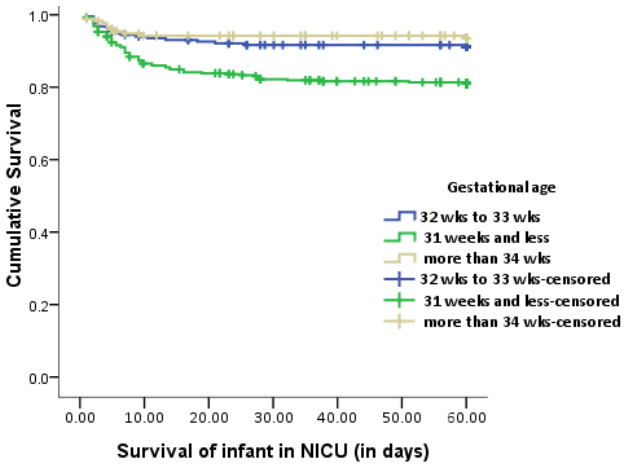
KAPLAN MEIER SURVIVAL GRAPHS

8a: Survival of male infants vs. female infants in the NICU



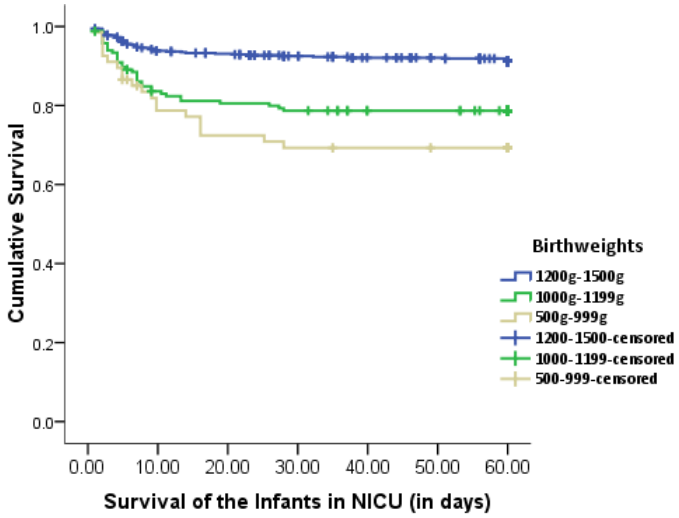
	Mean survival (days)	SE	95% CI	p-value (Log Rank)
Boys	53.043	0.894	51.290- 54.796	**0.307**
Girls	53.988	0.883	52.25- 55.719	
Overall	53.486	0.630	52.251-54.722	

Figure 8b: Survival of infants based on their gestational age



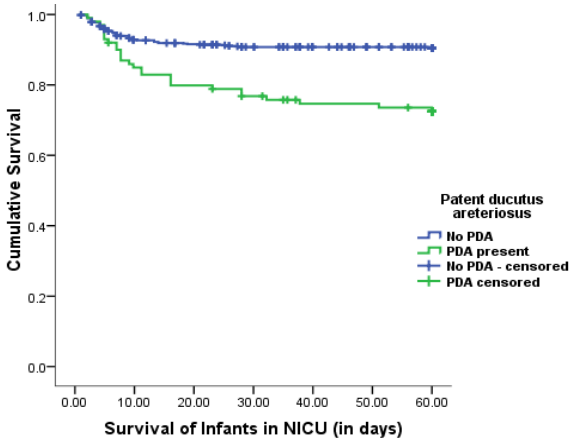
Gestational age	Mean survival (days)	S.E	95% CI	p value on Log-Rank
32-33 weeks	55.635	1.021	53.633-57.636	**P <0.001**
31 wks and less	50.662	1.035	48.633-52.691	
>34 weeks	56.776	1.039	54.741-58.812	
Overall	53.421	0.633	52.180-54.661	

Figure 8 c: Survival of infants based on the birth weight



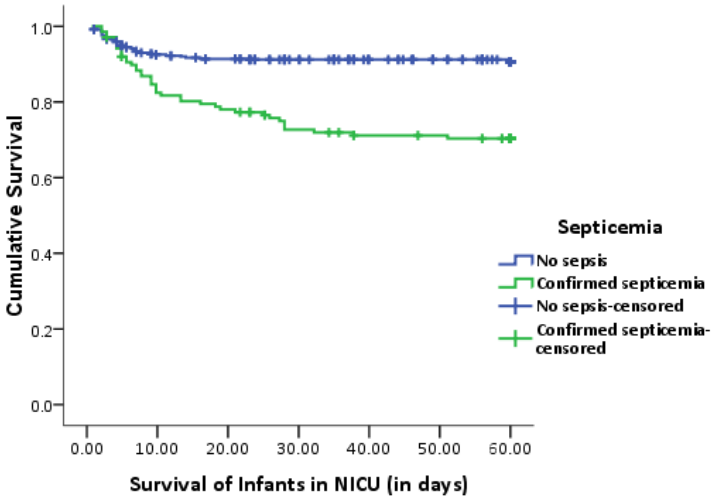
Birth wt. category	Mean survival (days)	S.E	95% CI	p value on Log-Rank
1200-1500	55.921	.615	54.714-57.127	**P<0.001**
1000-1199	48.878	1.687	45.573-52.184	
500-999	44.440	2.941	38.675-50.205	
Overall	53.421	.633	52.180-54.661	

Figure 8 d: Survival of infants based on presence of PDA



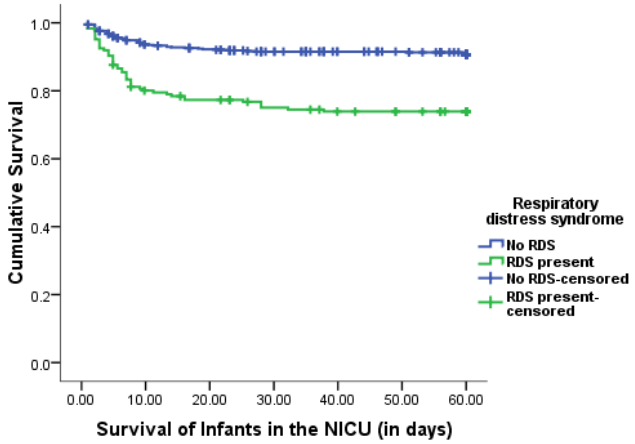
	Mean survival (days)	SE	95% CI	p value on Log-Rank
No PDA	55.215	0.598	54.043-56.387	**P<0.001**
PDA present	47.882	2.169	43.631-52.133	
Overall	54.237	0.597	53.066-55.408	

Figure 8 e: Survival of infants based on presence of Septicemia



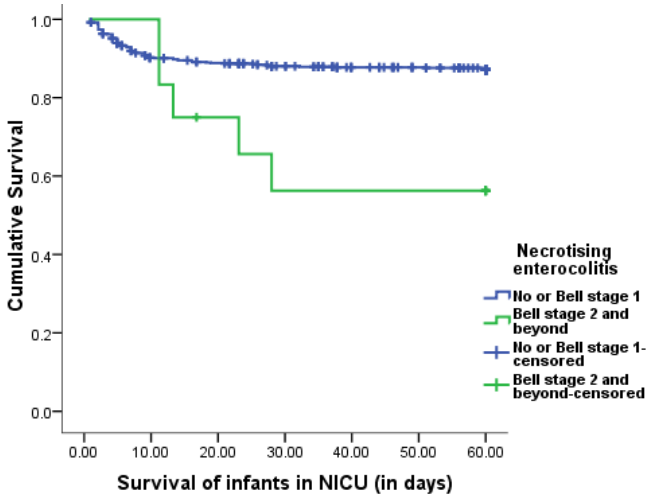
	Mean survival (days)	S.E	95% CI	Log-Rank p-value
No septicemia	55.240	.620	54.024-56.456	**<0.001**
Confirmed septicemia	46.279	1.891	42.573- 49.986	
Overall	53.622	.625	52.398- 54.847	

Figure 8 f: Survival of infants based on presence of Respiratory Distress syndrome



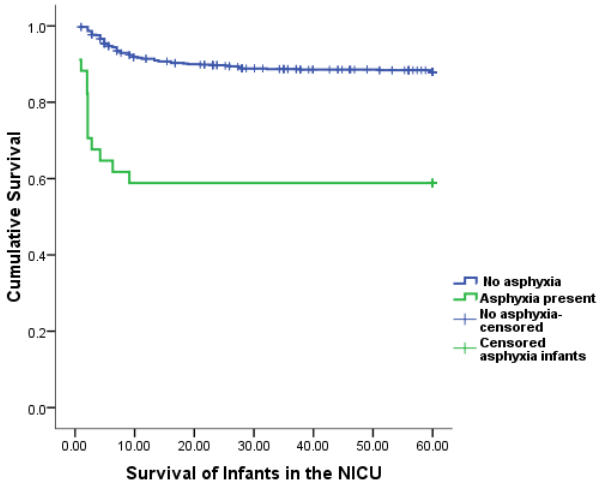
	Mean survival (days)	S.E	95% CI	p value Log –Rank (Mantel-Cox)
No RDS	55.577	0.612	54.377-56.778	**P <0.001**
RDS present	46.665	1.686	43.361-49.969	
Overall	53.421	0.633	52.180-54.661	

Figure 8 g: Survival of infants based on presence of severe NEC



	Mean survival (days)	S.E	95% CI	P Value on Log-Rank (Mantel-Cox)
NEC <Stage2	53.607	0.633	52.367-54.847	P=0.005
NEC ≥Stage 2	41.516	6.335	29.098-53.933	
Overall	53.421	0.633	52.180-54.661	

Figure 8 h: Survival of Infants based on the presence of Perinatal asphyxia



	Mean survival (days)	S.E	95% CI	p-value on Log-Rank test
No Perinatal asphyxia	54.202	0.608	53.00-55.39	P<0.001
Asphyxia present	36.41	4.842	26.92-45.9	
Overall	53.421	0.633	52.180-54.661	

B. COX PROPORTIONAL HAZARDS MODEL

The Cox proportional Hazards model was done to explore the relationship between the various risk factors (found to be significant in the Kaplan Meier graphs) on the **survival time** of the children in the cohort. The Cox model explores the independent effect of each of the risk factors on the **time to death** after taking into account ("adjusting") the effects of the other risk factors.[382,383] Before testing the proportional hazards assumption we plotted the "log-log plots". Since the curves were parallel indicating that the hazards are proportional across the groups we went ahead and did the Cox Proportional hazards regression model. The log-log plots are shown in the "Appendix section".

The Hazard Ratio which is obtained from the Cox model is an estimate of the ratio of the hazard rate (of death) between two groups (the group with the morbidity and the group without the morbidity) *at any given point of time*. The group without the morbidity is considered as the "reference group". If the hazard of death is greater than 1, then the hazard of death is greater for the individual in that group compared to the hazard of death in the reference group.

After plotting the Log-log plots a bivariate analysis between the group with the morbidity and the group without the morbidity was done using the Cox proportionate hazards model to obtain the unadjusted hazards ratio. If hazards ratio was found to be significant ($p<0.05$) then the variables were entered into a step-wise multivariate regression model to estimate the independent risk of death. The final model is presented in **table 16** (below).

In the final model after adjusting for the other risk factors, gestational age was not found to be significant.

Table 16: Final model of Cox proportional hazards model on the time to death

Risk Factor	Regression Coeff. (SE)	Wald	p-value	Adjusted Hazards Ratio (HR)	95.0% CI for HR	
					Lower	Upper
Birth wt. 1000-1199 g	.791 (.247)	10.222	.001	2.205	1.358	3.581
Birth wt. <1000 g	.957 (.303)	9.957	.002	2.604	1.437	4.719
NEC	.838 (.482)	3.018	.082	2.312	.898	5.953
RDS	.800 (.231)	12.041	.001	2.226	1.417	3.498
Septicemia	1.031 (.221)	21.765	.000	2.803	1.818	4.321
PDA	.597 (.256)	5.439	.020	1.817	1.100	3.001
Perinatal asphyxia	1.421 (.365)	15.144	.000	4.143	2.025	8.475

After controlling the effects of the other variables –

- ***at any given point in time****, the likelihood of death is 2.6 times in the category (500 g-999 g) and two times in the birth weight category (1000 g-1199 g) as compared to those whose birth weights were in the category (1200-1500 g).*
- *the likelihood of death is three times more at any given point of time in infants with septicemia, compared to infants without septicemia and this is significant* (p <0.001)
- *the likelihood of death is two times more at any given point of time in infants with PDA, compared to infants without PDA and this is significant* (p <0.02)
- *the likelihood of death is two times more at any given point of time in infants with RDS, compared to infants without RDS and this is significant*
- *the likelihood of death is four times more at any given point of time in infants with asphyxia a, compared to infants without asphyxia and this is significant* (p <0.001).

- *the likelihood of death is two times more at any given point of time in infants with NEC, compared to infants without NEC and this is moderately significant* (p = 0.08)

Comparison between Multivariate Logistic regression Model (table 15) and Cox proportional Hazard model (table 16): ***Significantly the same risk factors – Birth weight less <1000 g, Birth weight of 1000-1199 g, NEC, RDS, PDA, Septicemia and Perinatal asphyxia predicted mortality independently in both models.***

5.1.8 OUTCOMES AT THE TIME OF DISCHARGE FROM NICU

643 of the total of 776 (82.9%) were discharged alive from the nursery. Sixty infants (7.73%) had died during their period of nursery stay and 73 (9.4%) infants were discharged prior to completion of treatment against medical advice. The practice in the NICU was to keep babies till they reached 1800 g or until they breast feeding well. The 73 infants who were discharged before completion of treatment are not included for analysis in the second phase of the study. Forty one of the 73 children were terminally ill and left the nursery in a moribund condition. We were able to confirm that twenty of them had died. The remaining children were very sick when they left the NICU so it is likely they too would have expired. Thirty two infants among those who went against medical advice left in a stable condition. We were able to trace 8 of them. Four of these infants survived and came back for the assessment at two years of age. We were able to contact the parents of another four infants over the telephone. They were alive at two

years; however the parents were unwilling to bring them for the assessment and were apparently developing normally.

Figure 9 on page 134, shows the outcomes of the infants in the NICU

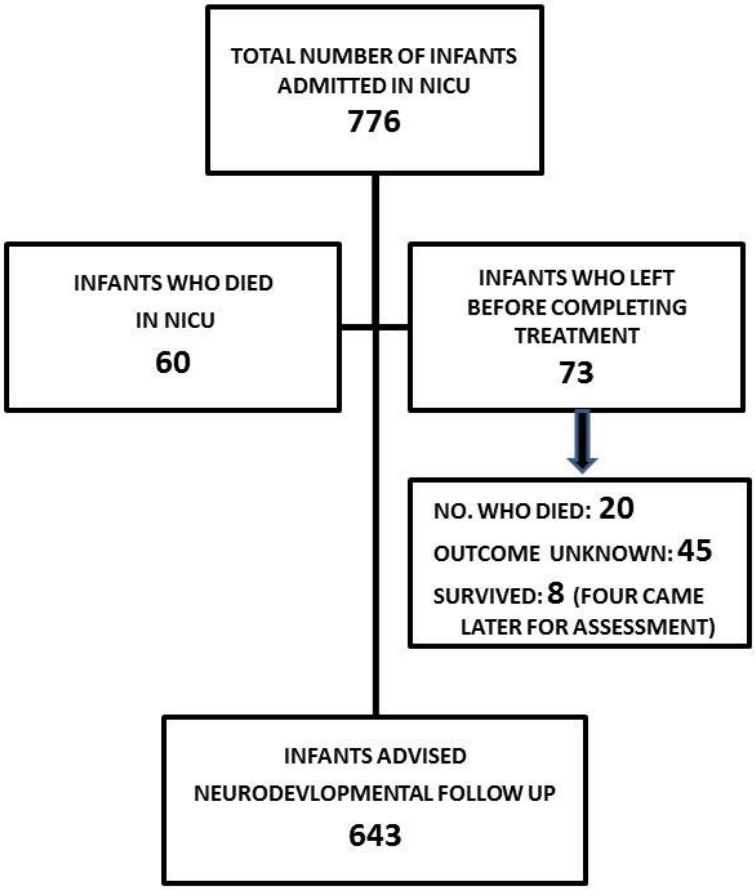
5.1.9 SURVIVAL in NICU

Of the 776 children admitted into NICU 60 expired and 73 left before completion of treatment. Of the 73, eight children were alive and the outcomes of 65 infants are not known, although most of them were very sick when they left the NICU

The **survival rate was 92.26**% (**89.4-94.54,** 95% CI)

The **adjusted survival rate** (assuming that those whose outcome is not known had also died was **83.89% (80.22-87.14,** 95% CI)

Figure 9: THE OUTCOMES OF INFANTS WHO WERE ADMITTED IN THE NICU



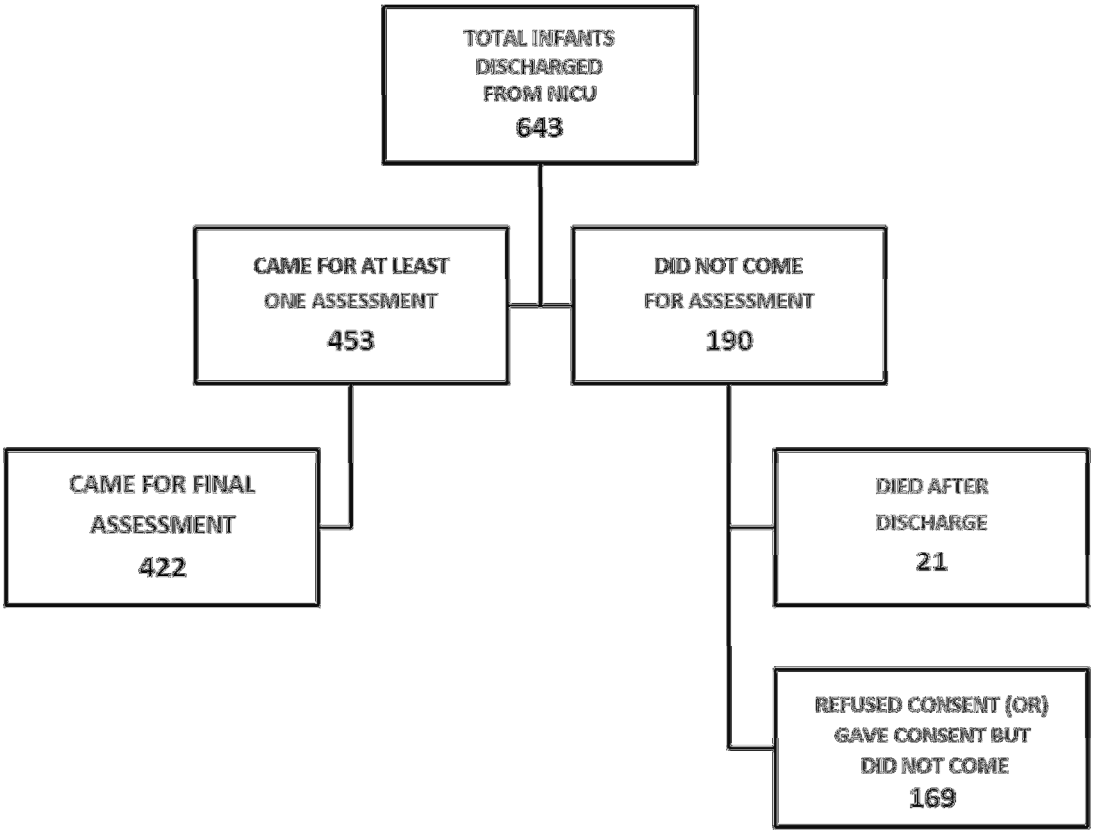
5.2 SECTION 2 - THE RESULTS OF PHASE 2 (THE FOLLOW-UP PHASE).

After excluding the infants who had died and the infants who left the NICU against medical advice before the completion of the treatment, the remaining 643 infants were scheduled for prospective follow-up of their growth, neurologic status and development, till the final neurodevelopmental assessment at 18 - 24 months corrected gestational age. These infants were followed up regularly according to the protocols of the High Risk Infant follow-up Clinic of the Institution. As the principal investigator of the study, I saw the infants along with the Neonatologists and the Occupational therapist in the High risk infant clinic. During these visits the development of the infants were assessed and neurologic examination was done using the Amiel-Tison Neurologic assessment tool. Hearing and vision were also assessed according to standard protocols as described in the "Patients and Methods" section.

Of the 643 infants who were discharged after completion of treatment in NICU, 190 infants did not come for any of the assessments. Twenty one of them died within a few months after being discharged from nursery. In most of them the cause could not be ascertained. Of the remaining 169, the parents of 122 infants refused to give consent to come for the follow-up phase, because of the distance and the inconveniences involved. Most of them could not be contacted and so we have no idea about their outcome. Parents of forty seven of the 169 infants gave consent but did not come for any of the assessments. Some of them came for a few visits to the High risk infant clinic and then stopped coming. So eventually only 453 (70.45%) came for at least one assessment (motor assessment using the Peabody assessment at one year ***and/or*** the final

developmental assessment). 422 of the 643 infants came till the final neurodevelopmental assessment. So our follow-up rate was 65.6%. For the purpose of the analysis, ***all infants who did not come for the final neurodevelopmental assessment, irrespective of the cause are considered lost to follow-up***. This group is analyzed further in **section 4**. The **figure 10** (below) gives a visual summary of the children during the follow-up phase.

Figure 10: Flow chart showing the summary of the children who entered the Developmental Follow-up phase



This section therefore considers the developmental outcomes of the 422 infants who came for the final assessment. The section is arranged in the following manner -

5.2.1: This sub-section presents the results of the ***neurodevelopmental assessment***

5.2.2: Objective 1 of the study - ***the incidence of poor neurodevelopmental outcome and CP in this cohort is calculated.***

5.2.3 & 5.2.4 Presents the relationship between the ***post-natal growth status*** measured at the time of assessment and various factors (sex, gestational age, birth weight). Z scores of weight, head circumference and length were calculated using the WHO-ANTRHO software

5.2.5: Briefly compares the ***ELBW infants with the non-ELBW infants*** – their mean birth-weights, gestational ages and GQs.

5.2.6: This subsection explores the relationship between ***perinatal and neonatal risk factors and the final GQ*** through bivariate analysis and multivariate logistic regression model to give a final model which can predict poor neurodevelopmental outcomes (**Objective 2 of the study**)

5.2.7: As part of measuring the neurodevelopmental outcomes, children ***with significant language delay*** were analyzed. A logistic regression model to predict poor language is presented.

5.2.8: Discusses the details of the ***interim motor assessment at*** one year and considers its abilities to predict the results of the final neurodevelopmental assessment.

5.2.9: This sub-section presents a description of all the children who had ***neurologic abnormalities*** and those with significant developmental delay (GQ of less than 70).

5.2.1 THE RESULTS OF THE NEURODEVELOPMENTAL ASSESSMENT

The final neurodevelopmental assessment was done using the Griffith's Mental Developmental Scales (GMDS) and the General Quotient (GQ) obtained from the GMDS was considered the final outcome of the neurodevelopmental assessment. The neurologic status of the children was determined using the Amiel-Tison neurologic assessment (ATNA). Children with neurologic abnormalities, perform poorly in the developmental assessment (as mentioned earlier in **3.2.8, p.47**), so a low GQ is also an indicator of the presence of neurologic abnormalities in addition to the developmental delay.

Although initially it was planned that the final assessments using the GMDS would be done between 18 and 24 months corrected gestational age, only 348 infants (82.2%) could be assessed during this period. Thirteen infants (3%) were assessed between 16 and 18 months, 46 infants (10.9%) were assessed between 24 and 30 months and 17 infants (4.02%) were above 30 months corrected gestational age at the time of the final neurodevelopmental assessment. These adjustments had to be done for the convenience of the parents, many of whom were coming from faraway places. The mean age of the assessment was ***20.8 months (± 4) and median age of assessment was 19 months.***

a) **Results of the Final Neurodevelopmental Assessment**

423 of the 643 (65.6%) children came for the final neurodevelopmental assessment. In one child the assessment could not be completed because he was very apprehensive. So finally 422 children comprising 221 boys (52.4%) and 201 girls (48.6%) were assessed completely.

There were five children with cerebral palsy in the cohort. They are described more in detail in 5.2.9. In four of the five children with CP and in three other children with

profound developmental delay, the GQ could not be quantified accurately in view of their disabilities and therefore for the purpose of analysis they were arbitrarily given a GQ of <40. ***These 7 children were not included in the calculation of the mean GQ.***

The mean GQ of the study cohort after excluding these seven children, was 93.6 (SD ± 13.01) and the median GQ was 96. The comparison of the GQs between girls and boys are presented in **table 17** along with the histogram depicting the distribution of the GQs **(figure 11).** The mean GQ among the boys was 92.9 (±13.08) and among the girls was 94.97 (±12.8). There was a significant difference between the GQ of the boys and the girls ($p = 0.04$) with the girls having marginally better developmental outcomes compared to the boys.

Normality of the GQ distributions of the boys and girls was tested using standard tests (p-value on Shapiro-Wilk and p-value on the Kolmogorov-Smirnov test).[384] Both the tests showed that the p-value was below 0.01 which means that the distributions of the GQ in both boys and girls ***were not normally distributed***. Visual inspection of the histograms also showed that in both boys and girls the distributions were asymmetrical with tail to the left (negative skew). The negative skew indicates that there were more children with GQs in the higher range, indicating a good neurodevelopmental outcome.

Good neurodevelopmental outcome: Indeed there were 374 children (88.6%, 193 boys and 181girls) whose GQ was within the normal range of within 2 standard deviations (>76) and thus considered to have a good neurodevelopmental outcome. Among the children who were within normal limits, there were 292 children (69.2%, 143 boys and 149 girls) whose GQ was within one standard deviation (≥88) and there were 82 children (19.4%, 50 boys & 32 girls) whose GQ was between -1SD and -2SD (GQ of 76-87)

FIGURE 11: DISTRIBUTION OF THE GENERAL QUOTIENT OF THE GMDS IN THE BOYS AND GIRLS WHO HAD FINAL ASSESSMENT

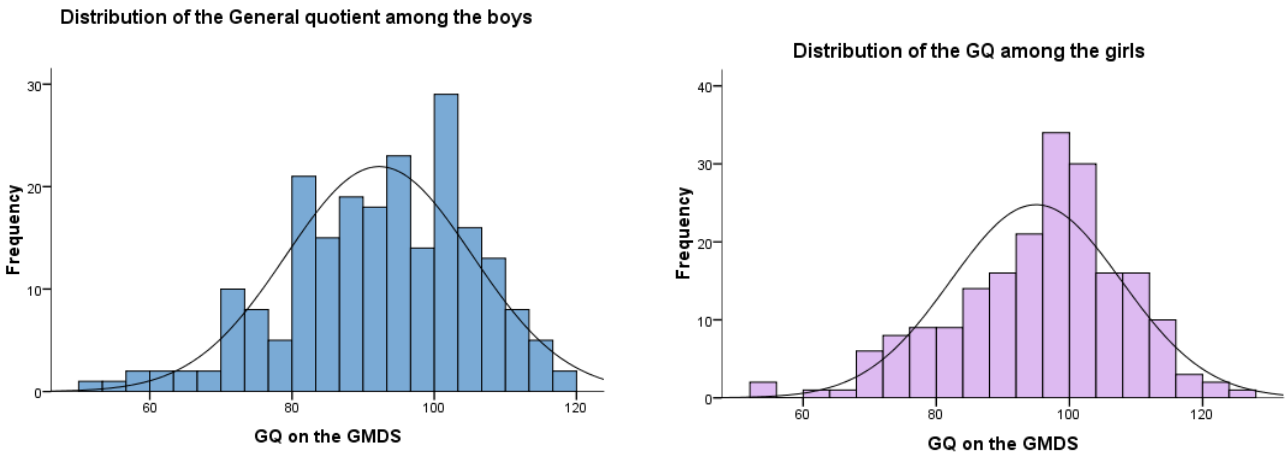


TABLE 17: COMPARISON OF THE GENERAL QUOTIENTS OF THE BOYS AND GIRLS

	General Quotient on the GMDS*	
	Boys	**Girls**
Numbers (%)	221 (52.4%)	201 (47.6%)
Mean	92.92	94.97
Median	94	97
Std. Deviation	13.08	12.82
Range (Min. to Max.)	50 - 117 (67)	53 – 124 (71)
Skewness	-0.551	-0.555
Kurtosis	0.103	0.343
P-value	0.04	
Normality tests		
Skewness Z-value	-3.32	0.312
Kurtosis Z-value	-3.23	0.912
Kolmogorov-Smirnov "p"	0.010	<0.001
Shapiro-Wilk "p"	<0.001	0.003

***Seven children with Cerebral Palsy and those with severe developmental delay (GQ<50) not included in the analysis although included in the total**

Poor neurodevelopmental outcome: 48 children (11.4%) of the 422 children had poor neurodevelopmental outcome (their GQs were more than 2SD below the mean). This comprised 28 (12.7%) of the total of 221 boys and 20 girls (9.9%) of the 201 girls. This includes the five children (3 boys and 2 girls) with cerebral palsy.

b) GQ of the children according to gestational age at birth

The **Figure 12 and table 18** compare the GQ of the 415 children who completed the study across various gestational ages. (Five children with CP and two children whose GQ could not be quantified are not included which is why there are 415 and not 422 children). The box-whisker graph (Fig. 12) and its summary are presented in **table 20** (below)**.** The median GQ was almost the same (96-98) for the four groups (<28 weeks, 28-31 weeks, 32-33 weeks and ≥37 weeks) and slightly lesser in the 34-36 weeks group (92.5). However on the Kruskall-Wallis test, the p-value was 0.424, showing that there was no significant difference between the five groups.

c) GQ of children according to birth weights

Figure 13 and table 19 shows the GQ of the children in the various ages in 5 weight categories. The median GQ was almost the same (95-97) between the groups except for one group. There was no significant statistical difference between the groups (p= 0.952) [The Kruskall Wallis test was used for comparison, rather than the one-way ANOVA, because the GQs in each group are not normally distributed].

FIGURE 12: THE GENERAL QUOTIENT DEPENDING UPON THE GESTATIONAL AGE AT BIRTH

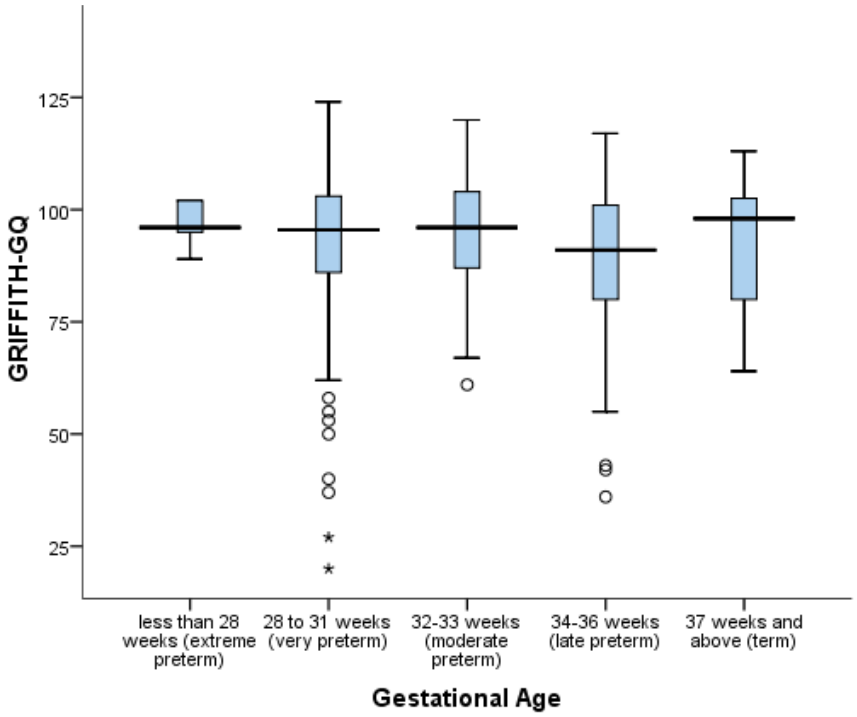


TABLE 18: GENERAL QUOTIENTS OF CHILDREN IN VARIOUS GESTATIONAL AGE CATEGORIES

	< 28 weeks	28-31weeks	32-33 weeks	34-36weeks	≥ 37weeks
Numbers	5	190	126	78	16
Mean GQ	96.80	93.62	94.94	91.18	92.56
5% Trimmed Mean	96.94	94.17	95.24	91.53	93.01
Median GQ	96.00	96.00	96.00	92.50	98.00
Std. Deviation	5.450	13.124	12.474	13.458	14.814
Minimum	89	50	61	55	64
Maximum	102	124	120	117	113
Range	13	74	59	62	49
Skewness	-.514	-.663	-.428	-.384	-.528
Kurtosis	-.667	.716	-.308	-.195	-.766
P-VALUE	0.424 (KRUSKALL-WALLIS)				

FIGURE 13: THE GENERAL QUOTIENT DEPENDING UPON THE BIRTH-WEIGHT AT BIRTH

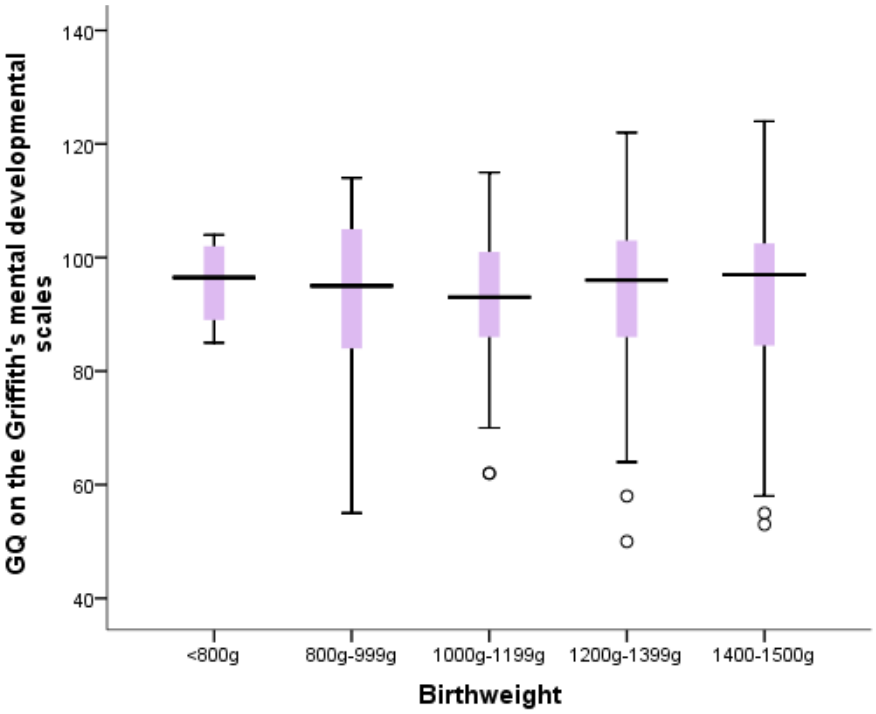


TABLE 19: GENERAL QUOTIENTS OF CHILDREN IN VARIOUS BIRTH-WEIGHT CATEGORIES

	<800g	800-999g	1000-1199g	1200-1399g	1400-1500g
Numbers	4	26	86	155	144
Mean GQ	95.50	91.96	92.94	93.97	93.72
5% Trimmed Mean	95.61	92.65	93.30	94.40	94.12
Median GQ	96.50	95.00	93.00	96.00	97.00
Variance	69.667	267.958	139.397	165.291	180.093
Std. Deviation	8.347	16.369	11.807	12.857	13.420
Minimum GQ	85	55	62	50	53
Maximum GQ	104	114	115	122	124
Range of GQ	19	59	53	72	71
Skewness	-.537	-.594	-.395	-.489	-.634
Kurtosis	-1.258	-.549	-.161	.325	.306
p-VALUE	0.952 (KRUSKALL-WALLIS)				

d) Comparing the sub-quotients between girls and boys among the subscales of the GMDS.

The GQ is a composite score based on the sub-quotients (SQ) obtained on five subscales (in children less than 24 months) and six subscales in older children. As mentioned earlier the GQ of the girls **(table 17)** was significantly better than the boys. **Table 20** shows the mean sub-quotients between girls and boys in all the 6 subscales. ***The median SQ in all the subscales except for the "Performance" subscale was better in girls as compared to the boys***. This was statistically significant ($p<0.05$) in three of the subscales.

5.2.2 INCIDENCE OF POOR NEURODEVELOPMENTAL OUTCOME AND CEREBRAL PALSY

One of the main objectives of the study was estimation of the incidence of poor neurodevelopmental outcome (GQ <2SD).

From the information presented above, ***the incidence of poor neurodevelopmental outcome was estimated to be:***

48/422 - 11.37% (8.6%-14.9% 95% CI) (This includes the children with cerebral palsy)

To calculate the incidence of cerebral palsy, the 31 children who had the one year assessment but did not come for the final assessment were also included. Although the developmental outcome in terms of their GQ cannot be ascertained from the one year assessment, they were neurologically normal at one year without any signs of CP.

So the incidence of cerebral palsy is 5/453 is 1.10%. (0.4%-2.63%, 95%CI).

Table 20: COMPARING THE SUB-QUOTIENTS (SQ) of the VARIOUS DOMAINS OF THE GMDS BETWEEN BOYS AND GIRLS

	LOCOMOTOR		PERSONAL - SOCIAL		HEARING & LANGUAGE		EYE-HAND		PERFORMANCE		PRACTICAL REASONING	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
Mean of SQ	105.36	106.03	92.06	97.04	84.58	88.30	98.32	102.35	89.32	88.72	86.14	87.58
5% Trim'd Mean	106.45	107.17	92.31	96.99	85.23	88.79	98.49	102.70	89.80	89.02	85.96	86.75
Median of SQ	107.00	112.00	94.00	96.00	88.00	91.00	98.00	103.00	92.00	90.00	87.00	87.00
Variance	425.71	376.19	258.34	311.41	308.46	263.38	239.084	226.61	244.15	234.16	138.03	160.2
Std. Dev.	20.633	19.396	16.073	17.647	17.563	16.229	15.462	15.054	15.625	15.302	11.749	12.657
Minimum SQ	50	39	45	58	31	34	50	58	45	49	66	65
Maximum SQ	154	142	132	144	128	122	140	145	123	122	110	129
Range of SQ	104	103	87	86	97	88	90	87	78	73	44	64
P-VALUE	0.732		0.003		0.026		0.008		0.693		0.993	

5.2.3 GROWTH of THE BABIES

The growth parameters (weight, length and head circumference) of the children in the cohort were monitored during every visit to the High Risk Infant Clinic (HRIC). The Z-scores of the final weight, length and head circumference at the time of the neurodevelopmental assessment was computed using the World Health Organization "ANTHRO" software.[376]

Infants were classified as -

- ***underweight*** if the Z- score of weight for age was if they were more than 2SD below the mean,
- ***microcephaly*** if the Z- score of head circumference for age was more than 2SD below the mean,
- ***short*** if the Z- score of length for the age was more than 2SD below the mean.

Table 21 compares the Z-scores of the various growth parameters of boys with that of the girls. Although the distributions of weight for age, weight for length and head circumference seem to be similar, the boys are significantly shorter than the girls (p=0.004). Another worrying aspect is that 36.3% of the children were underweight, 44% were short and 43.8% had microcephaly on comparing to the WHO standards.

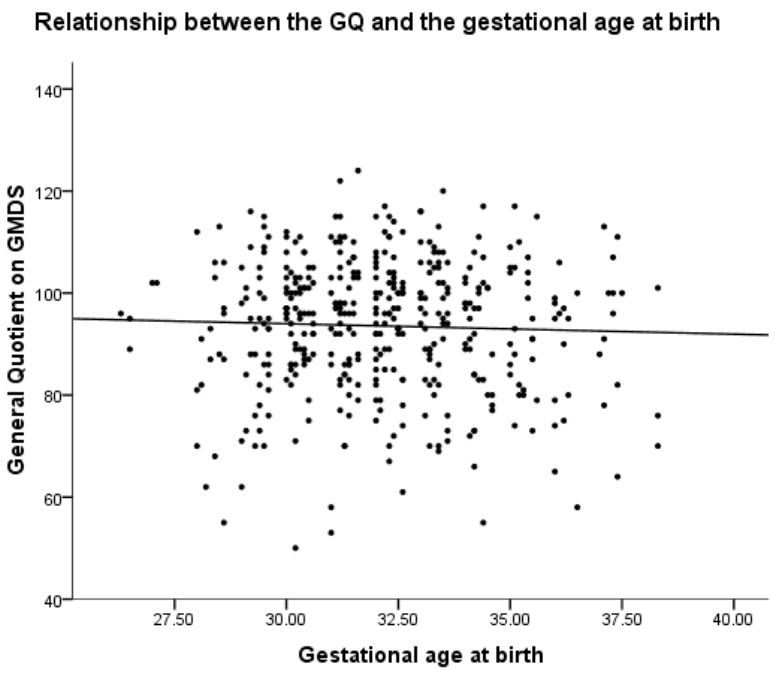
5.2.4 RELATIONSHIP BETWEEN GQ AND BIRTH WEIGHT & GESTATIONAL AGE.

The scatter plots shown in **Figure 14** explore if there was any linear relationship between the GQ & gestational age and GQ & birth-weight. It is very obvious that there is no relationship between the final GQ and the gestational age or birth weight. The R^2 for GQ vs. gestational age was 0.001 and for GQ vs. birth-weight was 0.003. This means that

TABLE 21: ANTHROPOMETRIC (GROWTH) PARAMETERS OF THE STUDY COHORT ESTIMATED AT THE TIME OF ASSESSMENT

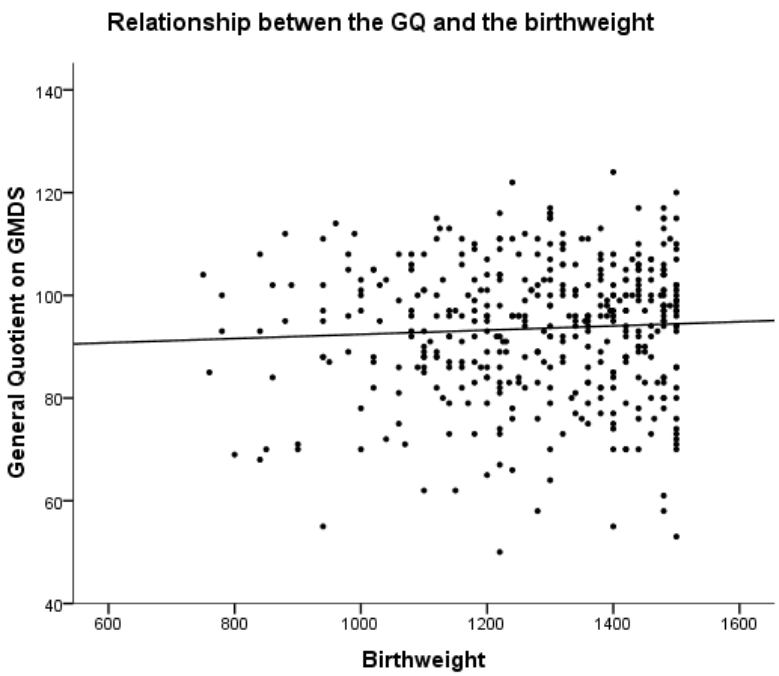
	Weight for length		Weight for age		Head circumference for age		Length for age	
	Boys	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
Mean (of the Z-scores) **95% CI**	-1.0383 -1.186 to -.89	-1.0247 -1.158 to-.89	-1.8462 -2.0 to-1.689	-1.6551 -1.81 to -1.50	-1.8804 -2.04-1.723	-1.8426 -1.98 -1.695	-2.1243 -2.30 to-1.946	-1.7098 -1.901 to 1.52
5% Trimmed mean	-1.0440	-1.0180	-1.8417	-1.6203	-1.8569	-1.8136	-2.1247	-1.6715
Median (of Z- scores)	-1.0500	-.9200	-1.8000	-1.6550	-1.8300	-1.8450	-2.0900	-1.7100
Variance	1.487	1.122	1.666	1.490	1.679	1.375	2.158	2.317
Std. Deviation	1.21949	1.05903	1.29080	1.22071	1.29594	1.17280	1.46900	1.52205
Minimum	-4.07	-4.93	-6.94	-5.93	-7.85	-6.79	-8.68	-9.83
Maximum	2.20	1.65	1.91	1.61	2.07	1.56	2.58	7.27
Range	6.27	6.58	8.85	7.54	9.92	8.35	11.26	17.10
% of children <2 SD	22%	21%	39.3%	33%	43.2%	44.5%	49.5%	38%
p-value	0.868(-0.215-0.181)		0.137 (-0.388-0.052)		0.751 (-0.253-0.183)		0.004 (-0.657-0.126)	

FIGURE 14: SCATTER PLOTS EXPLORING THE RELATIONSHIP BETWEEN GQ & GESTATIONAL AGE AND GQ & BIRTH-WEIGHT



Pearson's correlation coefficient 'r' is -0.036

R^2 is 0.001



Pearson's correlation coefficient 'r' is 0.055

R^2 is 0.003

gestational age accounts only 0.1% and birth weight accounts 0.3% of the variance in the General quotient in this cohort.

5.2.5 COMPARISON OF ELBW (<1000 g) vs. non ELBW (1000-1500 g)

The **table 22** (below) shows the results on comparing the GQ of the ELBW children with the GQ of children whose birth weights ≥1000 g.

Table 22: Comparison of ELBW infant with non-ELBW (≥1000 g) children

	ELBW (<1000 g)	Non ELBW (1000-1500 g)	p-value
Number	30	392	
Sex (Boys %)	43%	53%	
Mean GQ (SD)	92.4 (15.5)	93.6 (12.8)	0.918
Children with GQ <2SD (%)	20%	11%	0.123
Children with CP	0	5/392 (1.3%)	
Mean Gestational age	32.7	30.4	<0.001

There was a predominance of girls in the ELBW group. There was no significant difference in the mean GQ between the groups, although there is a slightly higher proportion of children with developmental delay in the ELBW group. The mean gestational age in the ELBW group in this cohort is significantly high (30 weeks), compared to Western cohorts where the ELBW babies are usually less than 27 weeks. Although the incidence of CP increases with decreasing birth weight, all the children with CP weighed more than 1000 g at birth, so ***ELBW was not a cause of CP in this cohort.***

Table 23: BIVARIATE ANALYSIS: PERINATAL & NEONATAL CHARACTERISTICS AND GROWTH WITH POOR DEVELOPMENTAL OUTCOME GQ <2SD

Risk Variables	Normal GQ No. (%)	GQ<76 (2SD) No(%)	P value	Relative Risk 95% CI
MATERNAL and PATERNAL CHARACTERISTICS				
PIH: No PIH PIH	**209**(87) **165**(90)	**30**(13) **18**(10)	0.384	0.970 0.906-1.038
Diabetes: No Diabetes Diabetes in pregnancy	**342**(88) **32**(94)	**46**(12) **2**(6)	0.404	0.937 0.855-1.026
Twins: Singletons Multifetal Pregnancy	**271**(89) **103**(89)	**35**(11) **13**(11)	0.947	0.997 0.924-1.076
Antenatal steroids: Received No steroids given	**307**(89) **67**(87)	**38**(11) **10**(13)	0.622	1.023 0.931-1.123
Delivery: Normal Delivery Cesarean or instrumental	**118**(85) **256**(90.4)	**21**(15) **27**(9.6)	0.090	0.938 0.867-1.016
Infertility treated: No treatment Conceived after treatment	**314**(87) **60**(94)	**44(**13) **4**(6)	0.161	.916 0.832-1.001
Mother's Education: >8th std. $\leq$ 8th Standard	**313**(89) **51**(84)	**38**(11) **10**(16)	0.211	1.067 0.949-1.199
Fathers' Education: >8th Std $\leq$ 8th Standard	**302**(89) **62**(84)	**36**(11) **12**(16)	0.177	1.066 0.958-1.187
NEONATAL COMPLICATONS				
PDA: No PDA PDA Present	**335**(89) **39**(89)	**43**(11) **5**(11)	0.998	0.998 0.373-2.67
Asphyxia: No asphyxia H/o asphyxia	**362**(89) **12**(80)	**45**(11) **3**(20)	0.284	1.12 (0.861-1.435)
IVH: Normal to grade 2 Grade 3 and 4	**363**(88) **2**(100)	**48**(12) **0**(0)	1.000	0.883 0.853-0.915
Septicemia: No Sepsis Confirmed Sepsis	**327**(89) **47**(89)	**42**(11) **6**(11)	0.990	0.999 0.902-1.108
Hypoglycemia: Absent H/o Hypoglycemia present	**342**(89) **32**(86)	**43**(11) **5**(14)	0.594	1.027 0.900-1.172
RDS: No RDS H/o RDS present	**295**(88) **79**(92)	**41**(12) **7**(8)	0.290	0.956 0.887-1.030
NEC: No or Bell stage 1 Bell stage2 & beyond	**370**(89) **4**(80)	**47**(11) **1**(0)	0.455	1.109 0.715-1.72
Hypotension: Absent Hypotension present	**332**(89) **42**(82)	**39**(11) **9**(18)	0.132	1.087 0.953-1.240
Any NICU morbidity: Absent NICU morbidity present	**138** (87.3) **236** (89.4)	**20** (12.7) **28** (10.6)	0.52	0.997 (0.91-1.05)

Table 23 (contd.) INFANT CHARACTERISTICS AND POST NATAL GROWTH PARAMETERS

Risk Variables	Normal GQ No. (%)	GQ <76 (-2SD) No. (%)	P value	Relative Risk 95% CI
Boys **Girls**	**193**(87) **181**(90)	**28**(13) **20**(10)	0.380	0.970 0.906-1.038
Growth: AGA SGA	**264**(90) **110**(85)	**28**(10) **20**(15)	0.083	1.068 0.984-1.160
Birth weight: 1200-1500g 1000-1199g 500-999g	**272** (89.2) **78** (89.6) **24** (75)	**33** (10.8) **9** (10.4) **8** (25)	0.301	
Gestational age: 32-33 weeks ≥ 34 weeks ≤ 31 weeks	**115** (91.3) **82** (83.7) **177** (89.4)	**11** (8.7) **16** (16.3) **21** (10.6)	0.185	
Weight for age Z score within ± 2 SD Z score >-2SD	 **249**(93) **124**(81)	 **19**(7) **29**(19)	**<0.001**	 1.146 1.055-1.246
Length for age Z score within ± 2 SD Z score >-2SD	 **217**(92) **155**(84)	 **18**(8) **30**(16)	**0.006**	 1.102 1.024-1.186
Head Circumference Z score within ± 2 SD Z score >-2SD	 **218**(92) **154**(84)	 **18**(8) **30**(16)	**0.006**	 1.104 1.025-1.188

5.2.6 BIVARIATE and MULTIVARIATE ANALYSIS OF POST-NATAL RISK FACTORS

In order to look at the antenatal, neonatal and perinatal factors which were associated with poor neurodevelopmental outcome (GQ <2SD), bivariate analysis (Chi-square) was done **(table 23).** On the bivariate analysis ***no antenatal or neonatal factors were associated with poor neurodevelopmental outcome.*** The maternal and paternal education levels were also not associated with poor neurodevelopmental outcome.

However the z-scores of anthropometric measurements at the time of assessment - weight for age ($p < 0.001$) at the time of assessment, length for age at the time of assessment ($p = 0.006$), and head circumference ($p = 0.006$) ***were significantly associated with poor neurodevelopmental outcome.***

The above factors were entered into a stepwise multivariate regression model. The best model to predict the GQ <2SD is presented **table 24** (below)**.**

Table 24: Final Multiple logistic regression model for predicting low GQ (<2SD) at the time of neurodevelopmental assessment

Predictor	B coefficient	p-value	Adjusted Odds Ratio (95% CI)
Weight for age	0.918	.007	2.504 (1.281-4.89)
Head circumference for age	1.295	0.149	1.646 (0.836-3.24)
Constant	-2.736	.000	.065

The model predicts that the odds of having a poor neurodevelopmental outcome is two and half times more in children whose Z-scores for weight is >2SD below the mean as compared to those who have Z-score weight in the normal range (±2SD of the mean weight for age). Children whose Z-score for head circumference is less than 2SD have 1.6 times the chance of having poor neurodevelopmental outcome as those with normal head circumference (±2SD of the mean HC for age). Hosmer and Lemeshow Test p-value was.614 (>0.05) indicating that the model is a good-fit. The Area under the curve (AUC) on the Receiver operator characteristic curve was 0.655 (0.569-0.741 95%CI, p <0.001).

5.2.7 SOCIAL QUOTIENT OF THE LANGUAGE SUBSCALE (H&L-SQ) ON THE GMDS AND ITS RELATIONSHIP TO GQ.

In this cohort it was observed that there were children who performed badly in the Hearing and language subscale, but had done well in the other scales, thus their final GQ was within normal limits. According to Ruth Griffiths "Hearing and Language subscale is the most intellectual of the scales and most intellectual children do well in this subscale".[161] Thus language abilities is a good indicator of intelligence as well. ***The correlation between the sub-quotient on the Language scale (SQ-HL) and the overall*** GQ ***was very high (Pearson's correlation coefficient "r" was 0.859, p <0.001***).

On the bivariate analysis (Chi square) the following risk factors were significantly associated with low sub-quotient on the Hearing and language scale (SQ- H&L <2SD) -

- Perinatal asphyxia (p=0.018),
- Twin pregnancy (p=0.036),
- Weight for age below 2SD (p=0.005),

- Head circumference below 2SD (p=0.044),
- Maternal education less than Std. 8 (p=0.012), and
- Male sex (p=0.048).

Except for weight and head circumference, ***the other variables which are related to poor sub-quotient in the language scale are not significantly related to poor GQ as evident from*** **Table 23**. This may be because of the larger sample size of children with poor language (SQ-HL <2SD) compared to the sample of children with poor overall development (GQ <2SD). There were more children (59 children) with SQ-HL <2SD compared to the 48 children with GQ <2SD.

The above variables were entered into a multivariate logistic regression model to obtain a model which could predict a low language sub-quotient. In the model below, in addition to the weight at 2 years which had predicted a low GQ (**table 25**), perinatal asphyxia and low maternal education were also independent predictors of low language sub-quotient.

Table 25 : Final Multiple logistic regression model for predicting language sub-quotient of <2SD (SQ-HL< 2SD)

Predictor	B coefficient	p-value	Unadjusted OR (95%CI)	Adjusted Odds Ratio (95% CI)
Maternal education below 8^{th}	0.764	0.029	2.31 (1.9 -4.5)	2.15(1.083-4.26)
Z- Weight for age below 2SD	0.694	0.017	2.2 (1.3-3.8)	2.00 (1.13-3.54)
Perinatal asphyxia	1.526	0.014	3.6 (1.66-11.2)	4.59 (1.36-15.41)
Constant	-2.285	.000		.102

Hosmer and Lemeshow Test p-value was >0.05 (p=0.810) implying the above model was good fit. The model predicts that the odds of having a poor language outcome is more than two times if the maternal education is less than the 8^{th} standard, twice if the Z-score

for weight is less than 2SD weight at two years of age, and more than 4 times if the child had perinatal asphyxia.

Although the language scores of boys were significantly lesser than the girls and male sex was significantly associated to low Hearing and Language sub-quotient on the bivariate analysis, in the final multivariate logistic regression model, male sex and the Z-score for HC less than 2SD did not predict poor language outcome thus were not included in the final model.

5.2.8 INTERIM ASSESSMENT USING THE PEABODY DEVELOPMENTAL MOTOR SCALES

At the end of one year, an interim motor assessment was done using the Peabody Developmental Motor Scales [2nd edition] (PDMS) by the Occupational therapist. 354 infants had the motor assessment at 12-14 months corrected gestational age. The Total Motor Quotient (TMQ) obtained on the PDMS is a composite score of the fine motor and gross motor abilities of the child.

Of the 354 children, 323 infants returned for the final assessment. The mean TMQ of the children was 101.9 ($\pm$8.3) and the mean of the TMQ of the boys was 101.3 ($\pm$8.6) and that of the girls was 102.6 ($\pm$8). Unlike the GQ, there was no statically significant difference between the boys and girls (p=0.129) in the TMQ scores. The PDMS was done to assess the motor developmental progress and to provide therapy for those who had motor delay.

There were 31 infants who came for the motor assessment at one year but did not come for the final developmental assessment. The motor development of 29 of these 31 infants was within normal limits but two of the infants had low TMQ scores. None of the

children had any neurologic abnormality, thus ruling out cerebral palsy. However since these 31 children did not have a developmental assessment there is no certainty about their final neurodevelopmental outcome.

Can the developmental outcome at 18 - 24 months be predicted depending on the motor outcome at one year of age?

As mentioned earlier 323 children had ***both*** the one year motor assessment using PDMS and the final neurodevelopmental assessment using the GMDS. So using the TMQ and GQ scores of these infants the linear regression technique was used to look for the relationship between the TMQ and the GQ, to see if the TMQ at one year could be used to predict the GQ.

Both Pearson's correlation coefficient "r" and R^2 obtained from the linear regression were highly significant ($p < 0.001$) indicating that there was definite association between TMQ and GQ. The Pearson's correlation coefficient "r" was 0.665 indicating that there was a moderate correlation between TMQ and GQ. On doing the linear regression to quantify the association between TMQ and GQ the R^2 was 0.442. This means that only 44.2% of the variation in GQ could be explained by the TMQ and so the TMQ only partially predicts the final GQ.

The final regression equation to predict GQ using the TMQ is -

GQ = -1.342 + 0.939*TMQ.

The rather poor ability of the TMQ to predict the GQ is ***not surprising***, because the PDMS only looks at the motor abilities of the child and domains like language and cognition cannot be predicted using the PDMS scores at one year. Another reason is that

rate of development is dissimilar in the different domains. So children who have a normal motor development need not have a normal language development and vice versa.

This being the case, it was not possible to accurately predict the neurodevelopmental outcome based on the motor abilities at one year. These children who came for the assessment at one year but did not come for the final neurodevelopmental assessment were considered as "lost to follow-up". However the data of these children have been used in the subsequent Sensitivity Analysis section.

5.2.9 INDIVIDUAL DESCRIPTIONS OF THE CHILDREN WITH SEVERE DEVELOPMENTAL DELAY AND NEUROLOGIC ABNORMALITIES (including CEREBRAL PALSY)

Among the 48 children with poor neurodevelopmental outcome (GQ <2SD or GQ <76), there were 31 children who were the most affected and had GQ ≤70. The **Table 26** presents a comprehensive record of the complications of these children.

Children were classified as neurologically normal or abnormal based on the Amiel-Tison neurologic examination. Fifteen children had neurologic abnormalities. The scoring is described in "Patients and methods section" **(4.6.3)**. So the incidence of neurologic abnormalities in the cohort was 3.6% (15 out of 422).

All the neurologically abnormal children had significant developmental delay (their GQ was less than 70) and microcephaly. Nine of the 15 children had abnormalities in the tone. Five children had cerebral palsy and four children had hypotonia. The remaining six

TABLE 26: BRIEF DESCRIPTION OF PATIENTS WHO WERE PROFOUNDLY DELAYED (GQ ≤ 70)

S.no	GQ	SEX	Birth Wt.	G.A	OBSTETRIC, MEDICAL AND FAMILY HISTORY	COMPLICATIONS IN N.I.C.U	ABNORMAL ATNA	Z score Wt.	Z score HC	COMPLICATIONS AFTER N.I.C.U DISCHARGE	FINAL DIAGNOSIS
1.	<40	Boy	1350	30	PREVIOUS LOW BIRTH WEIGHT (1.66 kg)	NIL	**YES**	-2.64	-2.78	NONE	**SPASTIC BILATERAL C.P (QUADRIPARETIC) - GMFCS 5**
2.	<40	Boy	1260	31	TWIN PREGNANCY	H.M.D Required CPAP For 4 days, CYSTIC P.V.L	**YES**	-1.22	-3.78	SYMPTOMATIC EPILEPSY	**SPASTIC BILATERAL C.P (QUADRIPARETIC) – GMFCS-5**
3.	<40	Boy	1280	35	ABNORMAL DOPPLER, IUGR, OLIGOHYDRAMNIOS	NIL	**YES**	-3.02	-4.63	NONE	**MICROCEPHALY, HYPOTONIC, SEVERE G.D.D, AUTISTIC**
4.	<40	Boy	1230	28	NONE	ASPHYXIA, RECURRENT APNEA D15	**YES**	-3.08	-2.66	NONE	**HYPOTONIA, SEVERE G.D.D**
5.	<40	Boy	1440	31	ABNORMAL DOPPLER, INFERTILITY, TRIPLET PREGNANCY	SUSPECTED SEPSIS, HEARING IMPAIRMENT	**YES**	-2.47	-2.8	NONE	**SPASTIC BILATERAL C.P (QUADRIPARETIC) - GMFCS 5 HEARING IMPAIRED**
6.	<40	Boy	1460	36	PRE-ECLAMPSIA	ASPHYXIA,	**YES**	-4.66	-4.12	NONE	**NEURONAL MIGRATION DISORDER, SEVERE G.D.D**
7.	<40	Girl	1030	35	ABNORMAL DOPPLER, Primary INFERTILITY	HYPOGLYCEMIA MYOCARDIAL DYSFUNCTION. SEPSIS, CHOLESTASIS	**YES**	-2.33	-6.09	LATE H.D.N with INTRACRANIAL HEMORRHAGE	**SPASTIC UNILATERAL C.P (GMFCS 1), EPILEPSY MICROCEPHALY**
8.	50	Boy	1220	30	PRE-ECLAMPSIA	VENTILATION FOR RDS, PNEUMOTHORAX, A.K.I CARDIAC ARREST, NFNB SEPSIS, HYPOGLYCEMIA,	**YES**	-1.14	-3.15	NONE	**SEVERE G.D.D WITH CORTICAL VISUAL IMPAIRMENT DUE TO HYPOXIC BRAIN DAMAGE**
9.	53	Girl	1500	31	POLYHYDRAMNIOS Primary INFERTILITY	FACIAL DYSMORPHISM NOTED	**YES**	-2.24	-2.88	NONE	**SUSPECTED DYSMORPHISM, HYPOTONIA, SEVERE G.D.D**
10.	63	Girl	1500	34	PREECLAMPSIA Both Parents <8th standard	NIL	**NO**	-2.9	-1.2	NONE	**HYPOTONIA, SEVERE G.D.D**
11.	55	Boy	940	28	MATERNAL BRONCHIECTASIS Both Parents <8th standard,	E.L.B.W, ACUTE KIDNEY INJURY	**NO**	-3.12	-4.85	NONE	**MICROCEPHALY, SEVERE G.D.D**
12.	58	Boy	1480	30	PRE-ECLAMPSIA	NIL	**NO**	-0.85	-1.14	NONE	**AUTISM**
13.	58	Boy	1280	36	ABNORMAL DOPPLER	RECURRENT HYPOGLYCEMIA	**NO**	-2.86	-2.49	NONE	**SEVERE G.D.D**
14.	61	Girl	1480	32	ECLAMPSIA, MATERNAL S.L.E Both Parents <8th standard,	NIL	**YES**	-1.89	-2.22	NONE	**SPASTIC BILATERAL C.P (DIPLEGIC) C.P (GMFCS 3) EPILEPSY**

S.no	GQ	SEX	Birth Wt.	G.A	OBSTETRIC, MEDICAL AND FAMILY HISTORY	COMPLICATIONS IN N.I.C.U		Z score Wt.	Z score HC	COMPLICATIONS AFTER N.I.C.U DISCHARGE	FINAL DIAGNOSIS
15.	62	Boy	1110	28	P.P.R.O.M	RECURRENT APNEA	**NO**	-2.94	-1.59	NONE	**SEVERE G.D.D**
16.	62	Boy	1150	29	ABRUPTION PLACENTAE, P.P.R.O.M for 10 days	RECURRENT APNEA	**YES**	-1.99	-2.21	RESPIRATORY ARREST at 2 m.	**SEVERE G.D.D**
17.	64	Boy	1300	37	NIL	FACIAL DYSMORPHISM NOTED SEVERE I.U.G.R	**YES**	-6.94	-7.85	NONE	**SUSPECTED SECKEL SYNDROME**
18.	65	Boy	1200	36	I.U.G.R	NIL	**NO**	-1.96	-1.94	NEPHRECTOMY (L) DYSPLASTIC KIDNEY	**DEVELOPMENTAL DELAY**
19.	66	Girl	1240	34	TWIN PREGNANCY	PDA	**NO**	-2.68	-2.91	PERSISTENT PDA	**DEVELOPMENTAL DELAY**
20.	67	Boy	1220	32	PREECLAMPSIA INFERTILITY (TUBAL BLOCK)	NIL	**NO**	-3.69	-4.14	NONE	**MICROCEPHALY WITH DEVELOPMENTAL DELAY**
21.	68	Boy	840	28	PRE-ECLAMPSIA	E.L.B.W	**NO**	-0.81	-0.33	SUSPECTED AUTISM	**DEVELOPMENTAL DELAY WITH HYPERACTIVE BEHAVIOUR**
22.	69	Girl	910	33	TWIN PREGNANCY (Other twin is No.23)	E.L.B.W	**YES**	-5.7	-3.22	NONE	**SEVERE GROWTH DELAY WITH DEVELOPMENTAL DELAY**
23.	70	Girl	850	33	TWIN PREGNANCY (Other twin is No.22)	E.L.B.W	**YES**	-5.7	-3.3	NONE	**SEVERE GROWTH DELAY WITH DEVELOPMENTAL DELAY**
24.	70	Girl	1420	31	NIL	RDS REQUIRED VENTILATION	**NO**	-2.57	-0.25	NONE	**DEVELOPMENTAL DELAY**
25.	70	Boy	900	29	PRE-ECLAMPSIA	E.L.B.W, R.O.P with PLUS disease	**NO**	-1.67	-0.54	NONE	**DEVELOPMENTAL DELAY**
26.	70	Boy	1300	29	Primary INFERTILITY, TWIN PREGANCY.	NIL	**NO**	-1.59	-0.85	NONE	**DEVELOPMENTAL DELAY**
27.	70	Boy	1000	28	P.P.R.O.M for 1 day	SEPTICEMIA	**NO**	-1.18	-1.04	NONE	**DEVELOPMENTAL DELAY**
28.	70	Boy	1400	31	NIL	NIL	**NO**	-2.18	-1.04	NONE	**DEVELOPMENTAL DELAY**
29.	70	Boy	1440	32	ABNORMAL DOPPLER,	NIL	**NO**	-1.98	-1.24	NONE	**DEVELOPMENTAL DELAY**
30.	70	Girl	1500	38	I.U.G.R, OUTBORN and HYPOGLYCEMIA on arrival	HYPOGLYCEMIA	**NO**	-2.95	-1.38	NONE	**DEVELOPMENTAL DELAY**
31.	70	Boy	1420	33	OLIGOYDRAMNIOS, ABNORMAL DOPPLER	CYTOMEGALOVIRUS (CMV) ELISA POSITIVE	**NO**	-3.04	-4.65	HEARING IMPAIRMENT	**CMV INFECTION SEQUELAE - MICROCEPHALY, HEARING IMPAIRED, Dev. DELAY**

(Grey Filling indicates children with Cerebral Palsy)

had normal tone; however they had significant deficits when scored on the Amiel Tison neurologic examination.

The children have been individually described below-

1) CHILDREN WITH INCREASED TONE (CEREBRAL PALSY)

Cerebral palsy was diagnosed using the Surveillance of Cerebral Palsy in Europe (SCPE) algorithm.[366] There were 5 children with definite features of cerebral palsy **(Children nos. 1,2,5,7 and 14** in **table 26**). All these children were detected to have abnormal tone in the latter half of the first year. The functional motor outcomes for children with cerebral palsy were graded using the five levels defined in the Gross Motor Function Classification System (GMFCS)[367] from 1 for minimal motor impairment to 5 for severe motor impairment with dependence on others for most daily activities.

- Four of these children (80%) had Spastic Bilateral Cerebral Palsy. Three of the bilateral spastic children (Children nos. 1,2 & 5) both upper and lower limbs were involved (quadriparetic) and they were GMFCS level-5. Their GQ could not be quantified in view of the extensive involvement.
- Fourth child with bilateral spastic CP had Diplegia and was GMFCS level 3.
- Fifth child with CP had Spastic unilateral CP (Left hemiplegic CP) and she was GMFCS level 1.

The children with CP are described below -

First child: Child 1 had an uneventful period in NICU and he did not have any infection in the NICU. The mother's antenatal period was also normal. The neurosonogram at 2 months did not shown any ventriculomegaly or evidence of PVL or IVH. His older

sibling was also born with low birth weight (1.66 kg). However he was brought for his first check up at seven months corrected GA and was detected to have spasticity. He was severely disabled and was GMFCS level V. His MRI **(Figure 15)** showed a paucity of white matter with periventricular hyperintensities and "wavy margin" of the ventricles suggestive of periventricular leukomalacia.

Second child: Child no. 2 was the second of twin gestation. His neurosonogram done at 2 months showed extensive cystic lesion in the periventricular region **(Figure 16)**. The twin sister is normal. He was severely disabled and was GMFCS level V.

Third child: Child no. 5 was one of triplets and his siblings were normal. His neurosonogram at two months showed mild ventriculomegaly. In addition to spastic bilateral CP (Quadriplegic CP) he also had cortical visual impairment and bilateral hearing impairment.. He was severely disabled with GMFCS level V. His MRI **(Figure 17)** shows extensive periventricular hyperintensities.

The fourth child: Child no. 7 had spastic Unilateral (Left side) CP. This child had cholestasis when she was discharged from the NICU. This was unfortunately resulted in late hemorrhagic disease and intracranial hemorrhage **(Figure 18).** She went on to have Left sided hemiplegia and microcephaly. In spite of the severe cognitive and communication compromises she was independently ambulant and was GMFCS level I. ***It could be argued that the cause of the CP in this child is post-natal. However she is included because she had multiple co-morbidities in the Neonatal period, which could have predisposed to the intracranial hemorrhage postnatally***.

The fifth child: Child no.14 had spastic bilateral (diplegic type) and she was able to move her upper limbs and was able to crawl on her hands and knees without a reciprocal movement (GMFCS level III). Her mother was on corticosteroids for Systemic Lupus Erythematosus. She had reasonably good verbal skills and her low GQ is primarily because of her difficulties in ambulation. Her early neurosonogram were normal and unfortunately she did not return for the neurosonogram at 6 weeks. The mother brought the child only at one year with seizures and signs of spasticity. Her MRI **(Figure 19)** shows periventricular white matter loss with ventriculomegaly and mildly wavy ventricular margins.

2) CHILDREN WITH HYPOTONIA

There were four children who were detected to have significant hypotonia without any other signs like ataxia or extrapyramidal symptoms. These children also had decreased age appropriate social interactions, delayed parachute reflexes and profound global delay. In two of these children the developmental delay was very profound and it was difficult to score them on the GMDS.

First child: Child no 4 **-** This child had birth asphyxia and multiple apneic episodes in NICU. He had profound developmental delay with hypotonia.

Second child: Child no. 9 - This child had hypotonia with significant developmental delay. She was noted to have some abnormal facial features like hypertelorism, small palpebral fissure, and large ears and was therefore suspected to have an underlying dysmorphic state.

Figure 15: MRI showing a paucity of white matter with periventricular hyperintensities and a “wavy margin” of the ventricles

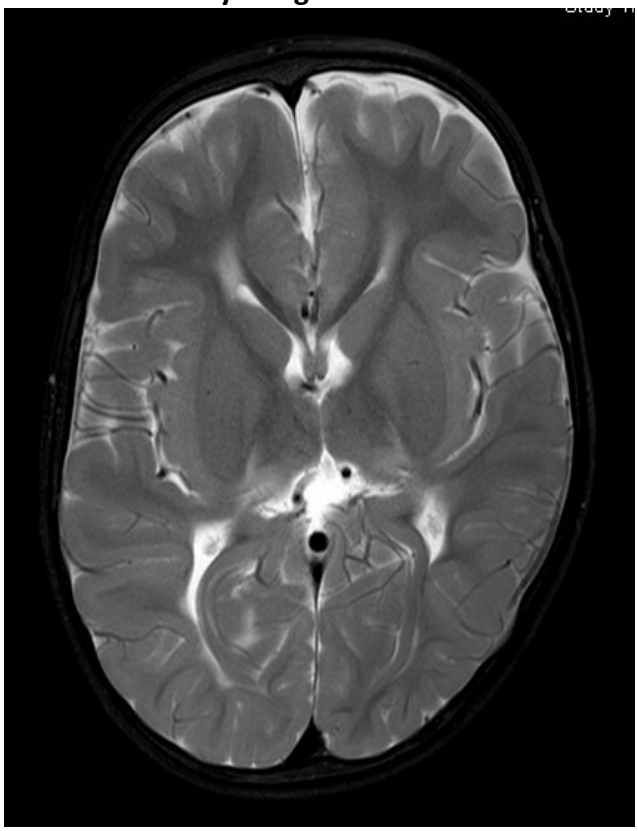


Figure 16: Cranial ultrasound showing cystic changes in the bilateral periventricular white matter

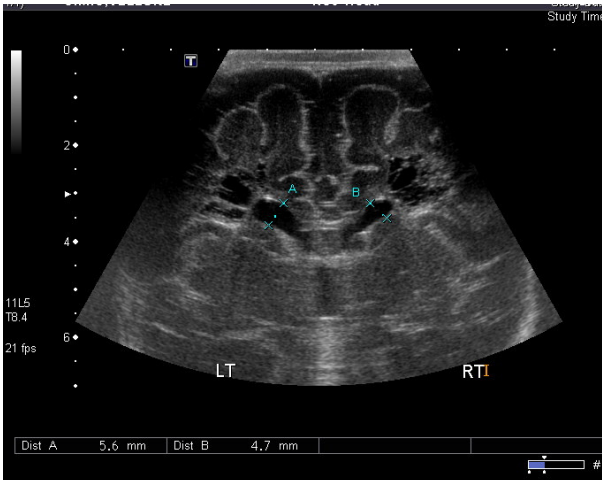


Figure 17:MRI showing hyperintensities in the periventricular region

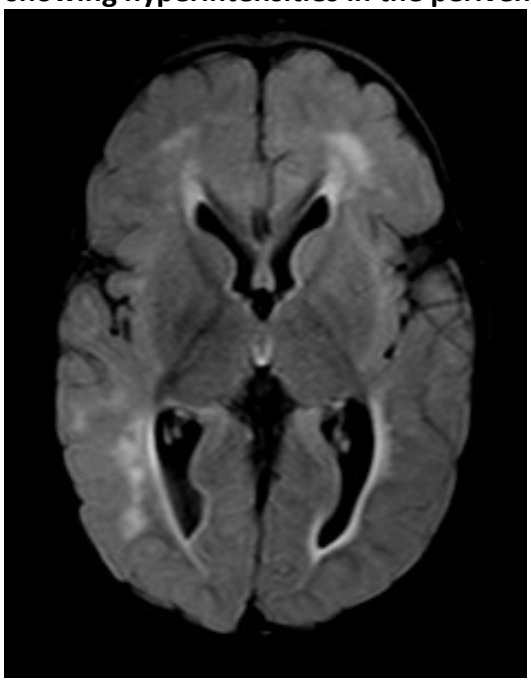


Figure 18: CT scan subdural hematoma over right frontal and temporal and occipital regions causing midline shift

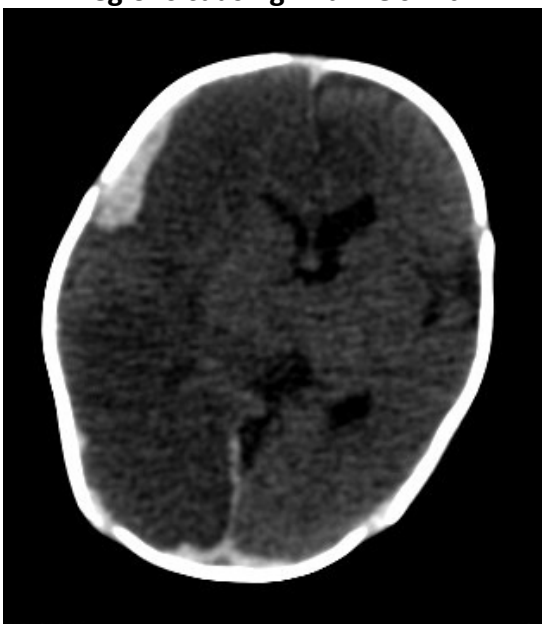


Figure 19: MRI showing mildly enlarged ventricles with wavy margins. Paucity of periventricular white matter

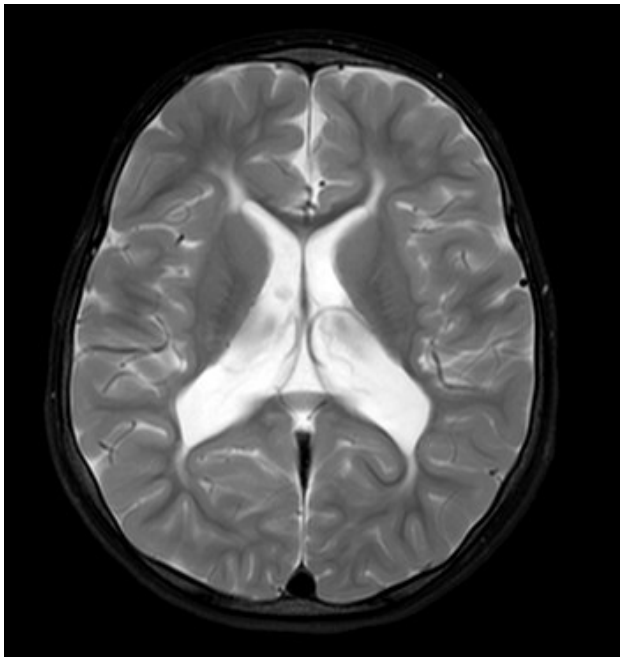
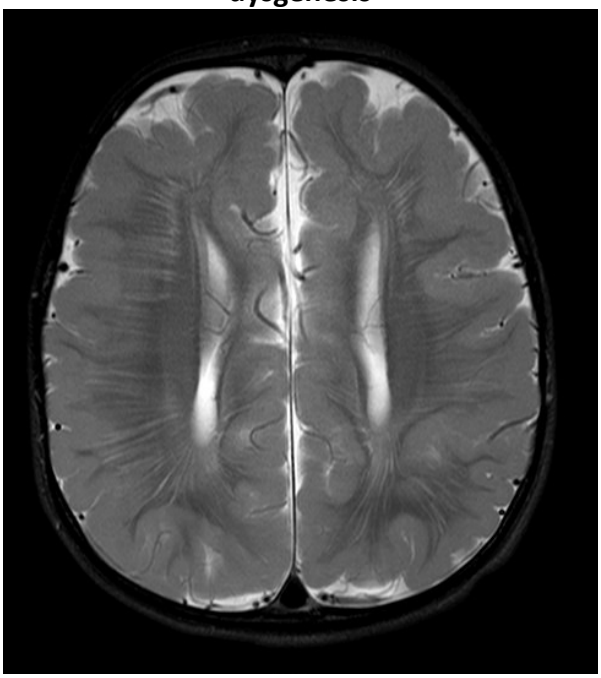


Figure 20: MRI showing bilateral pachygyria-polymicrogyria complex with callosal dysgenesis



Third child: Child no. 10 **-** This boy child had a relatively uneventful NICU stay. He had hypotonia and profound developmental delay. MRI was not done and so the etiology is not known.

Fourth child: Child no. 3 - This child had autistic traits with profound delay and he is described below (along with the other autistic children). His MRI of the brain was normal.

3) CHILDREN WITH NORMAL TONE, BUT HAD NEUROLOGICALLY ABNORMAL ON AMIEL-TISON NEUROLOGIC ASSESSMENT.

These children had normal tone, but they had microcephaly, their social interactions were not age appropriate, parachute reflexes were absent and they had much delayed motor skills, so they were considered abnormal on the ATNA.

First child: Child no.6 had perinatal asphyxia at birth. However after that he had a relatively uneventful stay in the NICU. He was detected have bilateral micro-cornea and bilateral cataract which was operated in the first year. His muscle tone was normal but he had microcephaly with profound developmental delay (we could not quantify his GQ). MRI showed features of ***Neuronal migration disorder*** – polymicrogyria and pachygyrias and dysgenesis of corpus callosum **(Figure 20)**. He may be having sequelae of TORCH infection (in view of the small for gestational age status, eye finding, neuronal migration disorder and profound developmental delay).

Second child: Child no.8 **-** This child had multiple neonatal complications (RDS, pneumothorax, and hypoglycemia). He had a cardiorespiratory arrest in NICU. On

follow-up he was detected to have profound developmental delay and cortical visual impairment.

Third child: Child no.17 was born severely growth retarded and was suspected to have features of ***Seckel*** syndrome. He has remained profoundly microcephalic, growth retarded and had severe developmental delay in his motor and language milestones.

Fourth child: Child no. 16 - This child had recurrent apnea in the NICU and at 2 months had a respiratory arrest from which he was resuscitated. He had profound delay in his motor milestones, although his head circumference was almost normal.

Fifth and sixth children: Children 22 and 23 were twins**.** They were born with severe IUGR and subsequent growth continued to have post-natal growth retardation. Both the children have significant motor delay.

4) CHILDREN WITH AUTISM

Three children did not satisfy the criteria for moderate or severe deficits on the ATNA and were neurologically normal; however they were positive on the Modified Checklist for Autism in Toddlers (M-CHAT).

Child no.3: This child was conceived after the mother was treated for infertility. He did not have any complications in the neonatal period and the neurosonogram were normal. His vision and hearing are also normal. However he had microcephaly and profound developmental delay. He also had autistic features, exacerbated by the profound delay and is currently on developmental therapy and follow-up.

Child no. 12 was brought for the neurodevelopmental assessment at 18 months of age. He was noted to have features of autism like poor eye contact, abnormal interest in rotating objects, hyperactivity and poor communication and fulfilled the criteria for autism on the DSM-IV. Interestingly the parents did not think he was abnormal and they were reluctant to accept that he had a significant problem. Unfortunately they did not return and so we could not do any more formal tests for the confirming the diagnosis of autism.

Child no. 21: When this child was brought for the assessment at 19 months of age he was detected to have features suspicious of autistic spectrum. He fulfilled 5 of the 6 "critical" items on the Modified Childhood autism tool (M-CHAT). He was started on early intervention and he started improving. At 3 years of age, his language and communication had improved and he displayed considerable improvement in his social behavior. However he continues to be very hyperactive and is on regular follow-up for his behavior.

5) CHILD WITH PERINATAL CMV INFECTION SEQUELAE

Child no. 31 was born small for gestational age and CMV IgM was positive at birth. His hearing report on the Neonatal ABR was "bilateral referred". He was suspected proved to have bilateral deafness on the BAER and the OAE. Although his motor milestones were normal, he was very delayed in the language milestones.

There were factors in the other children such multifetal gestation, absent end diastolic uterine artery flow, hypoglycemia, antepartum hemorrhage, pre-eclampsia and intrauterine growth retardation which would affect the neurodevelopmental outcome.

5.3 SECTION 3 - ANALYSIS OF THE SMALL FOR GESTATIONAL AGE INFANTS

One of the secondary objectives of the study was to determine if the survival and neurodevelopmental outcomes of the small for gestational age babies were different from those who were born appropriate for gestational age. The third percentile of Fenton's charts was used to decide if the infant was small or appropriate for gestational age.

Of initial 776 infants who were admitted in the NICU, 239 (30.7%) of the infants were small for gestational age (SGA). There were more SGA girl babies (53.8%) than SGA boys. Majority of the infants (almost 90%) who were less than 33 weeks of gestation were appropriate for gestational age. All infants whose gestational age was 34 weeks and more were small for gestational age, because of the ceiling of 1500 g in the study

This section is arranged in the following manner -

5.4.1: ***The range of gestational age in a given weight category*** is depicted. This was done to emphasize the heterogeneity of the children in this cohort

5.4.2: Compares all the ***SGA babies with all AGA babies***. However this results in a comparison between late preterm and term SGA babies and AGA preterms, as explained in the section

5.4.3: Compares the neonatal morbidities and survival of SGA ***babies <34 weeks (PT-SGA) with AGA babies of <34 weeks (PT-AGA).***

5.4.4: Compares the ***growth and developmental outcomes between PT-SGA and PT-AGA who are <34 weeks.***

5.5.5: Since many preterms were underweight (Z- score of weight for age was <2SD) at the time of assessment, this section reviews the ***factors which could predict a preterm infant being underweight at 2 years***.

5.3.1 RELATIONSHIP BETWEEN BIRTHWEIGHT AND GESTATIONAL AGE

Table 27 (below) depicts the relationship between the birth weight and the gestational age distribution in this cohort. It is obvious that for a given birth-weight there is a wide variation in the gestational age. So infants in the category 750-1000 g could have a gestational age anywhere from 26 weeks to 34 weeks. This severe intrauterine growth retardation explains why many infants continued to remain severely underweight even after two years.

Table 27: Relationship between Birth-weight categories and Gestational age

	750-999 g (ELBW)	1000-1199 g	1200-1500 g
Mean GA (95% CI)	30.9 (29.8-31)	30.9 (30.5-31.3)	32.3 (32.3-32.7)
Median GA (weeks)	30.4	30.4	32.3
Std. Deviation	1.9	2.3	2.3
Minimum GA (weeks)	26	26	28
Maximum GA (weeks)	34	38	40
Range of GA (weeks)	8	12	12

5.3.2 COMPARING BETWEEN SGA AND AGA INFANTS

Among the 643 children who were discharged alive from the NICU, 201 (31.3%) were small for gestational age at birth. There were 98 boys and 103 girls in this group. Of the final 422 children who came for the assessment, 131 (31%), 66 boys and 65 girls came for the assessment were SGA.

Comparisons between SGA and AGA in this cohort will predominantly be a comparison between "small for gestational age late preterms and term babies" and "appropriate for gestational age preterms". This is because of the birth-weight ceiling of 1500 g in this study, so all infants who were above 34 weeks were small for gestational age and majority of the less than 33 week babies were appropriate for gestational age.

Table 28 shows the results of the comparison the AGA babies with the SGA babies.

Morbidities in NICU

Only the perinatal and neonatal factors which are significantly different between the two groups are presented.

- Diabetes in pregnancy resulted in more premature births so there are more AGA babies.
- PIH resulted in more growth retarded babies.
- The higher rate of Cesarean among the SGA group is related to the higher incidence of PIH.
- As expected there was higher incidence of RDS in the AGA group, because of prematurity and this explains the greater incidence of CPAP and ventilation in the AGA group.
- Other complications of premature infants like PDA, hypocalcaemia and ROP were also more common among the AGA infants.
- Although not statistically significant severe IVH (Grades III and IV) was also more common among the AGA babies.
- Hypoglycemia was more common among the small for gestational babies.

TABLE 28: COMPARISON OF THE INFANTS WHO WERE SGA WITH THOSE WHO WERE AGA

		AGA	SGA	p-value
Perinatal and Neonatal risk factors (among the initial 776)				
1.	Diabetes in pregnancy	8.8%	3.8%	**0.013**
2.	Hypertension in pregnancy	38.8%	48.9%	**0.002**
3.	Cesarean section	60.6%	79.6%	**<0.001**
4.	Acute kidney injury	4.6%	0.9%	**0.045**
5.	RDS	32.2%	5.1%	**0.001**
6.	Ventilation	18.9%	8.5%	**0.001**
7.	Hypotension	23.4%	14%	**0.003**
8.	Hypoglycemia	5.7%	15.9%	**< 0.001**
9.	Hypocalcaemia	20.8%	7.1%	**<0.001**
10.	PDA	16%	6.5%	**<0.001**
11.	Severe IVH (Grade 3 and 4)	2.9%	0.9%	**0.122**
12.	ROP	17.9%	10.6%	**0.099**
13	Deaths	14.8%	5.7%	**0.014**
Developmental outcome (GQ) (Children whose GQ could not quantified not included)				
% of children with GQ <76		9.6%	15.3%	**0.091**
GQ- Mean [±2SD]		94.2 (±12.8)	92.1 (±13.3)	**1.000**
Median GQ		96	93.5	
Range of GQ		50-124	58-117	
Cerebral Palsy (no. of children)		4	1	**0.591**
Weight at assessment				
% of children with weight < 2SD below mean		27.1%	56.9%	**<0.001**
Mean Z-score (±2SD) of Weight		-1.56 (1.14)	-2.47 (1.35)	**<0.001**
Length at assessment				
% of children with length < 2SD below mean		38.3%	63.6%	**<0.001**
Mean of Z-Score (±2SD) of Length		-1.74 (1.24)	-2.64 (1.72)	**<0.001**
Head Circumference (HC) at assessment				
% of children with HC < 2SD below mean		27.1%	56.9%	**<0.001**
Mean of Z-Score (±2SD) of HC		-1.79 (1.08)	-2.28 (1.6)	**<0.001**

- The AGA group had significantly more neonatal complications like hypotension, thrombocytopenia and acute kidney injury.
- Because the AGA group had more life threatening complications it is not surprising that the AGA group had greater mortality.
- Some complications like perinatal asphyxia, NEC and septicemia were not statistically different between the groups.

Neurodevelopmental outcomes

At the time of the neurodevelopmental assessment there was a significantly higher proportion of babies with a lower GQ among SGA babies. The mean GQ between the two groups however was not statistically significant **(table 28)**. Cerebral palsy, although the numbers were very small was more among the infants who were AGA

Growth

The growth parameters (weight, length and head circumference) at the time of the assessment were significantly more affected among the SGA infants, than among the AGA infants. Almost 60% of the SGA babies continued to have growth retardation while only about 27% of the AGA infants were underweight.

So in AGA infants, neonatal mortality and morbidity mainly due to the complications of prematurity contribute to their outcomes. While neonatal morbidities and mortality are less in the SGA infants, they are more likely to be affected in their growth, head circumference and their developmental outcomes.

5.3.3 COMPARISON OF PRETERM AGA AND PRETERM SGA

As mentioned above the comparison of *all* the AGA babies with *all* SGA babies was invariably a comparison between the preterm babies and moderately preterm intrauterine growth retarded & term growth retarded babies. Therefore to make a comparison between SGA and AGA, it was necessary to study the infants who were less than 34 weeks to look for differences between the babies who were preterms and small for gestational age (PT-SGA) and the babies who were preterm and appropriate for gestational age (PT-AGA). The results of this analysis are presented in **table 29.**

Of the initial sample of 776 babies there were 600 infants who were less than 34 weeks gestational age, of these ***538(89.7%) infants were AGA and 62 (10.3%) infants were SGA. The neonatal morbidities and survival is estimated based on this group***

Of the 422 who came for the final assessment, 324 infants were less than 34 weeks gestational age. Of these ***290 (89.5%) infants were AGA and 34 infants (10.5%) were SGA babies***. ***The growth and developmental outcomes are estimated based on this group.***

A. Morbidities of PT-SGA compared with PT-AGA

On comparing the two groups (Preterm AGA with Preterm SGA) -

- There were more girls in the preterm SGA group compared to the preterm AGA group
- Maternal PIH was more common in the SGA group and as mentioned the growth retardation may be the result of the PIH.
- There were more babies who were born Cesarean in the SGA group, possibly because of the PIH.

TABLE 29: COMPARISON OF PRETERM SGA BABIES WITH PRETERM AGA BABIES

		PT- AGA	PT-SGA	p-value
Perinatal and Neonatal risk factors				
1.	Girls	44.4%	66.1%	**0.001**
2.	Hypertension in pregnancy	37%	59.7%	**0.001**
3.	Cesarean section	60.8%	75.8%	**0.012**
4.	RDS	47.8%	8.8%	**0.001**
5.	CPAP	34.5%	14.5%	**0.001**
6.	Hypoglycemia	5.8 %	18 %	**0.001**
7.	Thrombocytopenia	32.2%	54.1%	**<0.001**
8.	Mortality in NICU	10.5%	14.5%	**0.368**
Developmental outcome (GQ)				
% of children with GQ <2SD		9.6%	11.8%	**0.696**
GQ- Mean [±2SD]		93.4 (±14.7)	93.8 (±12.9)	**0.769**
Median GQ		96	93.5	
Cerebral Palsy (no. of children)		4	0	
Weight*				
% of children with weight < 2SD below mean		26.2%	60.6%	**<0.001**
Mean Z-score (±2SD) of Weight		-1.41 (1.09)	-2.30 (1.41)	**<0.001**
Length*				
% of children with length < 2SD below mean		38.1%	54.5%	**0.06**
Mean of Z-Score (±2SD) of Length		-1.59 (1.20)	-2.31 (1.66)	**0.002**
Head Circumference (HC)*				
% of children with HC < 2SD below mean		34.8%	63.6%	**<0.001**
Mean of Z-Score (±2SD) of HC		-1.66 (1.07)	-2.36 (1.12)	**<0.001**

*At the time of the neurodevelopmental assessment

- RDS was five times more common in the AGA preterms. It is well known that conditions like pregnancy induced hypertension which results in chronic intrauterine stress induces lung maturity in preterms and protects against developing RDS [385]. This may be reason why SGA babies had much lesser incidence of RDS
- CPAP use was also higher among the preterm AGA babies.
- Hypoglycemia was more common in the preterm SGA group possibly because of the combination of prematurity and growth retardation which can both independently cause hypoglycemia.
- Thrombocytopenia was more common in the preterm AGA group..
- Other factors like maternal history of infertility, twin gestation, perinatal asphyxia, NEC, septicemia, hypotension, hypercalcemia, PDA, severe IVH, ROP were not significantly different between the two groups
- Though proportionately the mortality among the PT-SGA babies were more than the PT-AGA babies, this difference was not significant (p=0.368)
- The mean GQ was similar between the two groups indicating that there was not much difference in the development of preterm SGA as compared to preterm AGA
- Significantly the growth parameters were more affected in the SGA group. About 56-64% of the SGA babies continued to be growth retarded (in their weight, length and head circumference) as compared to about 30-35% of the AGA babies.

Thus in conclusion there are significant differences in the morbidities between PT-AGA and PT-SGA in the neonatal period. Because they are more advanced in gestational age,

PT-SGA infants are protected from the complications of prematurity. However PT-SGA babies are significantly more growth retarded,

5.3.4 NEURODEVELOPMENTAL & GROWTH OUTCOMES OF PT-AGA vs. PT-SGA

There are more infants with GQ less than 2SD in the PT-SGA group, but this was not statistically significant. The mean GQ between the two groups appear almost similar. Although all the children with CP were in the PT-AGA group, because of the small numbers no inference of any association can be made out.

At the time of assessment, there was a significant difference in the post-natal growth. The SGA babies were more affected and majority of them did not catch up by 2 years

Did the GQ differ significantly between those who remained underweight (<2SD of Z score for weight) and those who had caught up in their weight?

Among the preterm SGA (PT-SGA) there were 13 (39.4%) who **caught up** and 20 (60.6%) who continued to have poor post-natal growth and remained underweight. The mean GQ of those who caught up was 97.9 ($\pm$13.8) and in those who continued to have post-natal growth retardation was 91.2 ($\pm$12). However this was not significantly different (p=.191).

Among the preterm infants who were appropriate for gestation at birth (PT- AGA) there were 26.2% infants who had post-natal growth retardation and the remaining 73.8% were within the normal range. The mean GQ of those who weight was normal was 95.9 ($\pm$11.9) and the mean of the infants who had post-natal growth retardation was 89.45 ($\pm$13.9). This difference was statistically significant.($p<0.001$).

These findings are shown in **table 30.**

Table 30: Comparison of GQ of infants who had adequate catch-up growth and those who had inadequate post-natal growth

	Adequate catch-up growth	Inadequate post-natal growth	p-value
PT-AGA	**%. of infants:** 73.8% **GQ(SD):** 95.9 (11.9)	**%. of infants:** 26.2% **GQ(SD):** 89.45(13.9)	<0.001
PT-SGA	**%. of infants:** 39.4% **GQ(SD):** 97.9 (13.8)	**%. of infants:** 60.6% **GQ(SD):** 91.2 (12)	<.191

So in the SGA group although there was a difference in the developmental outcome (mean GQ) between those who had caught up and those still remained underweight, this was not significant. But in the babies who were AGA at birth, those who had inadequate post-natal growth the developmental outcome was significantly worse than those whose post-natal weight gain was within normal limits.

So, are the NICU and neurodevelopmental outcomes of the SGA infants worse than that of the AGA infants ?

- There are definite differences in the neonatal complications between SGA and AGA infants however ***there is no difference in the survival***
- ***Developmental outcomes (mean GQ) appear similar*** between SGA and AGA
- ***More SGA babies have post-natal growth restriction compared to AGA babies***.
- In both groups the ***developmental outcome is worse in the infants who have post-natal growth restriction*** compared to those whose post-natal growth is normal
- The ***developmental outcome of AGA babies who have post-natal growth restriction is worse that SGA babies who have post-natal growth restriction***

5.3.5 POST-NATAL GROWTH RESTRICTION IN THE PREMATURE INFANTS.

About one third of the preterm babies remained underweight at two years. Are there any ***factors which could predict the infant being underweight at two year***s?

In order to answer this question the bivariate analysis of the perinatal, neonatal and post-natal factors of the preterm (<34weeks) babies was done to see if there were any predictors for being underweight (Weight of <2SD below the mean) after 18 months corrected gestational age. There were 225 (69.6%) the infants who had a normal weight (weight within 2SD of the mean) and 98 babies who were underweight (weight more than 2SD below mean) at the time of assessment.

From the bivariate analysis the following predictors in premature babies were associated with being underweight – being SGA at birth ($p < 0.001$), maternal education below Std. 8 ($p=0.003$), neonatal hypoglycemia ($p = 0.018$), and, Retinopathy of prematurity ($p = 0.047$), severe IVH ($p = 0.033$). These were entered into a multivariate regression model.

The best multivariate prediction model for being underweight at two years is given below:

Table 31: Multivariate logistic regression model predictive for the study children being underweight at the time of assessment

Variable	B coeff.	p-value	Adjusted OR (95%CI)
Small for gestation at birth	1.427	.000	4.165 (1.89-9.18)
Low maternal education (less than Std.8)	1.030	.003	2.802 (1.42-5.53)
Neonatal hypoglycemia	.791	.088	2.206 (0.89-5.48)
Constant	-1.219	<.001	0.295

The final predictive model (shown above) yielded an area under the ROC curve of 0.654 (0.584-0.723 95% CI; $p<0.001$) and the Hosmer-Lemeshow statistic indicated a good model fit ($p=0.473$).

The model predicts that being ***small for gestational age increases the odds by four times, low maternal education increases the odds by nearly three times and neonatal hypoglycemia increases the odds by two times of being underweight at two years.***

5.4 SECTION 4 - ANALYSIS OF THE CHILDREN WHO DID NOT COME FOR FOLLOW-UP.

Although 422 children were followed up until the final neurodevelopmental assessment, and this is probably the largest VLBW cohort which has been followed up, there was still a drop out of over 30%. Thirty of these children did not come for the final assessment but were seen at one year for the interim motor assessment. The majority of the "lost to follow-up" group did not come for any developmental assessment and therefore the developmental status of these children is not known. In many children we do not even know if they have survived. Although some of the parents did not give consent to join the study, for the sake of analysis, they are considered among the patients who were lost to follow-up.

COMPARING THE "LOST TO FOLLOW-UP" INFANTS WITH THOSE WHO UNDERWENT NEURODEVELOPMENTAL ASSESSMENT

In order to see if there was any significant differences between the children who were followed up and those who did not come for the follow-up and assessment the bivariate analysis by using the Chi-square test on the usual 2-way cross tabulations was done to look for any significant differences between perinatal and neonatal risk factors between the two groups. Associations were considered to be significant if the p-value was <0.05. The results are presented in **table 32.** There were 453 children who had at least one of the two assessments and 169 children who had **no** assessments. The children (21 children) who died after discharge from the nursery are excluded from the analysis.

Table 32: BIVARIATE COMPARISON OF THOSE WHO HAD ASSESSMENT WITH THOSE DID NOT COME FOR ASSESSMENT (DIED, DID NOT GIVE CONSENT AND LOST TO FOLLOW UP)

S. No	Characteristic/Risk factor	Assessment done (453)	No assessment (169)	P-value	OR (5% CI)
1.	Boys Girls	237 (52) 216 (47.6)	90 (53) 79 (46.7)	0.835	0.963 (0.676-1.372)
2.	Antepartum Hemorrhage (%)	53 (11.7)	24 (14.2)	0.399	1.249 (0.744-2.098)
3.	Pregnancy induced hypertension (%)	193 (42.6)	78 (46)	0.427	1.155 (0.810-1.647)
4.	Twins (%)	128 (28.2)	39 (23)	0.195	0.762 (0.504-1.150)
5.	Antenatal steroids (%)	86 (18.9)	32 (18.9)	0.989	0.997 (0.635-1.535)
6.	Cesarean or Instrumental delivery (%)	305 (67)	115 (68)	0.865	1.033 (0.708-1.509)
7.	Infertility (%)	87 (19.2)	21 (12.4)	0.047	0.597 (0.357-0.997)
8.	PPROM (%)	94 (20.7)	29 (17)	0.317	0.791 (0.499-1.253)
9.	Ponderal index > or < 2 (%)	84 (18)	23 (13.6)	0.203	0.723 (0.438-1.194)
10.	Birth weight less than 1200g (%)	126 (27.8)	36 (21)	0.100	0.702 (0.461-1.071)
11.	Gestational age less than 32 weeks (%)	214 (47)	70 (41)	0.195	0.790 (0.552-1.129)
12.	Mothers Education below Std 8 (%)*	64 (14.5)	21 (19.6)	0.193	1.435 (0.831-2.476)
13.	Perinatal asphyxia (%)	15 (3.3)	3 (1.8)	0.309	0.528 (0.151-1.84)
14.	IVH Grades III & IV 9%)	2 (0.44)	0 (0)	0.398	-
15.	Septicemia (%)	56 (12.4)	31 (18)	0.056	1.593 (0.986-2.573)
16.	Ventilation (IPPV & HFOV) (%)	54 (11.9)	24 (14.2)	0.445	1.223 (0.729-2.051)
17.	Gestational Age (<28 weeks) (%)	6/453 (1.4)	3/169 (2)	0.675	0.743 (0.184-3.004)
18.	Respiratory Distress Syndrome (%)	93 (20.5)	34 (20)	0.910	0.975 (0.628-1.513)
19.	Necrotising enterocolitis (>Bell stage 2) (%)	5 (1.1)	1 (0.59)	0.561	0.533 (0.062-4.599)
20.	Acute kidney illness (%)	8 (1.96)	1 (0.65)	0.272	0.329 (0.041-2.652)
21.	Hypoglycemia	38 (8.4)	17 (10)	0.514	1.221 (0.669-2.229)

The analysis presented in **table 32** shows that, except for maternal history of infertility, there is no significant difference between the two groups in the occurrence of perinatal or neonatal risk factors.

SENSITIVITY ANALYSIS

Sensitivity analysis was done to assess what impact the "lost to follow-up" would have on the results obtained from the present cohort of 422 children. This was done by considering two extreme possibilities – a "worst case scenario" and a "best case scenario" **(table 33)**.

The "worst case scenario" was where all the children who were lost to follow-up had a poor neurodevelopmental outcome (GQ <2SD) and the "best case scenario" was one in which all the children who were lost to follow-up had a good neurodevelopmental outcome (GQ of ≥2SD). For this analysis the children who had the one year motor assessment using the Peabody developmental Motor scales (PDMS), but did not come for the final neurodevelopmental assessment were included. Of the 31 children who came for the PDMS but did not come for the GMDS, 29 had Total motor quotient of more than 90 and hence using the Regression equation mentioned above (**see 5.2.8,** p.147 comparing TMQ with GQ) they would have a GQ of ≥2SD (normal developmental outcome). The other two children had TMQ in the "below average" (TMQ <90) category and therefore were classified as poor neurodevelopmental outcome (GQ <2SD). Children who had died after discharge from the nursery (21 children) were excluded.

Thus in the "worst case scenario" there were -

219 children with poor neurodevelopmental outcome (169 children who had no assessment, 48 children who had GQ <2SD and the 2 children who had low TMQ)

403 children (374 children with GQ ≥2SD and 29 children with normal TMQ) with good neurodevelopmental outcome.

In the best case scenario there were

572 (374 children who had GQ of ≥2SD, 169 children who had no assessment and 29 children who had a normal TMQ) with good neurodevelopmental outcome and

50 children (48 children with GQ <2SD and 2 children who had low TMQ) who had poor neurodevelopmental outcome

These were compared with the children of the study cohort (374 children with GQ ≥2SD and 48 children with poor neurodevelopmental outcome GQ <2SD)

The results are presented in **table 33**.

From **table 33,** it is clear that the relative risks in the three situations ["worst case scenario" or the "best case scenario" and the study cohort] are quite similar and the p-value is not significant in any the neonatal and perinatal factors in all the three scenarios. ***Thus it seems that the study cohort is not different from either of the extreme scenarios, so the children who were lost to follow-up are unlikely to affect the results obtained from this study cohort***.

The influence of the growth parameters on the developmental outcome, could not be estimated since the anthropometric measurements were collected only at the time of the neurodevelopmental assessment.

Table 33: SENSITIVITY ANALYSIS - Comparing the "Best-case" and "Worst case"

S. No	Risk Factor	Worst Case scenario p-value; OR(95%C.I)		Study cohort p-value; RR (95% C.I)		Best case scenario p-value; RR (95% C.I)	
N	Number	Children with GQ <76: 219 Children with GQ ≥76: 403		Children with GQ <76: 48 Children with GQ ≥76: 374		Children with GQ <76: 50 Children with GQ ≥76: 572	
1.	**Perinatal Asphyxia**	0.866	0.918 (0.340-2.480)	0.284	1.112 (0.861-1.435)	0.172	1.107 (0.89-1.36)
2.	**Acute Kidney illness**	0.901	0.915 (0.226-3.700)	0.226	2.691 (0.526-13.774)	0.114	1.87 (0.835-1.68)
3.	**Hypotension**	0.133	1.448 (0.891-2.351)	0.132	1.824 0.826-4.030	0.208	1.047 (0.962-1.14)
4.	**Antenatal steroids**	0.756	1.068 (0.704-1.622)	0.622	1.023 (0.931-1.123)	0.569	1.017 (0.955-1.084)
5.	**PPROM**	0.050	0.648 (0.420-1.002)	0.050	0.395 (0.152-1.030)	0.070	0.95 (0.91-0.993)
6.	**History of Infertility**	0.045	0.626 (0.395-0.993)	0.524	0.973 (0.899-1.053)	0.791	0.992 (0.955-1.052)
7.	**Twins**	0.272	0.809 (0.555-1.181)	0.947	0.997 0.924-1.076)	0.848	1.005 (0.953-1.06)
8.	**Type of Delivery**	0.487	0.883 (0.623-1.253)	0.090	0.938 0.867-1.016	0.134	0.962 (0.912-1.02)
9.	**NEC**	0.923	0.919 (0.167-5.060)	0.455	1.109 (0.715-1.72)	0.435	1.105 (0.776-1.58)
10.	**PIH**	0.789	1.046 (0.751-1.458)	0.384	0.970 0.906-1.038	0.408	0.98 (0.936-1.027)
11.	**Septicemia**	0.123	1.435 (0.905-2.276)	0.990	0.994 (0.401-2.465)	0.673	0.986(0.93-1.04)
12.	**RDS**	0.439	0.849 (0.561-1.285)	0.290	0.956 (0.887-1.030)	0.240	0.97 (0.92-1.02)
13.	**Ventilation**	0.370	1.249 (0.768-2.032)	0.573	1.280 (0.541-3.029)	0.745	1.149 (0.498-2.652)
14.	**Hypoglycemia**	0.436	1.252 (0.711-2.206)	0.594	1.027 (0.90-1.172)	0.764	1.01 (0.94-1.06)
15.	**Intraventricular Hemorrhage**	0.303	-	1.000	-	0.670	-
16.	**Low maternal education**	0.085	1.531 (0.941-2.491)	0.211	1.067 (0.949-1.199)	0.361	1.035(0.953-1.124)
17.	**Baby's Sex Boys vs. Girls**	0.413	0.871 (0.626-1.212)	0.380	0.970 (0.906-1.038)	0.273	0.974 (0.93-1.02)

REASONS FOR ATTRITION OF THE INFANTS FROM THE STUDY

There are many reasons for the non-compliance of parents of those infants who were lost to follow-up.

a. The institution where this study was done is a tertiary referral center and patients come from all over South India and the eastern part of India and Bangladesh visit the Centre. Many of those who were lost to follow-up and many of those refused consent were from far-off places.

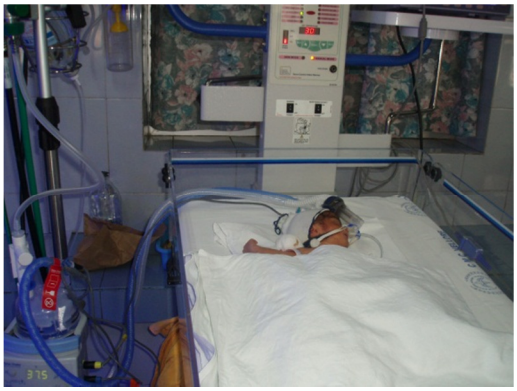
b. Many mothers came to Vellore for delivery because their homes are located here. After the child was discharged they went back to their regular places of stay and therefore could not come for the assessments.

c. Although all assessments were done free of charge, there was still loss incurred (in terms of cost of transportation, loss of wages) in bringing children for the assessment, which resulted in the attrition.

d. Some mothers refused to bring their children since they felt that their child was doing well and so did not require any assessments.

e. The converse could also be true. Other studies have shown that children who were are lost to follow-up especially those from the lower socio-economic status are likely to have higher rates of disability.[221,222]

DISCUSSION



6 DISCUSSION

Western studies have shown that the survival of VLBW infants have consistently improved since the early 1990s.[386] The survival of VLBW babies in India is about 68-86%.[91,92] The incidence of developmental delay from these studies range from 10-17%,[71,76,81] and that of cerebral palsy from 3-5%.[76,82–84] This is less than the incidence of 7.8% for CP and 25% obtained from Escobar's the meta-analysis of over 100 studies which looked at the outcomes of the VLBW infants.[59]

The hypotheses of this study were: (a) the occurrence of CP and developmental delay would be different from that of the Western countries (b) that risk factors in the perinatal and neonatal period would affect the developmental outcome at 18 months corrected gestational age. This hypothesis was tested on a large Indian cohort of very low birth weight infants who were followed up beyond 18 months of age. The primary questions that were answered are - how many of the VLBW survive? What is the developmental outcome after 18-24 months of life and do the complications in the perinatal influence their developmental outcome?

The Discussion of the study is divided into 3 sections:

Section 1: ***incidence of poor neurodevelopmental outcomes (cerebral palsy and developmental delay)*** in this cohort.

Section 2: The ***influence of the perinatal and neonatal morbidities on survival and the developmental outcome.***

Section 3: The ***findings of the Developmental follow-up and the Neurodevelopmental assessment***

6.1 SECTION 1 - INCIDENCE OF CEREBRAL PALSY AND DEVELOPMENTAL DELAY

This section comprises the following:

6.1.1: The incidence of poor neurodevelopmental outcome and cerebral palsy in the cohort

6.1.2: The neurodevelopmental outcomes among the ELBW babies of the cohort in comparison to other ELBW cohorts.

6.1.1 INCIDENCE OF POOR NEURODEVELOPMENTAL OUTCOME (CP AND DEVELOPMENTAL DELAY)

As mentioned earlier the results of outcomes (mortality in NICU) and poor the neurodevelopmental outcomes in the follow up phase study were -

- **Incidence of Poor Neurodevelopmental Outcome**: 48 out of 422 children had GQ less than 2SD below the mean) and so the incidence of **poor neurodevelopmental outcome** was **11.37% (8.6%-14.9% 95% CI). (*This includes the children with CP also)***
- **Incidence of Cerebral Palsy**: There were 5 children with Cerebral palsy in this cohort was and so the incidence of Cerebral palsy was **1.1% (0.4%-2.63%, 95%CI).**
- **Incidence of Hearing loss**: There were 2 children (**0.47%**) with hearing loss, one of whom was suspected to be secondary to CMV infection and the other child had spastic quadriparetic cerebral palsy.

- **Visual impairment:** There were 2 children (**0.47%**) with blindness both due to cortical visual impairment, secondary to the brain damage and not due to Retinopathy of prematurity.
- **Mean General quotient** of the cohort was **93.56 ± 13.5**.

The results of this cohort were compared with that of a similar cohort of 77 VLBW babies from Malaysia, another developing country.[387] In this Malaysian study the VLBW infants had neurodevelopmental assessment at 2 years using the Griffith's Mental Developmental Scales. The mean GQ of the VLBW infants was 94 (SD 15.7). The GQ of 3.9% of the children in this cohort was 2SD below the mean, 2.6% were blind and 3.9% had cerebral palsy.

The results were also comparable to a Western meta-analysis which showed that the mean developmental quotient of 1461 VLBW infants was 95.8 (SD 8).[388] (In this meta-analysis many different neurodevelopmental assessment tests were used).

The **table 34** (below) shows the comparison of the results of this study cohort with that of VLBW cohorts from other developing countries as shown in **34**.

Table 34: Comparison of the results of this cohort with that of other developing countries

	No. of children	CP (95%CI)	Developmental delay (95%CI)
Study Cohort	422	1.1% (0.4%-2.9%).	11.37% (8.6%-14.9%)
Mukhopadhyay *et al* (India)[76]	71	3%	16% (MeDQ <70),
Ho *et al* (Malaysia)[387]	77	3.9%	3.9%
Sangtawesin *et al* (Thailand)[199]	30	3.3%	23.3%
Ballot (South Africa)[200]	106	3.7%	8.5%
Escobar *et al* (meta-analysis)[59]	Over 9,000	7.7% (5.3-9)	25% (20.9-30.0)

Therefore the incidence of 1.1% for cerebral palsy and 11.37% for developmental delay obtained from this cohort is likely to be right for the following reasons -

1. Because of the sample size, the confidence intervals are within a narrow range [Incidence of CP: **1.1%** (95% CI - **0.4%-2.9%**) and the incidence of developmental delay: **11.37%** (95% CI is **8.6%-14.9%** 95% CI)]. This adds certainty to the results obtained and therefore we can state that we are 95% confident that the incidence of CP and developmental delay lie within these confident intervals.[389,390]
2. The incidence is quite comparable to what is obtained from the other studies on VLBW babies (**table 34**).
3. The sensitivity analysis (Section 4 of Results, **table 33**) showed that the infants who did not come for the final assessment are unlikely to have changed the results obtained.

6.1.2 DEVELOPMENTAL DELAY AND CP in ELBW INFANTS - COMPARING WITH OTHER COHORTS.

In this cohort - among the 422 children, there were 30 children with ELBW and their ***mean birth weight was 867g, mean gestational age was 30.7 weeks and mean GQ was 92.4 (±15.5)*** (**table 22**). ***Six (20%) of these children had developmental delay although none of them had cerebral palsy***. ***None of the ELBW babies had hearing or visual impairment***.

The ELBW babies of this cohort were compared to another cohort of 49 ELBW babies from Hong Kong.[391] who were followed up till 2 years of age. The mean gestational age of the ELBW babies from Hong Kong was 26.2 weeks and mean birth weight was 789 g,

six (12%) of the ELBW infants had CP, eight (16%) had significant developmental delay on the Griffith's Mental developmental Scales.

The ELBW babies of this cohort were also compared to a cohort from the NIHHD (data on ELBW during the period 2000-2002).[104] The ELBW infants in the NICHHD had a mean gestational age of 25.5± 2.2 weeks, their mean birth-weight was 750 g ± 144. The neurodevelopmental sequelae in the NICHHD cohort was that 5% of the infants had CP and 21% of the infants had MDI of <70 and 15% of the infants had PDI of <70 on the BSID, 1% of the infants were blind and 1% of the infants were hearing impaired.

Compared to the other cohorts, ELBW babies in this cohort are more mature at birth Since many of them are growth restricted there are fewer extremely preterm or very preterm babies. The mean gestational age in this cohort among the ELBW was 30 weeks while that of the NICHHD cohort was 25.5 weeks.

6.2 SECTION 2 - INFLUENCE OF ANTENATAL, PERINATAL AND NEONATAL RISK FACTORS OF SURVIVAL AND DEVELOPMENTAL OUTCOME.

This section is about the influence of the antenatal, perinatal and neonatal risk factors on the survival of the babies in the NICU and their influence on the neurodevelopmental outcomes.

This section is arranged in the following manner -

6.2.1: The ***rationale of using the third percentile of the Fenton's curves*** to classify infants into SGA and AGA.

6.2.2: The ***influence of antenatal and perinatal risk factors*** on the neurodevelopmental outcomes

6.2.3: The ***influence of neonatal complications*** on neurodevelopmental outcomes

6.2.4: Comparison of the ***neonatal morbidities of this cohort with that of a large Western cohort,*** to highlight the differences between the two cohorts.

6.2.5: ***Why the neurodevelopmental outcomes were not influenced by the neonatal complications in the NICU.***

6.2.1 CLASSIFYING THE INFANTS AS SGA OR AGA BASED ON THE 3RD PERCENTILE OF THE FENTON CURVES

Although there are some growth charts from India,[378,379,392,393] the sample sizes used for obtaining these curves are small and they are based on infants of a certain region which may not be representative of infants from other parts of the country. The Fenton's

curves[364] are the most commonly used intrauterine and post-natal growth curves in neonatal units internationally.[394] Although by definition, SGA babies are those who are *less than the 10th percentile* of birth weight-for-gestational age, the 3rd percentile on Fenton's curves was chosen. This is because, the 3rd percentile on the Fenton curves corresponds to the 10th percentile of the chart developed by Mathai. M[378] which is from this institution and the 10th percentile of the growth chart developed by Kandraju *et al*[379] which is most recent Indian growth chart and also has the largest sample size.

A global review looking at the rate of SGA found that nearly 50% of South Asian babies were SGA when the 10th percentile was considered the cut-off and 23% were SGA when the 3rd percentile was used as the cut-off.[5] Another study found that depending on the reference population used, the prevalence of SGA in India can vary from 12% to 74.8%.[395] Similarly, in this cohort, when the 3rd percentile of Fenton curves were used, 30.3% of the infants of the infants in our cohort were small for gestational age, and when the 10th percentile was used, 49.4% of the infants were small for gestational age.

The data about the intrauterine and post-natal growth which was compiled to draw the Fenton's curves were from large population based surveys from four Western countries (Sweden, Canada, Australia and the Center for Disease Control (CDC), USA).[396–399] The intrauterine weights used to obtain the curves were from the Canadian study with its large sample of over 600,000 babies born between 22 and 43 weeks. The Australian and Swedish databases were used to compile the intrauterine head circumference and length curves. The CDC data was used to derive the growth curves after 40 weeks. The pooled data for these various datasets were used to derive the percentiles and create a single growth chart that combined both sexes[394,400]. Even though it has been criticized, since the

curves are drawn using different databases, all being from developed countries, the Fenton curves were chosen for this cohort since it is an internationally accepted growth curve.

6.2.2 INFLUENCE OF MATERNAL & PERINATAL CHARACTERISTICS ON THE SURVIVAL AND NEURODEVELOPMENTAL OUTCOME

Some of the positive features in the mothers of this cohort were that 100% of the mothers had antenatal check-ups during pregnancy (**table 11**), there was only one teenage pregnancy and majority of the mothers had completed 10th standard. However this may not be representative of the mothers in Tamil Nadu. According to the National Family Health Survey-3 (NFHS-3), 22.3% of the women in Tamil Nadu were less than 18 years at the time of marriage and only 31.1% had 5-9 years of education. However the survey also showed that during the same period, 96.5% of the mothers receive antenatal care and 90% of the deliveries were institutional deliveries.[401]

A. MATERNAL COMPLICATIONS PRECEDING THIS PREGNANCY

About 20.9% of the mothers of the cohort had history of obstetric and medical complications **(table 11).** The data of the mothers of this cohort is similar to other studies from this country done on VLBW cohorts,[402,403] where a significant proportion of the mothers had antenatal complications (like PIH, antepartum hemorrhage, preterm premature rupture of membranes (PPROM) and Gestational diabetes). **(5.1.2,** p.112-115 **tables 14 and 23)**

Two maternal morbidities which lead to birth of VLBW or premature babies are maternal anemia and a previous history of delivering a low birth weight infant.[94,403] Both preterm

and IUGR are commoner in mothers with severe anemia.[404] There were only few mothers with anemia (probably because of the good antenatal care) in this cohort, and only about 8% of the mothers had previous history of having a low birth weight child. In this study the antenatal complications and maternal risk factors did not affect the survival or neurodevelopmental outcomes of the VLBW infants.

B. PREGNANCY INDUCED HYPERTENSION

As mentioned earlier **(table 11)**

- PIH was a major maternal complication in this cohort and more than one third of the babies, born to these mothers were growth restricted.
- The mortality rate in the babies born to PIH mothers was 7%.
- PIH did not influence the survival or neurodevelopmental outcomes of the infants in this study (**table 23**)

The results of this cohort have been supported by other studies which have shown that intrauterine growth restriction is a major complication of PIH.[405] Perinatal mortality due to PIH ranges from 6% in developed countries to about 30% in developing counties.[406] Although PIH was ***not*** significantly related to mortality in this cohort (**section 5.1.2,** p.112 and **table 14**), other studies have shown the mortality is higher in infants born to mother with PIH.[407]

However there are conflicting studies on the effects of PIH on the neurodevelopmental outcomes, which is to be expected given the heterogeneity of the condition.[405] One study showed that PIH did not affect the IQ or school performance of children at 9-10 years of age.[408] Another large study on VLBW infants showed that those born to PIH mothers had similar GQ scores and lesser incidence of cerebral palsy as compared to VLBW

babies who were born to normotensive mothers.[409] Other studies have shown that infants born to pre-eclamptic mothers had significantly better MDI and PDI scores on the Bayley's scales at 18 months, although their growth was significantly lesser than the infants born to mothers with normal blood pressure.[410] However in contrast one study showed babies who are have significant growth retardation following PIH are worse in their cognition, visuo-spatial and motor skills.[411]

C. MULTIFETAL GESTATIONS (5.1.2)

In this cohort –

- More than a quarter of the babies in the cohort were twins or triplets and almost all of them (97%) were premature and in addition, about a quarter were preterm and SGA. (however because of the weight ceiling of 1500 g for inclusion into the study, this is not truly representative of the babies born of multifetal gestations).
- There was slightly greater mortality among the twins [p=0.067, RR 1.05 (.99-1.1 95% CI)] compared to the singletons (**table 14**) and the main causes of death among the twins was septicemia followed by asphyxia.
- Multi-fetal gestation did not influence neurodevelopmental outcomes (**table 23**) although two children with CP were born of multi-fetal gestations.

It has been shown that twins have a relative risk of 5.4 and triplets have a relative risk of 9.4 of being premature compared to singletons.[412] Another major complication of multiple gestations is intrauterine growth retardation.[413]

There are conflicting reports about the mortality of twins compared to singletons. Some studies have shown that the mortality in twins is higher,[416] while a large cohort study

from the NICHHD-NRN registry which compared twins with matched singletons, showed that the risks of death, IVH and CLD were similar between the two groups.[417]

Studies which have compared the neurodevelopmental outcomes of premature twins to premature singletons including an Indian study, have not found any difference in the developmental quotients between twins and singletons.[418–420] However data from a large NICHHD cohort which looked at the outcomes of ELBW twins and triplets and compared them with singletons showed an increased risk of death ,neurodevelopmental impairment among the infants born of twin and triplet pregnancies.[421,422]

D. BIRTH AFTER ASSISTED CONCEPTION

In this cohort –

- There was no significant difference in the mortality or neurodevelopmental outcomes between those who were spontaneously conceived and those who were born by assisted conception techniques **(tables 14 and 23).**
- Many mothers were treated for infertility and many of these pregnancies resulted in multifetal gestations.

Systematic reviews have shown that multifetal pregnancies are a known risk when assisted conception techniques are used and that perinatal morbidity and mortality are more common in these infants.[423,424]

The information about neurodevelopmental outcomes after assisted conception is conflicting. A systemic review of eighty studies found that the developmental outcomes of children born through assisted conception was comparable to those who were conceived normally.[425] Another study however found that the developmental outcomes of children less than 26 weeks gestation, born after AC, were worse than gestation matched

peers who were conceived normally. However this was not seen in infants born after 27 weeks gestation.[426]

E. DIABETES COMPLICATING PREGNANCY

In this study –

- 7% of the mothers had diabetes complicating pregnancy and 15% of the infants were SGA.
- Maternal diabetes during pregnancy did not affect the survival or neurodevelopmental outcomes of the infants in this cohort (**tables 14 and 23**)

Gestational diabetes is prevalent in up to 18% of Indian mothers[427] as compared to 4% in European mothers.[428] A study from this institution showed that 4.7% of infants born to diabetic mothers were small for gestational age and 15.8% were preterm.[429] while Western studies have shown that 2% of infants born to diabetic mothers are small for gestational age.[430] Prematurity is known to be five times more common in diabetic mothers.[431] Unlike the results of this cohort infants of diabetic mothers are at higher risk of mortality.[432]

There are studies which show neurodevelopmental outcomes and the cognitive outcomes of infants born to diabetic mothers are worse compared to mothers without diabetes. However these studies were on term babies and none of them were done on VLBW infants.[433–435]

F. ANTENATAL CORTICOSTEROIDS

In this study there was no relationship between antenatal corticosteroids and the survival or the neurodevelopmental outcomes of the infants in this study (**tables 14 and 23**).

Antenatal corticosteroids have been shown to significantly improve survival and decrease incidence of intraventricular hemorrhage and respiratory distress syndrome in preterm infants.[436] Antenatal corticosteroids have also been shown to improve the neurodevelopmental outcomes.[212]

6.2.3 NEONATAL MORBIDITIES – THEIR INFLUENCE ON THE SURVIVAL AND THE NEURODEVELOPMENTAL OUTCOMES

One of the objectives of the study was to look at the neonatal complications which occurred in this cohort of VLBW babies and their effect on the eventual outcomes.

A. BIRTH WEIGHT AND GESTATIONAL AGE

In this study –

- Lower birth weight and lower gestational age was significantly associated with higher mortality. (**Tables 14. 15 and 16, figures 8 b and 8c**)
- However there was no relationship between birth weight or gestational age and the final neurodevelopmental outcome. (**Figure 14 and tables 18 and 23)**

The results of this study are in concurrence with other studies which have shown that lower gestational age and lower birth weight result in greater mortality (these studies have been reviewed in **3.1.1 and 3.1.2** p21-28**)**

In contrast to results of this study, lower birth-weights and lower gestational ages are associated with poorer neurodevelopmental outcomes and cerebral palsy (t**ables 3A & 4**). Even late preterms (>34 weeks) have a poorer outcome compared to normal term babies.[437] Bhutta *et al*[438] in a meta-analysis demonstrated that there was a very significant linear relationship between cognitive test scores and the birth-weight (R^2= 0.51; p

<0.001) and gestational age (R^2 = 0.49. p <0.001). The greater rates of neurodevelopmental impairment in smaller and less mature babies are because of the vulnerability of the immature brain and other organs to injury. Brain growth occurs linearly as gestation progresses[439] and at 34 weeks gestation the premature infants' brain is only 65% of that of the term infant.[437] The major organizational events in the development of the cerebellum, neurons and glia occur in the latter half of gestation. Complications of prematurity like RDS, apnea, hypoglycemia cause neuronal cell death which damage the preterm brain[440] and manifest later as neurodevelopmental impairments and behavior disorders.

The reason why gestational age and birth weights did not affect the neurodevelopmental outcomes in this cohort may be because the babies in this cohort were more mature at the time of birth and had lesser complications compared to babies from Western countries.

B. DIFFERENCES IN THE NEONATAL MORBIDITIES BETWEEN BOYS AND GIRLS

In this study –

- There was a significantly higher incidence of intraventricular hemorrhage and respiratory distress syndrome in the male infants compared to the female infants (p.121). Hence rates of CPAP and ventilation were also higher in the male infants (**table 12**).
- Premature preterm rupture of membranes was associated with birth of male infants (p=0.007), but PIH in the mother resulted in the higher incidence of birth of female infants (p=0.007) **(table 12 & 5.1.3,** p115**)**

- In spite of the differences in the neonatal complications, there was no difference in the mortality between girls and boys (p=0.718) (**5.1.4,** p.123).

Findings similar to this cohort have been described in other studies. Premature male babies (especially <800 g) also have a higher risk of RDS and BPD[442,443] and intraventricular hemorrhage.[444]

However unlike this cohort many studies have shown the male infants have a poorer survival compared to girl babies of the same gestational age. This is particularly true in extremely premature male infants who have higher mortality.[226,230] Survival of female infants was significantly better than male infants in many studies.[445,446] Studies have shown that Preterm premature rupture of membranes (PPROM) and pre-eclampsia in the mothers are also associated with birth of male babies.[447]

However the unusual finding in this study was that, ***very significantly, PIH was associated with the birth of girl babies.*** The reason for this finding is not known and therefor it is speculated that it may be because the girl babies born to mothers with PIH in this cohort were heavier - the median birth weight of girl babies was 1300 g compared to the median birth weight of 1280 g in male babies (however since the p-value was 0.783 for the difference between the weights, this finding may not be significant).

There were differences in the neurodevelopmental outcomes between boys and girls, which are discussed in Section 3 (6.3.2, *p.197)* ***of the Discussion.***

C. PERINATAL ASPHYXIA

- Asphyxia was significantly associated with mortality in this cohort **(tables 13- 16)**
- Although asphyxia did not affect the ***overall*** neurodevelopmental outcomes since it did not show a significant association with the General Quotient (**table 23**), the

multivariate logistic regression analysis showed that asphyxia was significantly associated with language delay (**table 25**).

Perinatal asphyxia is characterized by acidosis. The results in this cohort were similar to a large study which looked at the neurodevelopmental outcomes in ELBW infants with acidosis at birth (defined as pH <7.0 and Base excess >−12 mEq/L), which showed that acidosis was strongly related to death (OR=2.1, p <0.001).[448] In addition acidosis was predictive of poor neurodevelopmental impairments and cerebral palsy in the study, but as mentioned this was not a finding in the study cohort.

D. NECROTIZING ENTEROCOLITIS

In this study -

- Severe NEC was significantly associated with mortality **(tables 12-16)** and mortality increased with the severity of NEC and was 0% for stage I to 50% for stage 3 **(5.1.3,** p.118**)**
- However severe NEC was not associated with poor neurodevelopmental outcomes (**table 23**)

The findings in the study cohort have concurred with the findings from another cohort from South India which showed worsening mortality as the severity of NEC increased, with 0% mortality in stage 1, 15.4% mortality in Stage 2 was and 79.6% mortality in stage 3.[449] Although other studies have shown that NEC also significantly affected growth and neurodevelopmental outcomes,[276–278] this was not observed in this cohort.

i. RESPIRATORY DISTRESS SYNDROME

- Presence of RDS was strongly related to death in this cohort (**tables 13-15, figure 8f) *but*** *only* few children who died because of pulmonary complications related to RDS and most of the deaths were because of associated co-morbidities like septicemia, coagulopathy or severe IVH.
- RDS was not associated with neurodevelopmental outcomes in this cohort **(table 23)**

The findings similar to the study cohort were also reported from another Indian study, which showed that the mortality in RDS was related to other co-existing conditions like IVH and septicemia.[450]

As mentioned earlier (**5.1.3,** p116), the use of surfactant is very low in this cohort since CPAP is the first line of management of RDS in this institution. It has now been recommended, that surfactant be used only when CPAP has failed in low-income countries.[451,452]

E. INTRAVENTRICULAR HEMORRHAGE

In this cohort severe IVH was seen predominantly in the male infants, the mortality due to severe IVH was nearly 90% and it occurred only in infants less than 34 weeks **(tables 12-14).** Only two children survived after severe IVH and both of them had good neurodevelopmental outcome, so severe IVH did not influence the neurodevelopmental outcomes in this cohort **(table 23).**

The incidence of IVH increases with decreasing gestational age and it has been shown that for every week of increasing gestational age, the rates of IVH come down by

3.5%.[453] Like the findings in this study, many studies have documented that it is more common in male children.

Although not evident in this cohort, children who survive IVH in the neonatal period usually have significant neurodevelopmental sequelae (neurodevelopmental impairment, hydrocephalus, cerebral palsy and cortical visual impairment).[454,455]

F. **SEPTICEMIA**

In this study

- Septicemia was the main cause of mortality and majority of the deaths were because of Gram negative organisms (**figures 4 & 5, table 13**)
- In more than two-thirds of the babies the onset of septicemia was after 72 hours (late onset), so it is likely to be of nosocomial origin.
- Septicemia did not influence the neurodevelopmental outcomes **(table 23)**

The predominance of Gram negative organisms seen in this cohort is similar to what has been observed in other developing countries.[91,93,456–458] However these findings are in contrast to Western reports which show Gram-positive organisms to be the main cause of late-onset septicemia.[288,459,460] Septicemia in VLBW infants can result in periventricular leukomalacia which is major cause of cerebral palsy and significant neurodevelopmental impairment.[54,461]

SURVIVAL OF THE INFANTS IN THE NICU

- The survival rate was in this cohort was **92.26**% (89.4-94.54, 95% CI). The adjusted survival rate (assuming that those whose outcome is not known had also died was **83.89%** (80.22-87.14, 95% CI) **(5.1.9,** p.133**).**

- The survival improved with increasing gestational age

The survival in this study is better than other Indian studies (**3.1.1,** p.22-25). Almost all studies on VLBW infants from India and abroad have shown that survival improves as the birth weight and gestational age increases.

COMPARISON OF THE STUDY COHORT WITH THAT OF A NICHHD COHORT

The **table 35** (below) compares the perinatal and neonatal morbidities which occurred in this cohort with that of a cohort of VLBW infants from the NICHHD database.[96] (This particular article was chosen, since the infants are classified according to the weight. In the later studies from NICHHD the infants are classified according to their gestational age.)[34]

The use of antenatal corticosteroids and the rate of Cesarean section seem to be similar between the two cohorts. The proportion of the infants born of multifetal gestation who are more than 1000 g is almost similar between both the cohorts.

However there are many differences between the two cohorts.

- There is a much greater proportion of twins who weigh less than 1000 g. This may be because of the large number of twins who are born following assisted reproductive technology in Western countries.
- Not surprisingly there is a higher proportion of SGA babies in this cohort as compared to the NICHHD cohort.
- Septicemia being a major cause of neonatal morbidity and mortality in developing countries is more in the study cohort. Septicemia tends to increase with decreasing birth-weights in both the cohorts.

However the striking differences between the NICHHD study and the study cohort is that the incidence of RDS, surfactant use, CLD, severe IVH, severe NEC and PDA is much lesser in the study cohort. This is because all these are primarily complications seen in preterm babies and there is a larger proportion of SGA babies in our cohort. As shown in **table 27** for a birth-weight of less than 1000 g, the gestational age ranges from 25-36 weeks in our cohort, while in the NICHHD cohort the gestational age is more homogeneous and babies who weigh less than1000 g are usually less than 26 weeks.

There is a lower survival rate in the babies of the study cohort, especially in the lower birth-weight category. This could be because of the effect of septicemia, which is the main cause of death in the study cohort (**table 13).** However it is heartening to note that the survival seems almost equal in the highest birth-weight category.

Table 35: Comparison of the results of this study cohort with that of the NICHHD.

Risk Factors	751-1000 g		1001-1250 g		1251-1500 g	
	NICHHD Cohort (%)	Study Cohort (%)	NICHHD Cohort (%)	Study Cohort (%)	NICHHD Cohort (%)	Study Cohort (%)
Antenatal Steroids	76	72.5	74	72.4	70	62.5
Multiple births	79	28.8	21	25.9	25	28.7
SGA	17	35	24	25.9	29	31.8
Late septicemia	33	13.8	18	23.5	7	13.9
Cesarean section	60	61.3	60	55.5	50	66.5
RDS	63	38.8	44	32.5	26	16.8
Surfactant	68	0	47	25.4	28	7
BPD	34	0.5	15	2.1	7	0.7
IVH Grades III & IV	12	4.3	8	3.5	3	1.5
NEC ≥Grade 2	9	1.3	5	2.1	3	1.3
PDA	39	21	25	19.7	13	8.24
Survival	86	75	94	89.7	97	95.1

6.2.4 WHY DIDN'T NICU MORBIDITIES INFLUENCE NEURODEVELOPMENTAL OUTCOMES?

Why is that, even though the Western studies have shown that significant neurodevelopmental impairments and cerebral palsy are related to neonatal risk factors, these risk factors did not seem to affect the neurodevelopmental outcomes in this cohort of babies?

First, compared to the Western cohorts as shown in **table 35**, although the incidence of septicemia is higher among the babies in the study, the incidence of neonatal complications like severe IVH, NEC, PDA and RDS is much lesser in this cohort because of the higher proportion of SGA babies.

Second, as displayed in the **table 36** below**,** for each neonatal complication (other than severe IVH) only 32-50% of the babies, who had that particular complication, came for the assessment. (Except for severe IVH where only 12% of the babies who had severe IVH came for the assessment). The majority of the infants died in the nursery or after discharge and a smaller proportion were lost to follow-up. Moreover at the time of assessment, as shown in **table 36**, less than 20% of the survivors of each neonatal complication had poor neurodevelopmental outcomes.

So in conclusion the study babies had a ***lesser incidence of some complications*****,** ***higher mortality rate because of the complication, but better neurodevelopmental outcomes if they survived. Because of these reasons the number of children who had poor neurodevelopmental outcomes was not large enough to demonstrate a statistically significant association between neonatal complications and the neurodevelopmental outcomes***

Table 36: Proportion of children who were alive after neonatal morbidities

Neonatal risk factor	Alive at the time of assessment	Died in Nursery or after discharge	Lost to follow -up	Among the assessed whose GQ <2SD*
ELBW	49%	31%	20%	6/30 (20%)
Perinatal asphyxia	32%	56%	12%	3/15 (20%)
NEC (≥Grade 2)	42%	42%	17%	1/5 (20%)
RDS	50%	30%	20%	7/86 (8.1%)
Hypotension	33%	50%	17%	9/51 (17.6%)
PDA	50%	30%	20%	5/44 (11.4%)
Septicemia	41%	33%	26%	6/53 (11.3%)
Severe IVH	12%	88%	0	0/2 (0%)

* Estimated from **table 23**

However it must noted, that from the above table, it appears that the mortality because of PDA or RDS is very high (30%). That is not true. It is well known that in a VLBW infant multiple complications co-exist. A child with RDS who required ventilation, may have developed ventilator associated sepsis, which resulted in the release of pro-inflammatory cytokines and prostaglandins. This further leads to the opening of the ductus venosus resulting in PDA. This same child could have necrotizing enterocolitis and IVH. Thus the mortality in this child can be due to any of these causes and the child's mortality is included in RDS, Septicemia, PDA, NEC and IVH. So a child who had RDS at the time of death, probable died of septicemia or some other cause and not because of the RDS *per se*. ***In conclusion to this Section many neonatal risk factors were significantly associated with the death in the NICU. However despite the relatively large cohort, for the reasons mentioned above, none of neonatal factors affected overall neurodevelopmental outcome of the babies in our cohort. Only perinatal asphyxia was significantly associated with poor language outcome.***

6.3 SECTION 3 - OBSERVATIONS DURING THE DEVELOPMENTAL FOLLOW-UP

In this section the findings of the developmental follow-up phase are discussed. The section is arranged in the following manner -

6.3.1: ***The concept of "causal pathways"*** which lead to CP

6.3.2 ***The topography and the co-morbidities*** associated with CP.

6.3.3: ***Differences in the neurodevelopmental outcomes between girls and boys.***

6.3.4: ***Impact of being small for gestational age*** on the survival and neurodevelopmental outcome of the children in our cohort.

6.3.5: ***Effect of the post-natal growth*** on the developmental outcomes.

6.3.6: ***Language skills predictors of poor language*** in the study cohort.

6.3.7: Influence of ***some social factors particularly maternal educational level*** on the developmental and language outcomes.

6.3.1 CEREBRAL PALSY and "CAUSAL PATHWAYS"

There were five children with CP and their clinical summary is presented in **table 26.** Since their numbers were small there was no risk factor which was found to be associated with cerebral palsy. However, in many children, it may be a confluence of adverse antenatal, perinatal and neonatal events which leads to cerebral palsy rather than a single event. This has led to the concept of "causal pathway" – which is a sequence of multiple antecedents which are interdependent but finally confluences in neurodevelopmental impairment and cerebral palsy.[36] Thus looking at **table 26** it is clear that many children had factors which could have led to their impaired neurodevelopmental outcome. Some

of the risk factors which were seen in the children with CP and are known to be associated with cerebral palsy are considered below.

A. MULTIPLE GESTATIONS

Two of the five children were born of multifetal gestation (one was of twin pregnancy and the other child was one of triplets). Studies have consistently shown that multifetal gestations are associated with cerebral palsy.[462,463] A study from Australia showed that the prevalence for CP at one year of age was 28 per 1000 in triplets, 7.3/1000 in twins and 1.6/1000 in singleton pregnancies.[464] The causes of brain damage in multifetal gestation could be abnormal anastomoses, thrombogenesis following thromboplastin release after the death of the co-twin, prematurity and associated intrauterine growth retardation.[465]

B. CYSTIC PVL

Cystic changes on ultrasound are the strongest predictors for cerebral palsy in preterm infants.[356] One of the children was detected to have cystic PVL (**Figure 16**) on the neurosonogram taken at two months of age. The early scans (done on day 3 and day 7) were normal. De Vries in her seminal study showed that serial cranial ultrasonography till 40 weeks post-menstrual age is required to diagnose cystic PVL, since about a third of the cystic lesions are detected only after day 28[330] and these will not be picked up in the first two weeks..

Later in life the sequelae of PVL on the MRI are periventricular hyperintensities (representing glial scars), periventricular loss of white matter, distortion of the ventricular margins (leading to “wavy margins” on the MRI) and focal ventricular enlargement

adjacent to the regions of signal hyperintensities.[466] These MRI findings were observed in this child and two other children who had CP. **(Figures 15, 16 & 19).**

C. ABNORMAL UTERINE ARTERY DOPPLER

Some of the mothers of the children in **table 26** (including two of the children with CP) had absent or reversed end diastolic uterine artery velocity (AEDV or REDV). AEDV and REDV are ominous findings seen in fetal growth retardation and pre-eclampsia and result in fetal hypoxia; many studies have shown that abnormal uterine artery blood flow is associated with adverse neurodevelopmental outcomes including CP,[467–469] . This has been documented from an Indian study as well.[197]

D. MATERNAL SLE

The mother of one of the children with cerebral palsy (child no. 14 in **table 26**) had Systemic Lupus Erythematosus (SLE). Children born to mothers with SLE are known have higher risk of developing neurodevelopmental disorders, probably because of high level of circulating autoantibodies and cytokines, which in animal models, have been shown to affect the fetus.[470] Infants born mothers with SLE have much higher risk of perinatal arterial stroke which results in hemiplegic cerebral palsy.[471] However this is unlikely in this child because she had the spastic bilateral (diplegic) form of CP. This child's mother also had PIH and eclampsia which could have contributed to the "causal pathway" which finally led to CP.

E. CEREBRAL PALSY AS A CONFLUENCE OF MULTIPLE RISK FACTORS

As mentioned earlier CP is the culmination of multiple risk factors. This was probably the case in child 7 (**table 26**). She was born severely growth retarded and had multiple

complications in NICU (acidosis at birth, RDS, septicemia, hypoglycemia and cholestasis). Each of the risk factors is associated with neurodevelopmental impairment and cerebral palsy. At two months of age she developed intracranial hemorrhage (probably due to hemorrhagic disease because of persisting cholestasis) which finally resulted in left hemiplegic cerebral palsy **(figure 18)**. It could be argued that the child's CP was because of post-natal causes and not because of the VLBW. However she is included in view of the multiple risk factors which could have culminated to result in the final event which led to CP.

Post-natal causes like septicemia, meningitis, cerebral malaria, and intracranial hemorrhage account for a sizeable proportion of children with cerebral palsy. [472,473] In developing countries it is likely that these post-natal cases can affect the already vulnerable VLBW infant and result in CP.

F. CEREBRAL PALSY DESPITE NORMAL SERIAL CRANIAL ULTRASOUNDS

In one of the children with cerebral palsy (Child 1, **table 26**) the only risk factor was probably low birth weight since there were no other complications. However the older sibling was also low birth weight and so there are likely to be unidentified maternal, antenatal and possibly genetic causes which could have contributed to the child's neurodevelopmental impairment. Of particular importance is that the child's cranial ultrasound at 6 weeks was normal and there were no cystic changes. It has been shown that, some children with cerebral palsy have multiple normal cranial ultrasounds without any hyper-echoic lesions (indicative of hemorrhagic lesions) or hypo-echoic lesions (indicative of cystic lesions). It may be that these children have diffuse periventricular leukomalacia which cannot be detected even by high resolution ultrasound scans. But

they subsequently go on to develop ventriculomegaly and other signs of PVL.[474] **Figure 15** shows features of PVL in the MRI this child, which supports this point.

TOPOGRAPHY OF CEREBRAL PALSY AND THE CO-MORBIDITIES IN THE CHILDREN WITH CEREBRAL PALSY

In this cohort, there were –

- three children (60%) with spastic bilateral CP (spastic quadriplegia with all four limbs involved and all three were GMFCS level 5),
- one child (20%) with spastic unilateral CP (left hemiplegia - GMFSC level 1)
- One child (20%) with spastic bilateral CP (Diplegic CP - GMFCS level 3).

Initially spastic diplegia ("Little's disease") was the topographic type of CP described in preterm infants.[475] However in the study cohort the quadriplegic form seems to the most predominant. Data form a large CP registry from the UK showed that the topographic distribution of the CP in the birth weight group 1000-1499 (the birth weight category in which all the five CP children in the study cohort belonged) was as follows - Spastic Hemiplegia – 20%, Diplegia - 29.2% and Quadriplegia was 37.8%.[476] Therefore it seems that spastic quadriplegia is the more common topographic manifestation of cerebral palsy in the very low birth weight infants.

In addition to the children with spasticity, there were many children with hypotonia (**table 26**). Although initially classified among children with cerebral palsy, children with "central hypotonia" (hypotonia due to a cortical cause, manifesting with brisk tendon reflexes) are absent from contemporary CP classifications.[36] As seen in this cohort, hypotonia is commonly associated with significant developmental delay and intellectual

disability.[477] Although 1.5% of the children in the Cerebral palsy register of Victoria, Australia had hypotonia, they were not considered as CP.[478]

According to the definition of cerebral palsy[348] proposed by Bax and colleagues, "*the motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behavior and/or by seizure disorder*". Children with CP in this cohort, particularly the children with quadriplegic CP, in addition to the significant developmental delay, had multiple associated co-morbidities like visual and hearing impairment, microcephaly and epilepsy (**table 26**). In a study done in Canada, 80% of children with GMFCS level IV and V had a visual impairment, 40% had hearing impairment and 47% had epilepsy.[479]

6.3.2 DIFFERENCES IN NEURODEVELOPMENTAL OUTCOMES BETWEEN BOYS & GIRLS

The differences between boys and girls in the neurodevelopmental outcomes in the study cohort were -

- The mean GQ of the boys were slightly but significantly lower than that of the girls (Mean GQ of boys was 92.92 and that of girls was 94.97, p=0.04) (**table 17**)
- The boys fared worse than the girls in some domains of development like personal-social skills, hearing and language skills and eye-hand coordination activities (**table 20**).
- There was a larger proportion of boys than girls with GQ of less than 2SD (GQ <76) [12.7% boys to 9.9% girls] although this was not significant (**table 23,** see **5.2.1**)

- Among children whose GQ was less than 70 **(table 26**), 23 of the 31 (74.2%) children were boys as compared to 9 girls (25.8%)
- Among the children with CP there were 3 boys and 2 girls. All the 3 boys were more severely affected (GMFCS level V) compared to the girls with CP (one was GMFCS level I and the other GMFCS level II) (**table 26**).
- There were three boys with autistic symptoms while there were no girls with autistic features (**table 26**, **see 5.2.9,** p.154**)**

The findings in this cohort have been corroborated by other studies. Recent studies have shown that preterm boys were more likely to have moderate to severe CP, and low Bayley MDI and PDI scores compared to the girls, even when the neonatal neurosograms are normal.[480] The gender differences in the cognitive performance persist even when assessed at six years of age.[481] The language abilities of male VLBW infants are much less than female VLBW infants and normal children.[482] Similar to what was found in this study (see **table 20**), a study from Australia which looked at the neurodevelopmental outcomes of ELBW infants using the GMDS, showed that the performance on the Hearing and language scales and the overall GQ in boys were significantly lesser when compared to the girl children[483]

The reason for this male disadvantage in the developmental outcomes of VLBW children is not known. It has been shown in a study which, compared the white matter and grey matter (on the MRI) of eight year old preterm boys and girls with age and gender-matched controls, that the white matter volumes are significantly lesser in boys who were preterm compared to the normal male controls, while in girls who were preterm there was no difference when compared to the normal girl controls. Thus preterm boys may be

more vulnerable to brain injury.[484] Another reason why preterm boys are more vulnerable than girls is the "lung maturity hypothesis" which was mentioned earlier in the Literature review section (**3.4.1.).** Even after adjusting for perinatal, neonatal, post-natal factors, gestational age and birth weight, studies have shown that male sex remained an independent risk factor for adverse neurodevelopmental outcomes. Therefore there may be a still unknown constitutional reason for the gender specific brain susceptibility.[226,227]

6.3.3 CHILDREN WITH AUTISM IN THE COHORT

The Personal-Social subscale of the GMDS assesses the child's abilities of social interaction and independence in daily living skills. According to Ruth Griffiths "emotionally disturbed children" do poorly on this sub-scale.[161] Another study using the GMDS showed that the Hearing and Language sub-scales and Personal-Social sub-scales are the scales which are most affected in autism.[485] Even in our cohort these two sub-scales were significantly more affected in boys compared to the girls **(table 20)**. There were three children (all males) who had symptoms of autism **(table 26)**, and were positive on the Modified Checklist for Autism Toddlers (M-CHAT). Their clinical features have been described in **5.2.9** (p.154)**.**

Findings in this cohort are supported by other studies. It is well known that in the general population, autism is four times more common in male children than female children.[486] Male preterm infants are more also likely to have symptoms suggestive of autistic spectrum disorder.[487] The difficulties in the social and communicative domains and presence of autistic features are commoner in premature infants, who have had neonatal complications like RDS.[488] Autism is associated with the poor cognitive abilities as

demonstrated in the study by Kuban and associates, who showed that that in the ELBW babies, cognitive and neurosensory impairment was strongly associated with testing positive on the M-CHAT.[489] This could explain why the child with profound developmental delay (child no.3 in **table 26**) in this cohort had autistic symptoms.

The symptoms of autism in VLBW infants are likely to persist through life. The adolescents who were VLBW at birth have a higher risk of having autism and other psychiatric manifestations.[490] In VLBW children, autistic symptoms are associated with cognitive impairment even later in life. In a long term follow-up of preterm infants, it was shown that cognitive impairment was strongly related to autistic symptoms at 11 years of age.[491]

6.3.4 IMPACT OF BEING SMALL FOR GESTATIONAL AGE

In this study the survival and neurodevelopmental outcomes of the small for gestational age infants were compared to the infants who were born AGA. Among the infants admitted into the nursery about one third were SGA and among the 422 infants who came for the developmental follow-up, 131 infants (31%) were SGA.

Effect of SGA status on survival and developmental outcomes

From the **tables 28 and 29** the following facts are apparent:

- Being SGA did not affect the survival of the infants, neither was there any significant difference in the neurodevelopmental outcomes.
- In this cohort there was no significant difference in the neurodevelopmental outcomes of the SGA and the AGA babies since (a) the proportion of children

with GQ <2SD in both groups is not statistically different (b) mean GQ between the SGA and AGA groups are not statistically significant

- All the children with CP were AGA at birth (however this may be because of the much larger number of AGA babies).

However the findings in the study cohort are different from that of a study from the Vermont Oxford Network database which looked at the morbidities and mortality of the IUGR babies in a large cohort of nearly 20,000 VLBW babies who were less than 32 weeks.[492] They found that being small for gestational age was significantly associated with death [Odds ratio 2.77 (2.59-3.3 95%CI)]; necrotizing enterocolitis (OR, 1.27, 1.05-1.53, 95% CI); respiratory distress syndrome (OR 1.19; 1.03-1.36 95%CI) and severe IVH (OR 1.25, 0.98-1.59 95%CI). Other Western cohorts have also found that the mortality of SGA babies are higher than that of AGA babies.[493,494] This difference in the findings may be explained by the fact that the SGA babies in the study cohort had a higher gestational age and therefore did not have the complications of prematurity unlike the babies of the Western cohorts.

Western studies have also shown that the neurodevelopmental outcome of infants born SGA are worse than those born AGA. A retrospective study from the NICHHD cohort showed that SGA status was significantly associated with low MDI the Bayley's scales (odds ratio 2.08, p=0.018) and occurrence of CP (OR 2.55) compared to AGA babies[61] Other studies have shown that children who are born small for gestational age have lower school achievements and more behavioral problems (particularly inattention and hyperactivity).[495,496]

Effect of SGA status on the post-natal growth

The growth of SGA babies remain significantly affected at two years of age. In a study by Mukhopadhyay *et al*[497] who followed up a cohort of ELBW babies, at two years of age 41% were underweight, 68% were short and 32% had microcephaly. In another Indian study which followed up VLBW infants till 18 months 30.9% were underweight, 59% were short and 25% had microcephaly.[498] In the study cohort nearly 60% of the babies were underweight, 54.5% were short and 63.6% were microcephalic (**table 29**). Long term follow-up studies have shown that children who are born SGA are likely to be shorter than their peers in adolescence.[229,499] Therefore a significant proportion of SGA babies remain growth restricted throughout life.

6.3.5 POST-NATAL GROWTH AND NEURODEVELOPMENTAL OUTCOMES

This study also looked at the post-natal growth of the VLBW babies in the cohort and the relationship between the post-natal weight growth and developmental outcomes. The post-natal growth was estimated by the Z-scores of weight, length and head-circumference at the time of assessment estimated using the WHO-ANTHRO software. I will briefly discuss two important findings of our study pertaining to post-natal growth.

A. Developmental outcome is dependent on the post-natal growth

In this cohort it was found that the growth status (whether the baby was SGA or AGA) at birth was not significantly related to the developmental outcome at the time of assessment (p=0.083, table 23). The weight, length and head-circumference at the time of assessment were significantly related to the developmental outcomes (GQ). On the multivariate logistic regression, the Z-score or the weight at the time of assessment was

significantly associated with the final GQ. The Z-score of the head circumference also showed an association although this was not significant **(table 24).**

Other studies have supported these findings. It is a well-established fact now, that impaired post-natal growth is associated with poor cognitive performance. A prospective study by Latal-Hajnal[500] showed results similar to what was found in this study, that appropriateness of weight for gestational age at birth (whether SGA or AGA at birth) did not affect the neurodevelopmental outcome at two years, but the post-natal growth, assessed by the Z-scores for weight at two years, significantly affected the neurodevelopmental outcome**.** Ehrenkranz[501] showed poor growth during the NICU period was significantly associated with inadequate post-natal growth at 22 months and furthermore the rate of growth in the ICU significantly correlated with the neurodevelopmental outcomes at 18- 22 months. The study also showed that infants whose NICU weight gain was in the lowest quartile were the most likely to have neurodevelopmental impairment at 18-22 months. Other studies have shown that poor weight gain due to inadequate nutrition during the period of brain development in VLBW children, results in decreased brain cells which later leads to significant deficits in behavior and learning.[502]

B. Developmental outcomes in AGA and SGA are different depending upon their post-natal weight gain

On considering the developmental outcome depending on the post-natal growth of AGA and SGA babies the following findings were observed: .

- SGA infants who had adequate catch up growth had developmental outcomes similar to AGA infants whose weight remained appropriate for age (In this study

the GQ for the SGA babies who caught up was 97.9 vs. GQ of 95.9 for the AGA babies whose weight remained appropriate)

- Infants who were AGA at birth but had inadequate post-natal growth were the most affected. Their development was worse than the SGA babies who had inadequate post-natal growth. (In this study GQ of AGA babies with poor post-natal growth was 89.4 compared with the GQ of 91.2 for SGA babies who continued to have inadequate post-natal growth) (**table 30**)

Significantly both these findings have concurred with that of Latal-Hajnal and associates.[500] who have reported that the post natal growth status influences neurodevelopmental outcomes and not the growth status at birth.

The phenomenon of AGA infants having poor weight gain and having poor growth post-natally to the point of falling below the 2SD of the mean of the weight, later in life is termed "Weight catch down". The possible explanations for this "Weight catch down" is that the preterm AGA children who exhibit it, were already probably in a process of "catch down" even during the intrauterine period, but they were born before their weights fell below 10th percentile and hence their birth- weight was appropriate for gestational age. So, in these babies their post-natal growth restriction was just a continuation of their insufficient intra-uterine growth. These preterm AGA children who were likely to become IUGR had pregnancy continued, are probably more sensitive to restrictive extra-uterine environments than the SGA infants and so exhibit weight catch down with time. The implication of this phenomenon is that preterm AGA infants require strict growth and developmental monitoring like SGA children.[503,504]

Head circumference and developmental outcomes

In this study the Z-score for head circumference less than 2SD (microcephaly) was related to the poor developmental outcome on the bivariate analysis (**table 23**), although it was not significant in the multivariate analysis (**table 24**). Similarly microcephaly was also related to low scores on the language sub-scales on bivariate analysis.(see **5.2.7** p.145). Head circumference (Occipito-frontal circumference) is a very good predictor of brain volume in children who are less than 6 years of age[505] and a smaller head size at birth, below 33.5 cm indicates smaller brain volume.[506] Subnormal head circumference in VLBW children is associated with poorer IQ, academic skills and adaptive behavior in the school going age.[507] A large study has shown that subnormal head circumference (HC <2SD) is strongly related to lower MDI and PDI scores and cerebral palsy at two years of age in VLBW children.[508] These studies, thus, concur with the findings that subnormal head circumference in the post-natal period (at the time of assessment) is associated with adverse neurodevelopmental outcomes.

6.3.6 LANGUAGE OUTCOMES IN THE VLBW CHILDREN

Language skills in VLBW children: Speech and language are core skills in a child's development and markers of cognitive and social development.[509] Children with global developmental delay will have delayed language development and will use words only much later in life.[509] Acquisition of expressive and receptive language skills is thus a good indicator of a child's cognitive abilities.[510]

In this cohort we found that both boys and girls who scored low on the Hearing and Language subscale were most likely to have a poor GQ (**see 5.2.7** p145**).** The Sub-

quotient on the "Hearing and Language" sub-scale showed very good correlation to the GQ. Although it is too early, it is speculated that the children with low language abilities are likely to have difficulties in their learning and would be more delayed than their peers. On multivariate analysis it was found that ***maternal education, Z-score for weight below 2SD and perinatal asphyxia*** independently predicted poor language outcome indicated by Sub-quotient of Hearing and Language subscale below 2SD.

VLBW and preterm infants are known to have much reduced expressive and receptive language skills compared to normal control infants,[511] VLBW babies have lesser vocabulary size and poorer quality of word use, as well as lesser morphological and syntactic complexity.[512] In many preterm infants the language delays are because of cognitive impairment rather than any specific language impairment.[513] The language difficulties in VLBW babies persist through childhood and often lead to educational, behavioral and social problems.[514,515]

There are many biological, social and environmental factors which are believed to influence language development in VLBW infants. These include socio-economic status of the family, maternal education, gestational age, birth-weight, neurosensory deficits and complications like asphyxia, IVH, BPD, PDA which disrupt the oxygen regulation and cause hypoxic damage to specific language areas of the brain.[516–518]

Perinatal asphyxia is the only neonatal complication which showed association with developmental outcome. Although it was not associated with overall developmental delay (indicated by GQ) it was independently associated with poor language outcomes (**table 25**). Other studies have also shown that perinatal asphyxia results in specific speech and language deficits[519] and in cognitive deficits which also result in language difficulties.[520]

6.3.7 MATERNAL EDUCATION LEVEL AND ITS INFLUENCE ON THE NEURODEVELOPMENTAL OUTCOMES

This study was not designed to look for the effects of post-natal factors; particularly the influence of social factors on the developmental outcome but it occurred during the course of the study that the social and environmental factors can influence even early developmental outcomes. One social factor which was shown to be associated with the outcomes was low maternal education (in this study defined as educational level less than Std.8). Although low maternal education was not related to poor neurodevelopmental outcome (GQ <2SD) on the bivariate **(table 23)** or the multivariate analysis **(table 24)** which may be because of the small number of babies with GQ <2SD, low maternal education was significantly related to poor language outcomes (SQ-HL <2SD) on the bivariate and multivariate analyses (**table 25**). Maternal education was also an independent predictor for the child remaining underweight at the time of assessment **(table 31).** In **table 24,** it was shown that being underweight at the time of assessment was associated with poor neurodevelopmental outcome. So in short low maternal education is related to poor language outcomes and the child remaining underweight; and the child remaining underweight can lead to poor overall developmental outcome (GQ)

Developmental outcomes of VLBW infants are dependent on the "biologic factors" - antenatal & perinatal risk factors and the neonatal complications especially in the first two years. From early childhood, social factors like socio-economic factors, home environment, and parental education level play an important role in the subsequent development of the child.[521] VLBW infants who are likely to have developmental impairment because of their biologic risk factors are especially vulnerable in an adverse

social environment.[522] A study on VLBW infants showed that biological factors particularly cerebral ultrasonography findings (presence of ventriculomegaly, IVH or PVL) in the neonatal period was related strongly to the adverse developmental outcomes at one year of age. However as the age progressed, at 3.6 years, although the biologic factors were associated with outcome, social factors (occupational status of parents, maternal education and home environment) strongly influenced the developmental outcomes.[521]

The effect of social factors in the development of children was demonstrated in a seminal longitudinal study which showed that, even more than the various biological and medical factors, parental socio-economic status and particularly maternal education were the factors most predictive of intellectual performance at four years of age.[523] The relationship between maternal education and the developmental outcome of very low birth infants is multifactorial. Maternal socio-economic status has a close and direct association with maternal education level and women who are less educated are most likely to come from poor socio-economic background.[524] Furthermore women from the lower socio-economic status have a higher risk of having low birth weight babies.[525] Studies from the NICHHD cohort have shown that neurodevelopmental impairment (MDI of <70 on the Bayley's scales) are associated with lower maternal education level (less than high school).[212] Lower level of maternal education is also shown to be related poor IQ at 8 years of age in those who were VLBW.[526]

There may be many reasons why maternal education level influences the developmental outcome. Since a mother with low educational status is most likely exposed to more deprived social conditions, there may be many environmental risk factors like

malnutrition, repeated infection, environmental toxins (lead poisoning) which can further compromise her already compromised VLBW infant.[527] VLBW infants will require frequent hospital visits for developmental monitoring and better educated mothers are more likely to utilize health services and have greater autonomy in health related decisions regarding the child which are likely to have positive influence on the child's developmental outcome.[528]

Maternal educational level also influences the language development in children as shown in this cohort **(table 25).** Other studies have supported this finding since, maternal educational level has been shown to have a linear correlation with the child's expressive and receptive language capabilities and children whose mothers have lower education have early language delays.[529,530]

In conclusion, the major objective of medical practice is prevention of neonatal complications and amelioration of the developmental outcomes. The implication therefore is that with time, it may not be the neonatal complications which will influence the developmental outcome; but the socio-demographic factors. This was demonstrated in a study by Siegal *et al* who showed that infants who were classified "at risk" because of their neonatal morbidities but who were looked after by parents in a highly stimulating home environment, had scores in the normal range, compared to children who did not have any neonatal risk factors but was brought up in under-stimulating environments.[531]

The initial efforts to improve developmental outcomes of infants should focus rightly on maternal wellbeing, providing good perinatal care and prevention of preterm birth. However, after the birth of the VLBW baby, the major preventive measures consist of

protecting the fragile brain and the other organs. Neonatal morbidities are likely to have long lasting impact. Nevertheless in infants with significant biologic risks, a stimulating home environment may compensate partly for the damage in the perinatal period.[521] But in situations where there were significant biologic risks or in the absence of a stimulating home environment a comprehensive early intervention program is required to prevent further developmental impairment. A Cochrane review has shown that early intervention in premature babies has a positive influence on the cognitive and motor development.[532] The Child development Centre, Trivandrum has developed a simple early intervention package which can be taught to the mother. They have also shown that low birth weight and other high risk infants who have been administered this intervention model are comparable in their development to normal birth weight babies.[77,174] Therefore neonatal care does not end when the child is discharged from the Nursery. A stimulating home environment and a dedicated early intervention program is required to prevent the infant being trapped in a vicious cycle which can be counterproductive to his future growth and to attain the best neurodevelopmental outcomes.

.

7 SUMMARY OF THE FINDINGS OF THE STUDY

This study was done to ascertain the survival and neurodevelopmental outcomes of very low birth infants who were admitted in to the NICU of a tertiary level center. The study was done in two phases. Phase 1 dealt with the survival and the morbidities of the infants in the NICU and Phase 2 dealt with the neurodevelopmental outcomes of the infants who came for follow-up.

There were 776 infants who were admitted into the NICU. Of these 643 infants survived till discharge and were advised to come for follow-up. A final cohort of 422 infants completed the final developmental assessment. The results of the study are summarized below. The ***significant findings are highlighted.***

7.3 RESULTS OF PHASE 1

- There was a slight preponderance of male babies in the study (52.4%). ***Among the babies of the cohort 30.7% were small for gestational age.***
- The major antenatal risk factors was PIH in the mother and because of this majority of the infants were born by Cesarean section
- ***There were significant differences between boys and girls in the neonatal co-morbidities. Male infants had a significantly higher incidence of severe IVH and RDS.***
- ***Septicemia was the major cause of morbidity and was the cause of 58.3% of the deaths. Gram negative organisms predominated as the cause of neonatal septicemia and mortality***

- The mortality rates improved with increasing gestational age and besides septicemia, the other main causes of death were asphyxia and complications which are mainly seen in preterm babies (RDS, severe IVH and NEC)
- Sixty of the 776 babies died and 73 left before completion of treatment. ***The survival rate was 92.26% (89.4-94.54, 95% CI).*** The adjusted survival rate (assuming that those whose outcome is not known had also died was 83.89% (80.22-87.14, 95% CI*)*
- On multivariate analyses the risk factors that predicted death were – ***birth weight, perinatal asphyxia, septicemia, RDS, NEC and PDA***. Although lesser gestational age was associated with death in NICU, in the multivariate model it was not independently related to death.

7.4 RESULTS OF PHASE 2

- Of the 643 who left the nursery and were advised to come for follow-up, twenty babies died. Of the reminder 422 completed the final assessment (Follow-up of 65.6%). Thirty one babies who came for assessment at one year but did not come for the final assessment so 70.5% had at least one assessment.
- 221 boys (52.4%) and 201 girls (48.6%) completed the developmental follow-up
- ***The mean GQ of the study cohort was 93.6 (SD $\pm$ 13.01). The mean GQ among the boys was 92.9 ($\pm$13.08) and among the girls was 94.97 ($\pm$12.8). There was a significant difference between the boys and the girls (p = 0.04)***
- There were 48 children who had poor neurodevelopmental outcome (GQ of less than 2SD) below the mean and five children developed Cerebral Palsy***. The***

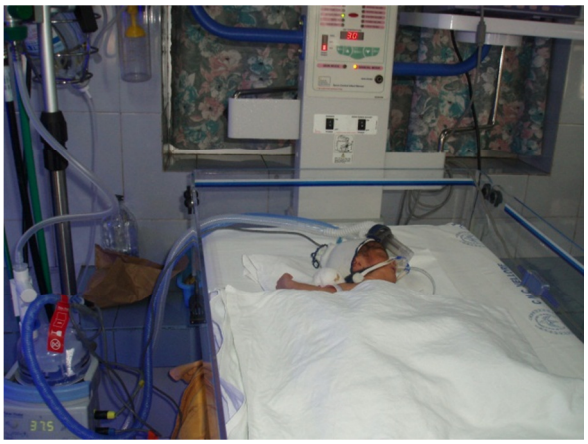
incidence of poor neurodevelopmental outcome (GQ <2SD) is 11.37% (8.6%-14.9% 95% CI) and incidence of Cerebral palsy in this study is 1.1 (0.39-2.63)

- ***Gestational age or birth-weight did not correlate with the General quotient***
- ***None of the antenatal, perinatal or neonatal risk factors were related to the neurodevelopmental outcome. However perinatal asphyxia in the neonatal period predicted low Hearing and Language sub-quotient.***
- T***here were differences between girls and boys in the neurodevelopmental outcomes.***
- ***The mean GQ of the boys was significantly less than that of the girls (mean GQ in boys was 92.92 compared to the GQ of 94.97 in girls, p=0.04)***
- Although sex of the baby was not related to the GQ on bivariate or multivariate analyses, larger proportion of boys had poor neurodevelopmental outcome compared to girls - 12.7% of the boys had poor neurodevelopmental outcome compared to 9.9% of the girls. There were also more boys (23 boys compared to 9 girls) who were profoundly delayed (GQ of <70)
- Boys fared significantly worse than the girls in certain sub-scales of the GMDS - (Personal –Social subscale, Hearing and language subscale and Eye-Hand coordination)
- ***There were more boys with cerebral palsy (3 boys compared to 2 girls). The boys were more disabled and all of them had quadriplegic cerebral palsy***.
- ***There were three boys with signs of autism, while there were no girls with autism***.

- ***Weight Z-score below 2SD at the time of assessment independently predicted low GQ.*** Head circumference below 2SD at the time of assessment was also related with low GQ although not significantly
- The language development of the boys was significantly worse than the girls
- ***Weight Z-score below 2SD, low level of maternal education, perinatal asphyxia, at the time of assessment independently predicted a low language sub-quotient (<2SD on SQ-H&L).***
- ***There was no difference in the survival or neurodevelopmental outcome of SGA babies compared to AGA babies.***
- ***The post-natal growth of the AGA and SGA influenced their developmental outcomes***. AGA and SGA babies who had good weight gain and whose Z-scores of the weight were in the normal limits at the time of assessment had the best neurodevelopmental outcomes. ***However AGA babies whose post-natal growth was poor (who had "weight catch down") had the worse neurodevelopmental outcome*** compared to SGA & AGA babies whose post-natal growth was adequate and SGA babies who had inadequate post-natal growth.
- ***Low maternal education, being small for gestation and neonatal hypoglycemia were significantly related to being underweight (Z-score of weight<2SD) at the time of assessment***
- ***Low maternal education was a significant predictor for both poor post-natal growth (Z-score of weight<2SD) and for poor language outcomes (<2SD on SQ-H&L)***

- ***Sensitivity analysis using "Best case" and "Worse case scenarios" showed that the exclusion of those who did not come for the final assessment (those who did not give consent, those who died and those who were lost to follow-up) did not affect the final results.***

LIMITATIONS, RECOMMENDATIONS, CONCLUSIONS AND IMPACT OF THE STUDY



8 LIMITATIONS OF THE STUDY

This is the largest cohort of Very Low birth weight babies followed up from the time of birth till 18-24 months of corrected gestational age. Yet the following limitations of the study must be considered –

1. Although this was the largest follow-up study of VLBW form India we were not able to determine the perinatal and neonatal risk factors which lead to poor developmental outcome. The reasons for this are clearly explained in **6.2.4** (p.190). However it has become clear from the study that neurodevelopmental outcomes are dependent not only on biologic factors, but also on the post-natal growth of the infants and social factors like maternal education and socio-economic status.

2. The final follow-up was only 65.6% who came for the final developmental assessment and 70.45% of the infants came for at least one assessment. The reasons for the loss to follow up has been discussed earlier in (section 4 (**5.4)** of the **Results section).** However in spite of the attrition rate, the sensitivity analysis showed that the results of the study were not affected because of the loss to follow up.

3. In the absence of a locally validated developmental assessment scale the results of the General Quotient obtained on the GMDS can be questioned. It would have also been good to have a local control population to interpret the test scores better. But it was very difficult to convince mothers of "normal" children to bring their children as controls. Although the Developmental Assessment Scale for Indian

Infants (DASII) is considered an Indian developmental assessment tool, it has been standardized only in Maharashtra. However the GMDS has been used for many years in the assessment of VLBW and ELBW infants. The psychologists and the Principal Investigator have many years of experience in using this tool and are confident of its efficacy. Despite all its limitations 88.6% of the infants in this study were within two standard deviations and 69.2% were within one standard deviation of the Western norms. Thus the GMDS appears to have served its purpose in the developmental assessment of infants between 18-36 months.

4. It is likely that the results obtained in this study may not reflect the true reality of the neurodevelopmental outcomes of the VLBW infants in this country since this was conducted in premier tertiary health center with excellent infrastructure and staffing for maternal and neonatal care. However the study proves beyond doubt that dedicated follow up can enhance the development of VLBW infants in this country, so that their neurodevelopmental outcomes are comparable to those from Western cohorts.

5. Long- term predictions in terms of future cognition may not be possible since the developmental follow-up was only till 18- 24 months in most babies and up till 36 months in a few babies. However, during the course of the study, it was possible to identify the babies who were at risk for developmental problems and commence early intervention and developmental therapy based on the results of the neurodevelopmental assessments.

9 RECOMMENDATIONS AND CONCLUSIONS

1. Since long term outcomes determine the success of the NICU care, it is mandatory that each tertiary level center invests in a multi-disciplinary developmental follow-up program. As the infants get discharged from the NICU their parents may have to continue developmental monitoring with their local pediatricians who may not recognize the risks the infant was exposed to, in the NICU or well informed about the guidelines of following up these children. Therefore the developmental follow-up programs should include networking with the local doctors, allied health workers, the schools, early intervention centers and community organizations who are involved in the care of these children after their discharge. There should be a system of getting feedback from the professionals who look after the child after discharge so that the NICUs are also aware about the child's progress and are aware of long term sequelae (if any) of these children.[69]

2. Research data and guidelines about neonatal practices from the Western countries cannot be extrapolated to this culturally diverse country. It is time to develop guidelines specific for this country. Therefore what is required are multicenter research networks like the National Institute of Child Health and Human Development (NICHHD) Neonatal Network, the Victorian Infant Collaborative Study (VICS) or the Vermont Oxford Neonatal Network. Multicenter networks result in partnership between academic centers and facilitate sharing of information. The results of the Networks may be more generalizable than the

results obtained by a single clinical center.[149,533] In India the NNF can be the umbrella body which coordinates multi-centric research and each center could contribute to a national database like the Neonatal Perinatal database. Information from the various centers around the country could make the National database equipped to reflect the neonatal practices from all over India. This would be useful in preparing guidelines, and for allocation of resources

3. There are different neurodevelopmental assessments done around the country. A uniform but versatile developmental assessment tool is the pressing need of the day. The DASII requires re-standardization to bring it up to date with the "I-pad" generation. This must be done in various sites and will require meticulous translation into multiple languages before it can truly considered the "gold standard" assessment tool. Many centers have started adapting the Bayley's Scale of Infant development (3rd edition) according to the local culture. However this has to be done in coordinated manner to reflect the practices of the entire country. "All psychological tests need revision from time to time. Changes in the behavior and activities of young children, in rearing practices, standards and expectations, throughout the whole social and material environment in which babies grow and develop take place over time and must be reflected in the content and standards of a test that purports to assess that development in a reliable, currently meaningful and valid way"[162]

4. Every follow-up study should have a concurrent component of intervention, even during the progress of the study. Many children will be identified to have

neurologic, sensory and developmental deficits and therapy should be started as soon as possible.

5. Since India has the largest number of high-risk (including VLBW) babies, there should be affordable, accessible and simple intervention models of developmental stimulation and early intervention. Like the Gadchiroli model for improving survival, there should be models for improving outcomes. A right step in this direction is the intervention package based on the Trivandrum Developmental Screening Chart. This package was shown to be very effective recently in providing home-based developmental stimulation[77,174] in high risk infants.

6. Neurodevelopmental follow up should go on till the child enters school. Before the school entry, these children should have a detailed evaluation, in order to identify those who are at risk of difficulties in the scholastic performance. Subsequently the school authorities should also be involved, so that the child can receive the appropriate educational support.

7. This study has revealed that poor neurodevelopmental outcome is closely associated with risk factors like low maternal education and poor post-natal weight gain which are modifiable to a great extent in order to yield better developmental outcomes. Although beyond the scope of this study it is well known that there are other social factors which are associated with long term outcomes of high risk infants - lack of social and emotion support to the mother, unemployment, large families etc. Improving prenatal care by educating mothers, promoting institutional deliveries, encouraging breast feeding and kangaroo

mother care and providing support to the mothers are very simple measure which will go a long way in improving outcomes. Unless these modifiable risk factors are identified and appropriate intervention provided the child's long term outcome may be poor.

10 IMPACT OF THE STUDY

Very Low birth infants are a heterogeneous group in terms of their etiology and their prognosis. These infants are exposed to multiple biologic, medical and social risks. Their developmental outcomes can range from normal development to profound developmental delay, neurosensory impairments and cerebral palsy. They are also likely to have long term problems in their growth, cognition, behavior and school performance. Thus information about their developmental progress is of utmost importance.

Despite all its limitations, this study is the report of the largest cohort of the VLBW babies who have been followed up in India till date. The incidences of neurodevelopmental impairment (Cerebral Palsy-1.10% and significant developmental delay-11.37%) are comparable to the best reports from Western countries and other developing countries. This study has also demonstrated that the VLBW infants in India are very different from the VLBW infants in Western cohorts in terms of the perinatal and neonatal risk factors. Another important finding from this study is that social factors play a very important role in the neurodevelopmental outcomes.

This study has substantiated that good perinatal care and dedicated follow-up can significantly influence the outcome of VLBW and bring it at par with the Western standards. Furthermore because of the appropriate tools of assessment which were used, the duration of follow-up and the multi-disciplinary team involved, this study can be a reference for future studies on neurodevelopmental outcomes of high risk infants.

11. BIBLIOGRAPHY

1. World Health Organization. International statistical classification of diseases and related health problems. 10th revision. World Health Organization, Geneva; 1992.

2. WHO, UNICEF. Low Birthweight [Internet]. Geneva: World Health Organization; 2004 [cited 2014 Oct 30]. Available from: http://www.who.int/reproductivehealth/publications/monitoring/9280638327/en/

3. Kramer MS. Determinants of low birth weight: methodological assessment and meta-analysis. Bull World Health Organ. 1987;65(5):663–737.

4. De Onis M, Blössner M, Villar J. Levels and patterns of intrauterine growth retardation in developing countries. Eur J Clin Nutr. 1998 Jan;52 Suppl 1:S5–15.

5. Lee AC, Katz J, Blencowe H, Cousens S, Kozuki N, Vogel JP, *et al*. National and regional estimates of term and preterm babies born small for gestational age in 138 low-income and middle-income countries in 2010. Lancet Glob Health. 2013 Jul;1(1):e26–36.

6. WHO Expert Committee on Physical Status. Physical status: the use and interpretation of anthropometry. Geneva: World Health Organization; 1995.

7. WHO | Care of the preterm and/or low-birth-weight newborn [Internet]. WHO. [cited 2013 Nov 24]. Available from: http://www.who.int/maternal_child_adolescent/topics/newborn/care_of_preterm/en/

8. Blencowe H, Cousens S, Oestergaard MZ, Chou D, Moller A-B, Narwal R, *et al*. National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications. Lancet. 2012 Jun 9;379(9832):2162–72.

9. Lawn JE, Cousens S, Zupan J, Lancet Neonatal Survival Steering Team. 4 million neonatal deaths: when? Where? Why? Lancet. 2005 Mar 5;365(9462):891–900.

10. Villar J, Belizán JM. The relative contribution of prematurity and fetal growth retardation to low birth weight in developing and developed societies. Am J Obstet Gynecol. 1982 Aug 1;143(7):793–8.

11. Kelly A, Kevany J, de Onis M, Shah PM. A WHO collaborative study of maternal anthropometry and pregnancy outcomes. Int J Gynecol Obstet. 1996 Jun;53(3):219–33.

12. Zodpey S, Paul VK. PHFI, AIIMS and SC-State of India's Newborns (SOIN) 014 - a report. New Delhi: All India Institute of Medical Sciences and Save the Children.; 2014.

13. National Neonatology Forum NNPD Network. National Neonatal-Perinatal Database: Report 2002-2003. New Delhi: NNPD Nodal Center at Department of Pediatrics, WHO Collaborating Newborn Trainig and Research, All India Insititute of Medical Sciences; 2005.

14. Bang AT, Bang RA, Baitule S, Deshmukh M, Reddy MH. Burden of morbidities and the unmet need for health care in rural neonates--a prospective observational study in Gadchiroli, India. Indian Pediatr. 2001 Sep;38(9):952–65.

15. Martin J., Hamilton B., Sutton P. Births: Final data for 2003. National Vital statistics reports. Hyattsville, MD: National Center for Health Statistics; 2005.

16. Blanc AK, Wardlaw T. Monitoring low birth weight: an evaluation of international estimates and an updated estimation procedure. Bull World Health Organ. 2005 Mar;83(3):178–85.

17. UN Millennium Project | About the MDGs [Internet]. [cited 2014 Nov 3]. Available from: http://www.unmillenniumproject.org/goals/index.htm

18. Bhakoo ON, Kumar P. Current challenges and future prospects of neonatal care in India. Indian J Pediatr. 2013 Jan;80(1):39–49.

19. Paul VK, Sankar MJ, Saini S. Trek to MDG 4: State of Indian States. Indian J Pediatr. 2014 Oct;81(10):993–9.

20. Million Death Study Collaborators, Bassani DG, Kumar R, Awasthi S, Morris SK, Paul VK, *et al*. Causes of neonatal and child mortality in India: a nationally representative mortality survey. Lancet. 2010 Nov 27;376(9755):1853–60.

21. Bang AT, Paul VK, Reddy HM, Baitule SB. Why do neonates die in rural Gadchiroli, India? (Part I): primary causes of death assigned by neonatologist based on prospectively observed records. J Perinatol Off J Calif Perinat Assoc. 2005 Mar;25 Suppl 1:S29–34.

22. Semba R, Victora C. Low birth weight and neonatal mortality. In: Semba R, Bloem M, editors. Nutrition and Health in Developing Countries. 2nd ed. Totowa, NJ: Humana Press.; 2008. p. 63–86.

23. Bale J., Stoll B., Lucas A. Improving Birth Outcomes: Meeting the Challenge in the Developing World. Washington D.C: The National Academies Press; 2003.

24. Johansson S, Cnattigius S. Epidemiology of preterm birth. In: Nosarti C, Murray R, Hack M, editors. Neurodevelopmental Outcomes of Preterm Birth. Cambridge: Cambridge University Press; 2010. p. 1–16.

25. Petrou S. The economic consequences of preterm birth during the first 10 years of life. BJOG Int J Obstet Gynaecol. 2005 Mar;112 Suppl 1:10–5.

26. Petrou S, Mehta Z, Hockley C, Cook-Mozaffari P, Henderson J, Goldacre M. The impact of preterm birth on hospital inpatient admissions and costs during the first 5 years of life. Pediatrics. 2003 Dec;112(6 Pt 1):1290–7.

27. Bhat MA, Kumar P, Bhansali A, Majumdar S, Narang A. Hypoglycemia in small for gestational age babies. Indian J Pediatr. 2000 Jun;67(6):423–7.

28. Lissauer T, Steer P. Size and Physical Examination of the Newborn Infant. In: Fanaroff AA, Fanaroff JM, editors. Klaus and Fanaroff's Care of the High-Risk Neonate. 6th ed. Saunders; 2012.

29. Kok JH, den Ouden AL, Verloove-Vanhorick SP, Brand R. Outcome of very preterm small for gestational age infants: the first nine years of life. Br J Obstet Gynaecol. 1998 Feb;105(2):162–8.

30. Barker DJ. The fetal and infant origins of adult disease. BMJ. 1990 Nov 17;301(6761):1111.

31. Hales CN, Barker DJP. Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Int J Epidemiol. 2013 Oct;42(5):1215–22.

32. Bhargava SK, Sachdev HS, Fall CHD, Osmond C, Lakshmy R, Barker DJP, *et al*. Relation of Serial Changes in Childhood Body-Mass Index to Impaired Glucose Tolerance in Young Adulthood. N Engl J Med. 2004 Feb 26;350(9):865–75.

33. Aarnoudse-Moens CSH, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. Pediatrics. 2009 Aug;124(2):717–28.

34. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, *et al*. Neonatal outcomes of extremely preterm infants from the NICHD Neonatal Research Network. Pediatrics. 2010 Sep;126(3):443–56.

35. Marlow N. Neurocognitive outcome after very preterm birth. Arch Dis Child Fetal Neonatal Ed. 2004 May;89(3):F224–8.

36. Stanley F, Blair E, Alberman E. Cerebral Palsies: epidemiology and causal pathways. Cambridge: Cambridge University Press; 2000. 251 p.

37. Nelson KB, Ellenberg JH. Antecedents of cerebral palsy: I. univariate analysis of risks. Am J Dis Child. 1985 Oct 1;139(10):1031–8.

38. Nelson KB, Ellenberg JH. Antecedents of Cerebral Palsy. N Engl J Med. 1986;315(2):81–6.

39. Graham M, Trounce JQ, Levene M, Rutter N. PREDICTION OF CEREBRAL PALSY IN VERY LOW BIRTHWEIGHT INFANTS: PROSPECTIVE ULTRASOUND STUDY. The Lancet. 1987 Sep 12;330(8559):593–6.

40. Fazzi E, Galli J, Micheletti S. Visual Impairment: A Common Sequela of Preterm Birth. NeoReviews. 2012 Jan 9;13(9):e542–50.

41. Fazzi E, Signorini SG, Bova SM, Piana RL, Ondei P, Bertone C, *et al*. Spectrum of Visual Disorders in Children With Cerebral Visual Impairment. J Child Neurol. 2007 Jan 3;22(3):294–301.

42. Fleck BW, McIntosh N. Retinopathy of Prematurity Recent Developments. NeoReviews. 2009 Jan 1;10(1):e20–30.

43. Page JM, Schneeweiss S, Whyte HEA, Harvey P. Ocular Sequelae in Premature Infants. Pediatrics. 1993 Jan 12;92(6):787–90.

44. Cristobal R, Oghalai JS. Hearing loss in children with very low birth weight: current review of epidemiology and pathophysiology. Arch Dis Child Fetal Neonatal Ed. 2008 Nov;93(6):F462–8.

45. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJS. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. JAMA J Am Med Assoc. 2002 Aug 14;288(6):728–37.

46. Johnson S. Cognitive and behavioural outcomes following very preterm birth. Semin Fetal Neonatal Med. 2007 Oct;12(5):363–73.

47. Marlow N, Wolke D, Bracewell MA, Samara M, EPICure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med. 2005 Jan 6;352(1):9–19.

48. Saigal S, Hoult LA, Streiner DL, Stoskopf BL, Rosenbaum PL. School difficulties at adolescence in a regional cohort of children who were extremely low birth weight. Pediatrics. 2000 Feb;105(2):325–31.

49. Msall ME, Buck GM, Rogers BT, Catanzaro NL. Kindergarten readiness after extreme prematurity. Am J Dis Child 1960. 1992 Nov;146(11):1371–5.

50. Greenough A, Giffin FJ, Yüksel B. Respiratory morbidity in preschool children born prematurely. Relationship to adverse neonatal events. Acta Paediatr Oslo Nor 1992. 1996 Jul;85(7):772–7.

51. Botting N, Powls A, Cooke RWI, Marlow N. Attention Deficit Hyperactivity Disorders and Other Psychiatric Outcomes in Very Low Birthweight Children at 12 Years. J Child Psychol Psychiatry. 1997 Nov 1;38(8):931–41.

52. Perlman JM. Neurobehavioral Deficits in Premature Graduates of Intensive Care—Potential Medical and Neonatal Environmental Risk Factors. Pediatrics. 2001 Jan 12;108(6):1339–48.

53. Short EJ, Klein NK, Lewis BA, Fulton S, Eisengart S, Kercsmar C, *et al*. Cognitive and academic consequences of bronchopulmonary dysplasia and very low birth weight: 8-year-old outcomes. Pediatrics. 2003 Nov;112(5):e359.

54. Alshaikh B, Yusuf K, Sauve R. Neurodevelopmental outcomes of very low birth weight infants with neonatal sepsis: systematic review and meta-analysis. J Perinatol. 2013 Jul;33(7):558–64.

55. Van Vliet EOG, de Kieviet JF, Oosterlaan J, van Elburg RM. Perinatal infections and neurodevelopmental outcome in very preterm and very low-birth-weight infants: a meta-analysis. JAMA Pediatr. 2013 Jul;167(7):662–8.

56. Schulzke SM, Deshpande GC, Patole SK. Neurodevelopmental outcomes of very low-birth-weight infants with necrotizing enterocolitis: a systematic review of observational studies. Arch Pediatr Adolesc Med. 2007 Jun;161(6):583–90.

57. Hovi P, Andersson S, Eriksson JG, Järvenpää A-L, Strang-Karlsson S, Mäkitie O, *et al*. Glucose Regulation in Young Adults with Very Low Birth Weight. N Engl J Med. 2007 May 17;356(20):2053–63.

58. Arneson CL, Durkin MS, Benedict RE, Kirby RS, Yeargin-Allsopp M, Van Naarden Braun K, *et al*. Prevalence of cerebral palsy: Autism and Developmental Disabilities Monitoring Network, three sites, United States, 2004†. Disabil Health J. 2009 Jan;2(1):45–8.

59. Escobar GJ, Littenberg B, Petitti DB. Outcome among surviving very low birthweight infants: a meta-analysis. Arch Dis Child. 1991 Feb;66(2):204–11.

60. Eichenwald EC, Stark AR. Management and Outcomes of Very Low Birth Weight. N Engl J Med. 2008 Apr 17;358(16):1700–11.

61. De Jesus LC, Pappas A, Shankaran S, Li L, Das A, Bell EF, *et al*. Outcomes of Small for Gestational Age Infants < 27 Weeks' Gestation. J Pediatr. 2013 Jul;163(1):55–60.e1–3.

62. Malin GL, Morris RK, Riley R, Teune MJ, Khan KS. When is birthweight at term abnormally low? A systematic review and meta-analysis of the association and predictive ability of current birthweight standards for neonatal outcomes. BJOG Int J Obstet Gynaecol. 2014 Apr;121(5):515–26.

63. Sung IK, Vohr B, Oh W. Growth and neurodevelopmental outcome of very low birth weight infants with intrauterine growth retardation: comparison with control subjects matched by birth weight and gestational age. J Pediatr. 1993 Oct;123(4):618–24.

64. Gutbrod T, Wolke D, Soehne B, Ohrt B, Riegel K. Effects of gestation and birth weight on the growth and development of very low birthweight small for gestational age infants: a matched group comparison. Arch Dis Child Fetal Neonatal Ed. 2000 May;82(3):F208–14.

65. Morsing E, Asard M, Ley D, Stjernqvist K, Marsál K. Cognitive function after intrauterine growth restriction and very preterm birth. Pediatrics. 2011 Apr;127(4):e874–82.

66. Stephens BE, Vohr BR. Neurodevelopmental outcome of the premature infant. Pediatr Clin North Am. 2009 Jun;56(3):631–46, Table of Contents.

67. Nair MKC, Jain N. Follow-up studies - beyond survival. Indian Pediatr. 2013 Sep;50(9):830–1.

68. Vohr B, Wright LL, Hack M, Hirtz D. Follow-up care of high-risk infants. Pediatrics. 2004 Nov;114(5):1377–97.

69. Wang CJ, McGlynn EA, Brook RH, Leonard CH, Piecuch RE, Hsueh SI, *et al*. Quality-of-Care Indicators for the Neurodevelopmental Follow-up of Very Low Birth Weight Children: Results of an Expert Panel Process. Pediatrics. 2006 Jan 6;117(6):2080–92.

70. Chaudhari S, Bhalerao MR, Chitale A, Pandit AN, Nene U. Pune low birth weight study--a six year follow up. Indian Pediatr. 1999 Jul;36(7):669–76.

71. Chaudhari S, Otiv M, Chitale A, Pandit A, Hoge M. Pune low birth weight study--cognitive abilities and educational performance at twelve years. Indian Pediatr. 2004 Feb;41(2):121–8.

72. Chaudhari S, Otiv M, Hoge M, Pandit A, Mote A. Growth and sexual maturation of low birth weight infants at early adolescence. Indian Pediatr. 2008 Mar;45(3):191–8.

73. Chaudhari S, Otiv M, Khairnar B, Pandit A, Hoge M, Sayyad M. Pune low birth weight study, growth from birth to adulthood. Indian Pediatr. 2012 Sep;49(9):727–32.

74. Chaudhari S, Otiv M, Khairnar B, Pandit A, Hoge M, Sayyad M. Pune low birth weight study - birth to adulthood - cognitive development. Indian Pediatr. 2013 Sep;50(9):853–7.

75. Modi M, Saluja S, Kler N, Batra A, Kaur A, Garg P, *et al*. Growth and neurodevelopmental outcome of VLBW infants at 1 year corrected age. Indian Pediatr. 2013 Jun 8;50(6):573–7.

76. Mukhopadhyay K, Malhi P, Mahajan R, Narang A. Neurodevelopmental and behavioral outcome of very low birth weight babies at corrected age of 2 years. Indian J Pediatr. 2010 Sep;77(9):963–7.

77. Nair MKC, Krishnan R, Harikumaran Nair GS, George B, Bhaskaran D, Leena ML, *et al*. CDC Kerala 3: At-risk Baby Clinic Service Using Different Screening Tools - Outcome at 12 months Using Developmental Assessment Scale for Indian Infants. Indian J Pediatr. 2014 Aug 16;

78. Sharma PK, Sankar MJ, Sapra S, Saxena R, Karthikeyan CV, Deorari A, *et al*. Growth and neurosensory outcomes of preterm very low birth weight infants at 18 months of corrected age. Indian J Pediatr. 2011 Dec;78(12):1485–90.

79. Ramji S, Modi M, Gupta N. 50 years of neonatology in India, progress and future. Indian Pediatr. 2013 Jan 8;50(1):104–6.

80. Kumar P, Sankar MJ, Sapra S, Agarwal R, Deorari AK, Paul VK. Follow-up of high risk neonates. Indian J Pediatr. 2008 May;75(5):479–87.

81. Paul VK, Radhika S, Deorari AK, Singh M. Neurodevelopmental outcome of 'at risk' nursery graduates. Indian J Pediatr. 1998 Dec;65(6):857–62.

82. Sharma PK, Sankar MJ, Sapra S, Saxena R, Karthikeyan CV, Deorari A, *et al*. Growth and neurosensory outcomes of preterm very low birth weight infants at 18 months of corrected age. Indian J Pediatr. 2011 Dec;78(12):1485–90.

83. Chaudhari S, Kulkarni S, Pajnigar F, Pandit AN, Deshmukh S. A longitudinal follow up of development of preterm infants. Indian Pediatr. 1991 Aug;28(8):873–80.

84. Chaudhari S, Kulkarni S, Barve S, Pandit AN, Sonak U, Sarpotdar N. Neurologic sequelae in high risk infants--a three year follow up. Indian Pediatr. 1996 Aug;33(8):645–53.

85. McCauley BB, McCauley JE. Continuing Care: Parents's Retrospective. In: Taeusch W., Yogman MW, editors. Follow-up Management of the High Risk Infant. Boston: Little, Brown and Company; 1987. p. 331–7.

86. Ananth CV, Friedman AM, Gyamfi-Bannerman C. Epidemiology of moderate preterm, late preterm and early term delivery. Clin Perinatol. 2013 Dec;40(4):601–10.

87. Ashtekar S., Kumbhar S., Ashtekar R. Study of Premature Babies in Relation to its outcome and Antenatal Risk Factors at General Hospital Sangli. J Evol Med Dent Sci. 2014 Jul 28;3(30):8506–10.

88. Mukhopadhyay K, Louis D, Mahajan R, Kumar P. Predictors of Mortality and Major Morbidities in Extremely Low Birth Weight Neonates. Indian Pediatr. 2013 Jul 5;

89. Tagare A, Chaudhari S, Kadam S, Vaidya U, Pandit A, Sayyad MG. Mortality and morbidity in extremely low birth weight (ELBW) infants in a neonatal intensive care unit. Indian J Pediatr. 2013 Jan;80(1):16–20.

90. Thakur N, Saili A, Kumar A, Kumar V. Predictors of mortality of extremely low birthweight babies in a tertiary care centre of a developing country. Postgrad Med J. 2013 Jan 12;89(1058):679–84.

91. Basu S, Rathore P, Bhatia BD. Predictors of mortality in very low birth weight neonates in India. Singapore Med J. 2008 Jul;49(7):556–60.

92. Roy KK, Baruah J, Kumar S, Malhotra N, Deorari AK, Sharma JB. Maternal antenatal profile and immediate neonatal outcome in VLBW and ELBW babies. Indian J Pediatr. 2006 Aug;73(8):669–73.

93. Narayan S, Aggarwal R, Upadhyay A, Deorari AK, Singh M, Paul VK. Survival and morbidity in extremely low birth weight (ELBW) infants. Indian Pediatr. 2003 Feb;40(2):130–5.

94. Sehgal A, Telang S, Passah SM, Jyothi MC. Maternal and neonatal profile and immediate outcome in extremely low birth weight babies in Delhi. Trop Doct. 2004 Jul;34(3):165–8.

95. Hack M, Horbar JD, Malloy MH, Wright L, Tyson JE, Wright E. Very Low Birth Weight Outcomes of the National Institute of Child Health and Human Development Neonatal Network. Pediatrics. 1991 Jan 5;87(5):587–97.

96. Lemons JA, Bauer CR, Oh W, Korones SB, Papile LA, Stoll BJ, *et al*. Very low birth weight outcomes of the National Institute of Child health and human development neonatal research network, January 1995 through December 1996. NICHD Neonatal Research Network. Pediatrics. 2001 Jan;107(1):E1.

97. Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, *et al*. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol. 2007 Feb;196(2):147.e1–147.e8.

98. Horbar JD, Carpenter JH, Badger GJ, Kenny MJ, Soll RF, Morrow KA, et al. Mortality and neonatal morbidity among infants 501 to 1500 grams from 2000 to 2009. Pediatrics. 2012 Jun;129(6):1019–26.

99. Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). BMJ. 2012;345:e7976.

100. Larroque B, Bréart G, Kaminski M, Dehan M, André M, Burguet A, *et al*. Survival of very preterm infants: Epipage, a population based cohort study. Arch Dis Child - Fetal Neonatal Ed. 2004 Jan 3;89(2):F139–44.

101. Hack M, Fanaroff AA. Outcomes of children of extremely low birthweight and gestational age in the 1990s. Semin Neonatol SN. 2000 May;5(2):89–106.

102. Lorenz JM, Wooliever DE, Jetton JR, Paneth N. A quantitative review of mortality and developmental disability in extremely premature newborns. Arch Pediatr Adolesc Med. 1998 May 1;152(5):425–35.

103. Fanaroff AA, Stoll BJ, Wright LL, Carlo WA, Ehrenkranz RA, Stark AR, *et al*. Trends in neonatal morbidity and mortality for very low birthweight infants. Am J Obstet Gynecol. 2007 Feb;196(2):147.e1–8.

104. Wilson-Costello D, Friedman H, Minich N, Siner B, Taylor G, Schluchter M, *et al*. Improved neurodevelopmental outcomes for extremely low birth weight infants in 2000-2002. Pediatrics. 2007 Jan;119(1):37–45.

105. Horbar JD. The Vermont Oxford Network: evidence-based quality improvement for neonatology. Pediatrics. 1999 Jan;103(1 Suppl E):350–9.

106. Mukhopadhyay K, Louis D, Murki S, Mahajan R, Dogra MR, Kumar P. Survival and morbidity among two cohorts of extremely low birth weight neonates from a tertiary hospital in northern India. Indian Pediatr. 2013 Nov 8;50(11):1047–50.

107. Alleman BW, Bell EF, Li L, Dagle JM, Smith PB, Ambalavanan N, *et al*. Individual and center-level factors affecting mortality among extremely low birth weight infants. Pediatrics. 2013 Jul;132(1):e175–84.

108. Marlow N, Bennett C, Draper ES, Hennessy EM, Morgan AS, Costeloe KL. Perinatal outcomes for extremely preterm babies in relation to place of birth in England: the EPICure 2 study. Arch Dis Child Fetal Neonatal Ed. 2014 May;99(3):F181–8.

109. Acolet D, Elbourne D, McIntosh N, Weindling M, Korkodilos M, Haviland J, *et al*. Project 27/28: inquiry into quality of neonatal care and its effect on the survival of infants who were born at 27 and 28 weeks in England, Wales, and Northern Ireland. Pediatrics. 2005 Dec;116(6):1457–65.

110. Bhat BV, Adhisivam B. Trends and outcome of low birth weight (LBW) infants in India. Indian J Pediatr. 2013 Jan;80(1):60–2.

111. Kramer MS. Effects of energy and protein intakes on pregnancy outcome: an overview of the research evidence from controlled clinical trials. Am J Clin Nutr. 1993 Nov;58(5):627–35.

112. George K, Prasad J, Singh D, Minz S, Albert DS, Muliyil J, *et al*. Perinatal outcomes in a South Asian setting with high rates of low birth weight. BMC Pregnancy Childbirth. 2009;9:5.

113. Bang AT, Reddy HM, Bang RA, Deshmukh MD. Why do neonates die in rural Gadchiroli, India? (Part II): estimating population attributable risks and contribution of multiple morbidities for identifying a strategy to prevent deaths. J Perinatol Off J Calif Perinat Assoc. 2005 Mar;25 Suppl 1:S35–43.

114. Bang AT, Reddy HM, Deshmukh MD, Baitule SB, Bang RA. Neonatal and infant mortality in the ten years (1993 to 2003) of the Gadchiroli field trial: effect of home-based neonatal care. J Perinatol Off J Calif Perinat Assoc. 2005 Mar;25 Suppl 1:S92–107.

115. Bang AT, Bang RA, Reddy HM, Deshmukh MD, Baitule SB. Reduced incidence of neonatal morbidities: effect of home-based neonatal care in rural Gadchiroli, India. J Perinatol Off J Calif Perinat Assoc. 2005 Mar;25 Suppl 1:S51–61.

116. Bang AT, Bang RA, Baitule SB, Reddy MH, Deshmukh MD. Effect of home-based neonatal care and management of sepsis on neonatal mortality: field trial in rural India. Lancet. 1999 Dec 4;354(9194):1955–61.

117. Gogia S, Sachdev HS. Home visits by community health workers to prevent neonatal deaths in developing countries: a systematic review. Bull World Health Organ. 2010 Sep 1;88(9):658–66B.

118. Jana A.K. Interventions for promoting the initiation of breastfeeding: RHL commentary. WHO Reprod Health Libr World Health Organ 2009. 2009;

119. Lassi ZS, Haider BA, Bhutta ZA. Community-based intervention packages for reducing maternal and neonatal morbidity and mortality and improving neonatal outcomes. Cochrane Database Syst Rev. 2010;(11):CD007754.

120. Gogia S, Ramji S, Gupta P, Gera T, Shah D, Mathew JL, *et al*. Community based newborn care: a systematic review and metaanalysis of evidence: UNICEF-PHFI series on newborn and child health, India. Indian Pediatr. 2011 Jul;48(7):537–46.

121. National Neonatology Forum. Follow up of High Risk Newborns. National Neonatology Forum;

122. Wilson-Costello D, Friedman H, Minich N, Fanaroff AA, Hack M. Improved survival rates with increased neurodevelopmental disability for extremely low birth weight infants in the 1990s. Pediatrics. 2005 Apr;115(4):997–1003.

123. Allen MC. Neurodevelopmental outcomes of preterm infants. Curr Opin Neurol. 2008 Apr;21(2):123–8.

124. Vohr BR, Wright LL, Poole WK, McDonald SA. Neurodevelopmental outcomes of extremely low birth weight infants <32 weeks' gestation between 1993 and 1998. Pediatrics. 2005 Sep;116(3):635–43.

125. Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. Neurologic and developmental disability after extremely preterm birth. EPICure Study Group. N Engl J Med. 2000 Aug 10;343(6):378–84.

126. McCormick MC, Brooks-Gunn J, Workman-Daniels K, Turner J, Peckham GJ. The health and developmental status of very low—birth-weight children at school age. JAMA. 1992 Apr 22;267(16):2204–8.

127. The Scottish low birthweight study: I. Survival, growth, neuromotor and sensory impairment. Arch Dis Child. 1992 Jun;67(6):675–81.

128. Hack M, Klein NK, Taylor HG. Long-term developmental outcomes of low birth weight infants. Future Child Cent Future Child David Lucile Packard Found. 1995;5(1):176–96.

129. Chawla D, Agarwal R, Deorari A, Paul VK, Chandra P, Azad RV. Retinopathy of Prematurity. Indian J Pediatr. 2012 Apr 1;79(4):501–9.

130. Azad R. Prevention of Blindness Due to Retinopathy of Prematurity: A National Movement. Indian J Pediatr. 2014 May 4;

131. Vinekar A, Gilbert C, Dogra M, Kurian M, Shainesh G, Shetty B, *et al*. The KIDROP model of combining strategies for providing retinopathy of prematurity screening in underserved areas in India using wide-field imaging, tele-medicine, non-physician graders and smart phone reporting. Indian J Ophthalmol. 2014 Jan;62(1):41–9.

132. Paul B, Saha I, Mukherjee A, Biswas R, Roy S, Chaudhuri RN. Morbidity pattern of low-birth-weight infants in an urban slum of Kolkata, India. J Egypt Public Health Assoc. 2011;86(3-4):39–43.

133. Gladstone M. A review of the incidence and prevalence, types and aetiology of childhood cerebral palsy in resource-poor settings. Ann Trop Paediatr. 2010;30(3):181–96.

134. Raina SK, Razdan S, Nanda R. Prevalence of cerebral palsy in children < 10 years of age in R.S. Pura town of Jammu and Kashmir. J Trop Pediatr. 2011 Aug;57(4):293–5.

135. Singhi PD, Ray M, Suri G. Clinical spectrum of cerebral palsy in north India--an analysis of 1,000 cases. J Trop Pediatr. 2002 Jun;48(3):162–6.

136. Singhi P, Saini AG. Changes in the Clinical Spectrum of Cerebral Palsy over Two Decades in North India--An Analysis of 1212 Cases. J Trop Pediatr. 2013 Dec;59(6):434–40.

137. Hintz SR, Kendrick DE, Wilson-Costello DE, Das A, Bell EF, Vohr BR, *et al*. Early-childhood neurodevelopmental outcomes are not improving for infants born at <25 weeks' gestational age. Pediatrics. 2011 Jan;127(1):62–70.

138. Moore T, Hennessy EM, Myles J, Johnson SJ, Draper ES, Costeloe KL, et al. Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the EPICure studies. BMJ. 2012;345:e7961.

139. Aylward GP. Cognitive and neuropsychological outcomes: more than IQ scores. Ment Retard Dev Disabil Res Rev. 2002;8(4):234–40.

140. Hack M, Taylor HG, Schluchter M, Andreias L, Drotar D, Klein N. Behavioral outcomes of extremely low birth weight children at age 8 years. J Dev Behav Pediatr JDBP. 2009 Apr;30(2):122–30.

141. Moddemann D, Shea S. The developmental paediatrician and neonatal follow-up. Paediatr Child Health. 2006 May;11(5):295.

142. Fanaroff AA, Hack M, Walsh MC. The NICHD neonatal research network: changes in practice and outcomes during the first 15 years. Semin Perinatol. 2003 Aug;27(4):281–7.

143. Barrington KJ. The adverse neuro-developmental effects of postnatal steroids in the preterm infant: a systematic review of RCTs. BMC Pediatr. 2001 Feb 27;1(1):1.

144. American Academy of Pediatrics Committee on Fetus and Newborn. Hospital discharge of the high-risk neonate. Pediatrics. 2008 Nov;122(5):1119–26.

145. Marlow N. Measuring neurodevelopmental outcome in neonatal trials: a continuing and increasing challenge. Arch Dis Child Fetal Neonatal Ed. 2013 Nov;98(6):F554–8.

146. British Association of Perinatal Medicine. Classification of Health Status at 2 Years as a Perinatal Outcome - report of a BAPM/RCPCH working group. London; 2008.

147. O'Shea TM. Cerebral palsy in very preterm infants: new epidemiological insights. Ment Retard Dev Disabil Res Rev. 2002;8(3):135–45.

148. Vohr BR, Msall ME, Wilson D, Wright LL, McDonald S, Poole WK. Spectrum of gross motor function in extremely low birth weight children with cerebral palsy at 18 months of age. Pediatrics. 2005 Jul;116(1):123–9.

149. Vohr BR, O'Shea M, Wright LL. Longitudinal multicenter follow-up of high-risk infants: why, who, when, and what to assess. Semin Perinatol. 2003 Aug;27(4):333–42.

150. Vohr BR. Neurodevelopmental Outcomes of Extremely Preterm Infants. Clin Perinatol. 2014 Mar;41(1):241–55.

151. Newborn C on F and. Age Terminology During the Perinatal Period. Pediatrics. 2004 Jan 11;114(5):1362–4.

152. Barrera ME, Rosenbaum PL, Cunningham CE. Corrected and uncorrected Bayley scores: Longitudinal developmental patterns in low and high birth weight preterm infants. Infant Behav Dev. 1987 Jul;10(3):337–46.

153. Lems W, Hopkins B, Samsom J. Mental and Motor Development in Preterm Infants - the Issue of Corrected Age. Early Hum Dev. 1993 Sep;34(1-2):113–23.

154. Siegel LS. Correction for prematurity and its consequences for the assessment of the very low birth weight infant. Child Dev. 1983 Oct;54(5):1176–88.

155. Wilson SL, Cradock MM. Review: Accounting for Prematurity in Developmental Assessment and the Use of Age-Adjusted Scores. J Pediatr Psychol. 2004 Jan 12;29(8):641–9.

156. Hack M, Klein NK, Taylor HG. Long-term developmental outcomes of low birth weight infants. Future Child Cent Future Child David Lucile Packard Found. 1995;5(1):176–96.

157. Palta M, Sadek-Badawi M, Evans M, Weinstein MR, McGuinnes G. Functional assessment of a multicenter very low-birth-weight cohort at age 5 years. Newborn Lung Project. Arch Pediatr Adolesc Med. 2000 Jan;154(1):23–30.

158. Sølsnes AE, Skranes J, Brubakk A-M, Løhaugen GCC. Executive Functions in Very-Low-Birth-Weight Young Adults: A Comparison between Self-report and Neuropsychological Test Results. J Int Neuropsychol Soc. 2014 May;20(05):506–15.

159. Vohr BR, Msall ME. Neuropsychological and functional outcomes of very low birth weight infants. Semin Perinatol. 1997 Jun;21(3):202–20.

160. Bayley N. Bayley Scales of Infant and Toddler Development. Third Edition. San Antonio TX: Harcourt Assessment.;

161. Griffiths, Ruth. The abilities of babies: a study in mental measurement. New York, NY, US: McGraw-Hill; 1954. 229 p.

162. Griffiths R. Griffiths Mental Development Scales - Revised: Birth to 2 years (GMDS 0-2) - Manual. Revised by Michael Huntley. Hogrefe Ltd, Oxford, U.K: Association for Research in Infant and Child Development (ARICD); 1996.

163. Phatak, P. Developmental Assessment Scales for Indian Infants (DASII) – Revised Baroda Norms Manual. Baroda; 1997.

164. Vohr BR. Cognitive and functional outcomes of children born preterm. In: Nosarti C, Murray RM, Hack M, editors. Cambridge: Cambridge University Press; 2010. p. 141–63.

165. Soltirovska Salamon A, Groenendaal F, van Haastert IC, Rademaker KJ, Benders MJNL, Koopman C, *et al*. Neuroimaging and neurodevelopmental outcome of preterm infants with a periventricular haemorrhagic infarction located in the temporal or frontal lobe. Dev Med Child Neurol. 2014 Jun;56(6):547–55.

166. Struck A, Almaazmi M, Bode H, Sander S, Hay B, Schmid M, et al. [Neurodevelopmental outcome of very low birth weight infants born at the Perinatal Centre in Ulm, Germany]. Z Für Geburtshilfe Neonatol. 2013 Apr;217(2):65–71.

167. Claas MJ, Bruinse HW, Koopman C, van Haastert IC, Peelen LM, de Vries LS. Two-year neurodevelopmental outcome of preterm born children ≤ 750 g at birth. Arch Dis Child Fetal Neonatal Ed. 2011 May;96(3):F169–77.

168. Hack KEA, Koopman-Esseboom C, Derks JB, Elias SG, de Kleine MJK, Baerts W, *et al*. Long-term neurodevelopmental outcome of monochorionic and matched dichorionic twins. PloS One. 2009;4(8):e6815.

169. Anand D, Platt MJ, Pharoah POD. Comparative development of surviving co-twins of vanishing twin conceptions, twins and singletons. Twin Res Hum Genet Off J Int Soc Twin Stud. 2007 Feb;10(1):210–5.

170. Gutbrod T, Wolke D, Soehne B, Ohrt B, Riegel K. Effects of gestation and birth weight on the growth and development of very low birthweight small for gestational age infants: a matched group comparison. Arch Dis Child Fetal Neonatal Ed. 2000 May;82(3):F208–14.

171. Bührer C, Grimmer I, Metze B, Obladen M. The CRIB (Clinical Risk Index for Babies) score and neurodevelopmental impairment at one year corrected age in very low birth weight infants. Intensive Care Med. 2000 Mar;26(3):325–9.

172. Disabilities C on CW. Developmental Surveillance and Screening of Infants and Young Children. Pediatrics. 2001 Jan 7;108(1):192–5.

173. Juneja M, Mohanty M, Jain R, Ramji S. Ages and Stages Questionnaire as a screening tool for developmental delay in Indian children. Indian Pediatr. 2012 Jun;49(6):457–61.

174. Nair MKC, Krishnan R, Nair GH, Bhaskaran D, Leena ML, George B, *et al*. CDC Kerala 4: TDSC Items Based Developmental Therapy Package Among Low Birth Weight Babies–Outcome at 18 months Using DASII. Indian J Pediatr. 2014;1–6.

175. Bera A, Ghosh J, Singh AK, Hazra A, Mukherjee S, Mukherjee R. Effect of kangaroo mother care on growth and development of low birthweight babies up to 12 months of age: a controlled clinical trial. Acta Paediatr Oslo Nor 1992. 2014 Jun;103(6):643–50.

176. Baburaj S, Abraham B, Vinod PV, Raj S, Mohandas MK. Growth and development of high risk graduates till one year from a rural neonatal intensive care unit in south India. Int J Biomed Res. 2013;4(12):695–700.

177. Kumar R, Bhave A, Bhargava R, Agarwal GG. Prevalence and risk factors for neurological disorders in children aged 6 months to 2 years in northern India. Dev Med Child Neurol. 2013;55(4):348–56.

178. Patel V, DeSouza N, Rodrigues M. Postnatal depression and infant growth and development in low income countries: a cohort study from Goa, India. Arch Dis Child. 2003;88(1):34–7.

179. Sutcliffe AG, Soo A, Barnes J. Predictive value of developmental testing in the second year for cognitive development at five years of age. Pediatr Rep. 2010;2(2):e15.

180. Hack M, Taylor HG, Drotar D, Schluchter M, Cartar L, Wilson-Costello D, *et al*. Poor Predictive Validity of the Bayley Scales of Infant Development for Cognitive Function of Extremely Low Birth Weight Children at School Age. Pediatrics. 2005 Jan 8;116(2):333–41.

181. Ment LR, Vohr B, Allan W, *et al*. Change in cognitive function over time in very low-birth-weight infants. JAMA. 2003 Feb 12;289(6):705–11.

182. Bowen JR, Gibson FL, Leslie GI, Arnold JD, Ma PJ, Starte DR. Predictive value of the Griffiths assessment in extremely low birthweight infants. J Paediatr Child Health. 1996 Feb;32(1):25–30.

183. Aylward GP. The Conundrum of Prediction. Pediatrics. 2005 Jan 8;116(2):491–2.

184. Chaudhari S. Developmental assessment tests: scope and limitations. Indian Pediatr. 1996 Jul;33(7):541–5.

185. Chaudhari S, Kulkarni S, Pandit A, Koundinya UK. Neurological assessment at three months as a predictor for developmental outcome in high risk infants. Indian Pediatr. 1993 Apr;30(4):528–31.

186. Amiel-Tison C. Neuromotor status. In: Taeusch WH, Yogman MW, editors. Follow-up Management of the High Risk Infant. Boston: Little, Brown and Company; 1987.

187. Gosselin J, Gahagan S, Amiel-Tison C. The Amiel-Tison Neurological Assessment at Term: conceptual and methodological continuity in the course of follow-up. Ment Retard Dev Disabil Res Rev. 2005;11(1):34–51.

188. Drillien CM. Abnormal Neurologic Signs in the First Year of Life in Low-birthweight Infants: Possible Prognostic Significance. Dev Med Child Neurol. 1972 Oct 1;14(5):575–84.

189. Pedersen SJ, Sommerfelt K, Markestad T. Early motor development of premature infants with birthweight less than 2000 grams. Acta Paediatr Oslo Nor 1992. 2000 Dec;89(12):1456–61.

190. Chaudhari S, Bhalerao M, Chitale A, Patil B, Pandit A, Hoge M. Transient tone abnormalities in high risk infants and cognitive outcome at five years. Indian Pediatr. 2010 Nov;47(11):931–5.

191. Bracewell M, Marlow N. Patterns of motor disability in very preterm children. Ment Retard Dev Disabil Res Rev. 2002;8(4):241–8.

192. Amiel-Tison C, Gosselin J. Neurologic Development from Birth to Six Years - Guide for Examination and Evaluation. Baltimore: The John Hopkins University Press; 2001.

193. Butt K, Lim K, Society of Obstetricians and Gynaecologists of Canada. Determination of gestational age by ultrasound. J Obstet Gynaecol Can JOGC J Obstétrique Gynécologie Can JOGC. 2014 Feb;36(2):171–83.

194. Leviton A, Blair E, Dammann O, Allred E. The wealth of information conveyed by gestational age. J Pediatr. 2005 Jan;146(1):123–7.

195. Aylward G. Methodologic considerations in neurodevelopmental outcome studies of infants born prematurely. In: Nosarti C, Murray RM, Hack M, editors. Neurodevelopmental Outcomes of Preterm Birth. Cambridge: Cambridge University Press; 2010. p. 164–75.

196. Ballabh P. Advances in Neonatal Neurology, An Issue of Clinics in Perinatology,. Elsevier Health Sciences; 2014. 312 p.

197. Lakshmi CVS, Pramod G, Geeta K, Subramaniam S, Rao MB, Kallapur SG, *et al*. Outcome of very low birth weight infants with abnormal antenatal Doppler flow patterns: a prospective cohort study. Indian Pediatr. 2013 Sep;50(9):847–52.

198. Chaudhari S, Kulkarni S, Pandit A, Deshmukh S. Mortality and morbidity in high risk infants during a six year follow-up. Indian Pediatr. 2000 Dec;37(12):1314–20.

199. Sangtawesin V, Singarj Y, Kanjanapattanakul W. Growth and development of very low birth weight infants aged 18-24 months at Queen Sirikit National Institute of Child Health. J Med Assoc Thail Chotmaihet Thangphaet. 2011 Aug;94 Suppl 3:S101–6.

200. Ballot DE, Potterton J, Chirwa T, Hilburn N, Cooper PA. Developmental outcome of very low birth weight infants in a developing country. BMC Pediatr. 2012;12:11.

201. Khan NZ, Muslima H, Parveen M, Bhattacharya M, Begum N, Chowdhury S, *et al*. Neurodevelopmental outcomes of preterm infants in Bangladesh. Pediatrics. 2006 Jul;118(1):280–9.

202. Serenius F, Källén K, Blennow M, *et al*. Neurodevelopmental outcome in extremely preterm infants at 2.5 years after active perinatal care in sweden. JAMA. 2013 May 1;309(17):1810–20.

203. Ishii N, Kono Y, Yonemoto N, Kusuda S, Fujimura M, Neonatal Research Network, Japan. Outcomes of infants born at 22 and 23 weeks' gestation. Pediatrics. 2013 Jul;132(1):62–71.

204. Hintz SR, Kendrick DE, Wilson-Costello DE, Das A, Bell EF, Vohr BR, *et al*. Early-Childhood Neurodevelopmental Outcomes Are Not Improving for Infants Born at <25 Weeks' Gestational Age. Pediatrics. 2011 Jan;127(1):62–70.

205. Schlapbach LJ, Adams M, Proietti E, Aebischer M, Grunt S, Borradori-Tolsa C, *et al*. Outcome at two years of age in a Swiss national cohort of extremely preterm infants born between 2000 and 2008. BMC Pediatr. 2012 Dec 28;12:198.

206. Gargus RA, Vohr BR, Tyson JE, High P, Higgins RD, Wrage LA, *et al*. Unimpaired outcomes for extremely low birth weight infants at 18 to 22 months. Pediatrics. 2009 Jul;124(1):112–21.

207. Doyle LW, Roberts G, Anderson PJ, Victorian Infant Collaborative Study Group. Outcomes at age 2 years of infants < 28 weeks' gestational age born in Victoria in 2005. J Pediatr. 2010 Jan;156(1):49–53.e1.

208. Bodeau-Livinec F, Zeitlin J, Blondel B, Arnaud C, Fresson J, Burguet A, *et al*. Do very preterm twins and singletons differ in their neurodevelopment at 5 years of age? Arch Dis Child Fetal Neonatal Ed. 2013 Nov;98(6):F480–7.

209. Sommer C, Urlesberger B, Maurer-Fellbaum U, Kutschera J, Müller W. Neurodevelopmental outcome at 2 years in 23 to 26 weeks old gestation infants. Klin Pädiatr. 2007 Feb;219(1):23–9.

210. Giannì ML, Picciolini O, Vegni C, Gardon L, Fumagalli M, Mosca F. Twelve-month neurofunctional assessment and cognitive performance at 36 months of age in extremely low birth weight infants. Pediatrics. 2007 Nov;120(5):1012–9.

211. Hoekstra RE, Ferrara TB, Couser RJ, Payne NR, Connett JE. Survival and Long-Term Neurodevelopmental Outcome of Extremely Premature Infants Born at 23–26 Weeks' Gestational Age at a Tertiary Center. Pediatrics. 2004 Jan 1;113(1):e1–6.

212. Vohr BR, Wright LL, Dusick AM, Mele L, Verter J, Steichen JJ, *et al*. Neurodevelopmental and functional outcomes of extremely low birth weight infants in the National Institute of Child Health and Human Development Neonatal Research Network, 1993-1994. Pediatrics. 2000 Jun;105(6):1216–26.

213. Ment LR, Vohr B, Oh W, Scott DT, Allan WC, Westerveld M, *et al*. Neurodevelopmental outcome at 36 months' corrected age of preterm infants in the Multicenter Indomethacin Intraventricular Hemorrhage Prevention Trial. Pediatrics. 1996 Oct;98(4 Pt 1):714–8.

214. Veelken N, Stollhoff K, Claussen M. Development of very low birth weight infants: a regional study of 371 survivors. Eur J Pediatr. 1991 Sep;150(11):815–20.

215. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2006;(3):CD004454.

216. Soll R. Synthetic surfactant for respiratory distress syndrome in preterm infants. Cochrane Database of Systematic Reviews [Internet]. John Wiley & Sons, Ltd; 1996 [cited 2014 Nov 24]. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001149/abstract

217. Ment LR, Oh W, Ehrenkranz RA, Philip AG, Vohr B, Allan W, *et al*. Low-dose indomethacin and prevention of intraventricular hemorrhage: a multicenter randomized trial. Pediatrics. 1994 Apr;93(4):543–50.

218. Smith PB, Ambalavanan N, Li L, Cotten CM, Laughon M, Walsh MC, *et al*. Approach to Infants Born at 22 to 24 Weeks' Gestation: Relationship to Outcomes of More-Mature Infants. Pediatrics. 2012 Jun;129(6):e1508–16.

219. Stephens BE, Vohr BR. Neurodevelopmental outcome of the premature infant. Pediatr Clin North Am. 2009 Jun;56(3):631–46, Table of Contents.

220. Hintz SR, Kendrick DE, Vohr BR, Poole WK, Higgins RD, National Institute of Child Health and Human Development Neonatal Research Network. Changes in neurodevelopmental outcomes at 18 to 22 months' corrected age among infants of less than 25 weeks' gestational age born in 1993-1999. Pediatrics. 2005 Jun;115(6):1645–51.

221. Wariyar UK, Richmond S. Morbidity and preterm delivery: importance of 100% follow-up. Lancet. 1989 Feb 18;1(8634):387–8.

222. Wolke D, Söhne B, Ohrt B, Riegel K. Follow-up of preterm children: important to document dropouts. The Lancet. 1995 Feb;345(8947):447.

223. Tin W, Fritz S, Wariyar U, Hey E. Outcome of very preterm birth: children reviewed with ease at 2 years differ from those followed up with difficulty. Arch Dis Child Fetal Neonatal Ed. 1998 Sep;79(2):F83–7.

224. Schmidt B, Asztalos EV, Roberts RS, Robertson CMT, Sauve RS, Whitfield MF, *et al*. Impact of bronchopulmonary dysplasia, brain injury, and severe retinopathy on the outcome of extremely low-birth-weight infants at 18 months: results from the trial of indomethacin prophylaxis in preterms. JAMA. 2003 Mar 5;289(9):1124–9.

225. Stevenson DK, Verter J, Fanaroff AA, Oh W, Ehrenkranz RA, Shankaran S, *et al*. Sex differences in outcomes of very low birthweight infants: the newborn male disadvantage. Arch Dis Child - Fetal Neonatal Ed. 2000 Jan 11;83(3):F182–5.

226. Hintz SR, Kendrick DE, Vohr BR, Kenneth Poole W, Higgins RD, Nichd Neonatal Research Network. Gender differences in neurodevelopmental outcomes among extremely preterm, extremely-low-birthweight infants. Acta Paediatr Oslo Nor 1992. 2006 Oct;95(10):1239–48.

227. Peacock JL, Marston L, Marlow N, Calvert SA, Greenough A. Neonatal and infant outcome in boys and girls born very prematurely. Pediatr Res. 2012 Mar;71(3):305–10.

228. Betty R Vohr WCA. School-age outcomes of very low birth weight infants in the indomethacin intraventricular hemorrhage prevention trial. Pediatrics. 2003;111(4 Pt 1):e340–6.

229. Hack M, Schluchter M, Cartar L, Rahman M, Cuttler L, Borawski E. Growth of very low birth weight infants to age 20 years. Pediatrics. 2003 Jul;112(1 Pt 1):e30–8.

230. Kent AL, Wright IMR, Abdel-Latif ME, New South Wales and Australian Capital Territory Neonatal Intensive Care Units Audit Group. Mortality and adverse neurologic outcomes are greater in preterm male infants. Pediatrics. 2012 Jan;129(1):124–31.

231. Fleisher B, Kulovich MV, Hallman M, Gluck L. Lung profile: sex differences in normal pregnancy. Obstet Gynecol. 1985 Sep;66(3):327–30.

232. McMillan EM, King GM, Adamson IY. Sex hormones influence growth and surfactant production in fetal lung explants. Exp Lung Res. 1989 Mar;15(2):167–79.

233. Catlin EA, Powell SM, Manganaro TF, Hudson PL, Ragin RC, Epstein J, *et al*. Sex-specific Fetal Lung Development and Müllerian Inhibiting Substance. Am Rev Respir Dis. 1990 Feb 1;141(2):466–70.

234. Jones HP, Karuri S, Cronin CM, Ohlsson A, Peliowski A, Synnes A, *et al*. Actuarial survival of a large Canadian cohort of preterm infants. BMC Pediatr. 2005 Nov 9;5(1):40.

235. Tau GZ, Peterson BS. Normal Development of Brain Circuits. Neuropsychopharmacology. 2009 Sep 30;35(1):147–68.

236. Ment LR, Vohr BR. Preterm birth and the developing brain. Lancet Neurol. 2008 May;7(5):378–9.

237. Constable RT, Ment LR, Vohr BR, Kesler SR, Fulbright RK, Lacadie C, *et al*. Prematurely born children demonstrate white matter microstructural differences at 12 years of age, relative to term control subjects: an investigation of group and gender effects. Pediatrics. 2008 Feb;121(2):306–16.

238. Clements JA, Avery ME. Lung surfactant and neonatal respiratory distress syndrome. Am J Respir Crit Care Med. 1998 Apr;157(4 Pt 2):S59–66.

239. Ballabh P. Intraventricular Hemorrhage in Premature Infants: Mechanism of Disease. Pediatr Res. 2010 Jan;67(1):1–8.

240. Pinto-Martin JA, Riolo S, Cnaan A, Holzman C, Susser MW, Paneth N. Cranial Ultrasound Prediction of Disabling and Nondisabling Cerebral Palsy at Age Two in a Low Birth Weight Population. Pediatrics. 1995 Jan 2;95(2):249–54.

241. Vasileiadis GT, Gelman N, Han VKM, Williams L-A, Mann R, Bureau Y, *et al*. Uncomplicated Intraventricular Hemorrhage Is Followed by Reduced Cortical Volume at Near-Term Age. Pediatrics. 2004 Jan 9;114(3):e367–72.

242. Stoll BJ, Hansen NI, Bell EF, Shankaran S, Laptook AR, Walsh MC, *et al*. Neonatal Outcomes of Extremely Preterm Infants From the NICHD Neonatal Research Network. Pediatrics. 2010 Sep;126(3):443–56.

243. Sweet DG, Carnielli V, Greisen G, Hallman M, Ozek E, Plavka R, *et al*. European consensus guidelines on the management of neonatal respiratory distress syndrome in preterm infants--2013 update. Neonatology. 2013;103(4):353–68.

244. Ballard PL, Ballard RA. Scientific basis and therapeutic regimens for use of antenatal glucocorticoids. Am J Obstet Gynecol. 1995 Jul;173(1):254–62.

245. Figueras-Aloy J, Serrano MM, Rodríguez JP, Pérez CF, Serradilla VR, Jiménez JQ, *et al*. Antenatal glucocorticoid treatment decreases mortality and chronic lung disease in survivors among 23- to 28-week gestational age preterm infants. Am J Perinatol. 2005 Nov;22(8):441–8.

246. Wright LL, Horbar JD, Gunkel H, Verter J, Younes N, Andrews EB, *et al*. Evidence from multicenter neworks on the current use and effectiveness of antenatal corticosteroids in low birth weight infants. Am J Obstet Gynecol. 1995 Jul;173(1):263–9.

247. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2006;(3):CD004454.

248. Hofmeyr G.J. Antenatal corticosteroids for women at risk of preterm birth: RHL commentary (last revised: 2 February 2009). WHO Reprod Health Libr Geneva World Health Organ. 2009 Feb 2;

249. Carlo WA, McDonald SA, Fanaroff AA, Vohr BR, Stoll BJ, Ehrenkranz RA, *et al*. Association of antenatal corticosteroids with mortality and neurodevelopmental outcomes among infants born at 22–25 weeks gestation. JAMA J Am Med Assoc. 2011 Dec 7;306(21):2348–58.

250. Jobe AH, Bancalari E. Bronchopulmonary Dysplasia. Am J Respir Crit Care Med. 2001 Jun 1;163(7):1723–9.

251. Bhandari A, Bhandari V. Pitfalls, Problems, and Progress in Bronchopulmonary Dysplasia. Pediatrics. 2009 Jan 6;123(6):1562–73.

252. Ehrenkranz RA, Walsh MC, Vohr BR, Jobe AH, Wright LL, Fanaroff AA, *et al*. Validation of the National Institutes of Health consensus definition of bronchopulmonary dysplasia. Pediatrics. 2005 Dec;116(6):1353–60.

253. Hughes CA, O'Gorman LA, Shyr Y, Schork MA, Bozynski ME, McCormick MC. Cognitive performance at school age of very low birth weight infants with bronchopulmonary dysplasia. J Dev Behav Pediatr JDBP. 1999 Feb;20(1):1–8.

254. Majnemer A, Riley P, Shevell M, Birnbaum R, Greenstone H, Coates AL. Severe bronchopulmonary dysplasia increases risk for later neurological and motor sequelae in preterm survivors. Dev Med Child Neurol. 2000 Jan;42(1):53–60.

255. Bhatia J, Parish A. Nutrition and the lung. Neonatology. 2009;95(4):362–7.

256. Yu VY, Orgill AA, Lim SB, Bajuk B, Astbury J. Growth and development of very low birthweight infants recovering from bronchopulmonary dysplasia. Arch Dis Child. 1983 Oct;58(10):791–4.

257. Vrlenich LA, Bozynski ME, Shyr Y, Schork MA, Roloff DW, McCormick MC. The effect of bronchopulmonary dysplasia on growth at school age. Pediatrics. 1995 Jun;95(6):855–9.

258. Giacoia GP, Venkataraman PS, West-Wilson KI, Faulkner MJ. Follow-up of school-age children with bronchopulmonary dysplasia. J Pediatr. 1997 Mar;130(3):400–8.

259. Doyle LW, Ford G, Davis N. Health and hospitalistions after discharge in extremely low birth weight infants. Semin Neonatol SN. 2003 Apr;8(2):137–45.

260. Bhandari A, Panitch HB. Pulmonary outcomes in bronchopulmonary dysplasia. Semin Perinatol. 2006 Aug;30(4):219–26.

261. Allen JL, Panitch HB. Lung function testing: chronic lung disease of infancy. Pediatr Pulmonol. 2001;Suppl 23:138–40.

262. Joshi S, Powell T, Watkins WJ, Drayton M, Williams EM, Kotecha S. Exercise-induced bronchoconstriction in school-aged children who had chronic lung disease in infancy. J Pediatr. 2013 Apr;162(4):813–8.e1.

263. Bhat R, Salas AA, Foster C, Carlo WA, Ambalavanan N. Prospective analysis of pulmonary hypertension in extremely low birth weight infants. Pediatrics. 2012 Mar;129(3):e682–9.

264. Wong PM, Lees AN, Louw J, Lee FY, French N, Gain K, *et al*. Emphysema in young adult survivors of moderate-to-severe bronchopulmonary dysplasia. Eur Respir J. 2008 Aug;32(2):321–8.

265. Yeh TF, Lin YJ, Hsieh WS, Lin HC, Lin CH, Chen JY, *et al*. Early postnatal dexamethasone therapy for the prevention of chronic lung disease in preterm infants with respiratory distress syndrome: a multicenter clinical trial. Pediatrics. 1997 Oct;100(4):E3.

266. Yeh TF, Lin YJ, Huang CC, Chen YJ, Lin CH, Lin HC, *et al*. Early dexamethasone therapy in preterm infants: a follow-up study. Pediatrics. 1998 May;101(5):E7.

267. Doyle LW, Ehrenkranz RA, Halliday HL. Early (< 8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Cochrane Database Syst Rev. 2014;5:CD001146.

268. Stark AR, Carlo WA, Vohr BR, Papile LA, Saha S, Bauer CR, *et al*. Death or neurodevelopmental impairment at 18 to 22 months corrected age in a randomized trial of early dexamethasone to prevent death or chronic lung disease in extremely low birth weight infants. J Pediatr. 2014 Jan;164(1):34–9.e2.

269. Jefferies AL. Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. Paediatr Child Health. 2012 Dec;17(10):573.

270. Kulkarni A, Vigneswaran R. Necrotizing enterocolitis. Indian J Pediatr. 2001 Sep;68(9):847–53.

271. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, *et al*. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978 Jan;187(1):1–7.

272. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. Pediatr Clin North Am. 1986 Feb;33(1):179–201.

273. Hull MA, Fisher JG, Gutierrez IM, Jones BA, Kang KH, Kenny M, *et al*. Mortality and management of surgical necrotizing enterocolitis in very low birth weight neonates: a prospective cohort study. J Am Coll Surg. 2014 Jun;218(6):1148–55.

274. Abdullah F, Zhang Y, Camp M, Mukherjee D, Gabre-Kidan A, Colombani PM, *et al*. Necrotizing enterocolitis in 20,822 infants: analysis of medical and surgical treatments. Clin Pediatr (Phila). 2010 Feb;49(2):166–71.

275. Fitzgibbons SC, Ching Y, Yu D, Carpenter J, Kenny M, Weldon C, *et al*. Mortality of necrotizing enterocolitis expressed by birth weight categories. J Pediatr Surg. 2009 Jun;44(6):1072–5; discussion 1075–6.

276. Hintz SR, Kendrick DE, Stoll BJ, Vohr BR, Fanaroff AA, Donovan EF, *et al*. Neurodevelopmental and growth outcomes of extremely low birth weight infants after necrotizing enterocolitis. Pediatrics. 2005 Mar;115(3):696–703.

277. Chacko J, Ford WD, Haslam R. Growth and neurodevelopmental outcome in extremely-low-birth-weight infants after laparotomy. Pediatr Surg Int. 1999;15(7):496–9.

278. Dilli D, Eras Z, Özkan Ulu H, Dilmen U, Durgut Şakrucu E. Does necrotizing enterocolitis affect growth and neurodevelopmental outcome in very low birth weight infants? Pediatr Surg Int. 2012 May;28(5):471–6.

279. Sonntag J, Grimmer I, Scholz T, Metze B, Wit J, Obladen M. Growth and neurodevelopmental outcome of very low birthweight infants with necrotizing enterocolitis. Acta Pædiatrica. 2000;89(5):528–32.

280. Rees CM, Pierro A, Eaton S. Neurodevelopmental outcomes of neonates with medically and surgically treated necrotizing enterocolitis. Arch Dis Child Fetal Neonatal Ed. 2007 May;92(3):F193–8.

281. Romantseva L, Msall ME. Advances in Understanding Cerebral Palsy Syndromes After Prematurity. NeoReviews. 2006 Jan 11;7(11):e575–85.

282. Stoll BJ, Hansen NI, Higgins RD, Fanaroff AA, Duara S, Goldberg R, *et al*. Very low birth weight preterm infants with early onset neonatal sepsis: the predominance of gram-negative infections continues in the National Institute of Child Health and Human Development Neonatal Research Network, 2002-2003. Pediatr Infect Dis J. 2005 Jul;24(7):635–9.

283. Stoll BJ, Hansen N. Infections in VLBW infants: studies from the NICHD Neonatal Research Network. Semin Perinatol. 2003 Aug;27(4):293–301.

284. Thakur N, Saili A, Kumar A, Kumar V. Predictors of mortality of extremely low birthweight babies in a tertiary care centre of a developing country. Postgrad Med J. 2013 Dec;89(1058):679–84.

285. Narayan S, Aggarwal R, Upadhyay A, Deorari AK, Singh M, Paul VK. Survival and morbidity in extremely low birth weight (ELBW) infants. Indian Pediatr. 2003 Feb;40(2):130–5.

286. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, *et al*. Late-Onset Sepsis in Very Low Birth Weight Neonates: The Experience of the NICHD Neonatal Research Network. Pediatrics. 2002 Jan 8;110(2):285–91.

287. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, *et al*. Changes in pathogens causing early-onset sepsis in very-low-birth-weight infants. N Engl J Med. 2002 Jul 25;347(4):240–7.

288. Hornik CP, Fort P, Clark RH, Watt K, Benjamin Jr. DK, Smith PB, et al. Early and late onset sepsis in very-low-birth-weight infants from a large group of neonatal intensive care units. Early Hum Dev. 2012 May;88, Supplement 2:S69–74.

289. Levit O, Bhandari V, Li F-Y, Shabanova V, Gallagher PG, Bizzarro MJ. Clinical and laboratory factors that predict death in very low birth weight infants presenting with late-onset sepsis. Pediatr Infect Dis J. 2014 Feb;33(2):143–6.

290. Makhoul IR, Sujov P, Smolkin T, Lusky A, Reichman B, Israel Neonatal Network. Pathogen-specific early mortality in very low birth weight infants with late-onset sepsis: a national survey. Clin Infect Dis Off Publ Infect Dis Soc Am. 2005 Jan 15;40(2):218–24.

291. Stoll BJ, Hansen N, Fanaroff AA, Wright LL, Carlo WA, Ehrenkranz RA, *et al*. Late-onset sepsis in very low birth weight neonates: the experience of the NICHD Neonatal Research Network. Pediatrics. 2002 Aug;110(2 Pt 1):285–91.

292. Stoll BJ, Gordon T, Korones SB, Shankaran S, Tyson JE, Bauer CR, *et al*. Late-onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network. J Pediatr. 1996 Jul;129(1):63–71.

293. Dammann O, Leviton A. Maternal Intrauterine Infection, Cytokines, and Brain Damage in the Preterm Newborn. Pediatr Res. 1997 Jul;42(1):1–8.

294. Graham EM, Holcroft CJ, Rai KK, Donohue PK, Allen MC. Neonatal cerebral white matter injury in preterm infants is associated with culture positive infections and only rarely with metabolic acidosis. Am J Obstet Gynecol. 2004 Oct;191(4):1305–10.

295. Stoll BJ, Hansen NI, Adams-Chapman I, Fanaroff AA, Hintz SR, Vohr B, *et al*. Neurodevelopmental and growth impairment among extremely low-birth-weight infants with neonatal infection. JAMA J Am Med Assoc. 2004 Nov 17;292(19):2357–65.

296. Mitha A, Foix-L'Hélias L, Arnaud C, Marret S, Vieux R, Aujard Y, *et al*. Neonatal infection and 5-year neurodevelopmental outcome of very preterm infants. Pediatrics. 2013 Aug;132(2):e372–80.

297. Pessoa-Silva CL, Hugonnet S, Pfister R, Touveneau S, Dharan S, Posfay-Barbe K, *et al*. Reduction of health care associated infection risk in neonates by successful hand hygiene promotion. Pediatrics. 2007 Aug;120(2):e382–90.

298. Pittet D, Allegranzi B, Boyce J, World Health Organization World Alliance for Patient Safety First Global Patient Safety Challenge Core Group of Experts. The World Health Organization Guidelines on Hand Hygiene in Health Care and their consensus recommendations. Infect Control Hosp Epidemiol Off J Soc Hosp Epidemiol Am. 2009 Jul;30(7):611–22.

299. Polin RA, Denson S, Brady MT, Committee on Fetus and Newborn, Committee on Infectious Diseases. Strategies for prevention of health care-associated infections in the NICU. Pediatrics. 2012 Apr;129(4):e1085–93.

300. Hellström A, Smith LE, Dammann O. Retinopathy of prematurity. The Lancet. 2013 Oct;382(9902):1445–57.

301. Darlow BA, Hutchinson JL, Henderson-Smart DJ, Donoghue DA, Simpson JM, Evans NJ, *et al*. Prenatal risk factors for severe retinopathy of prematurity among very preterm infants of the Australian and New Zealand Neonatal Network. Pediatrics. 2005 Apr;115(4):990–6.

302. Lad EM, Hernandez-Boussard T, Morton JM, Moshfeghi DM. Incidence of retinopathy of prematurity in the United States: 1997 through 2005. Am J Ophthalmol. 2009 Sep;148(3):451–8.

303. Mohsen L, Abou-Alam M, El-Dib M, Labib M, Elsada M, Aly H. A prospective study on hyperglycemia and retinopathy of prematurity. J Perinatol Off J Calif Perinat Assoc. 2014 Jun;34(6):453–7.

304. Kaempf JW, Kaempf AJ, Wu Y, Stawarz M, Niemeyer J, Grunkemeier G. Hyperglycemia, insulin and slower growth velocity may increase the risk of retinopathy of prematurity. J Perinatol Off J Calif Perinat Assoc. 2011 Apr;31(4):251–7.

305. Vinekar A, Dogra MR, Sangtam T, Narang A, Gupta A. Retinopathy of prematurity in Asian Indian babies weighing greater than 1250 grams at birth: Ten year data from a tertiary care center in a developing country. Indian J Ophthalmol. 2007;55(5):331–6.

306. Gilbert C. Retinopathy of prematurity: A global perspective of the epidemics, population of babies at risk and implications for control. Early Hum Dev. 2008 Feb;84(2):77–82.

307. Gilbert C, Fielder A, Gordillo L, Quinn G, Semiglia R, Visintin P, *et al*. Characteristics of Infants With Severe Retinopathy of Prematurity in Countries With Low, Moderate, and High Levels of Development: Implications for Screening Programs. Pediatrics. 2005 Jan 5;115(5):e518–25.

308. Kumar P, Sankar MJ, Deorari A, Azad R, Chandra P, Agarwal R, *et al*. Risk factors for severe retinopathy of prematurity in preterm low birth weight neonates. Indian J Pediatr. 2011 Jul;78(7):812–6.

309. Chaudhari S, Patwardhan V, Vaidya U, Kadam S, Kamat A. Retinopathy of prematurity in a tertiary care center--incidence, risk factors and outcome. Indian Pediatr. 2009 Mar;46(3):219–24.

310. Maini B, Chellani H, Arya S, Guliani BP. Retinopathy of prematurity: risk factors and role of antenatal betamethasone in Indian preterm newborn babies. J Clin Neonatol. 2014 Jan;3(1):20–4.

311. Pejawar R., Vinekar A., Bilagi A. National Neonatology Foundation practice guidelines 2010. 2010.

312. Msall ME, Phelps DL, DiGaudio KM, Dobson V, Tung B, McClead RE, *et al*. Severity of neonatal retinopathy of prematurity is predictive of neurodevelopmental functional outcome at age 5.5 years. Behalf of the Cryotherapy for Retinopathy of Prematurity Cooperative Group. Pediatrics. 2000 Nov;106(5):998–1005.

313. Msall ME, Phelps DL, Hardy RJ, Dobson V, Quinn GE, Summers CG, *et al*. Educational and social competencies at 8 years in children with threshold retinopathy of prematurity in the CRYO-ROP multicenter study. Pediatrics. 2004 Apr;113(4):790–9.

314. Van Dommelen P, Mohangoo AD, Verkerk PH, van der Ploeg CPB, van Straaten HLM, Dutch NICU Neonatal Hearing Screening Working Group. Risk indicators for hearing loss in infants treated in different neonatal intensive care units. Acta Paediatr Oslo Nor 1992. 2010 Mar;99(3):344–9.

315. Engdahl B, Eskild A. Birthweight and the risk of childhood sensorineural hearing loss. Paediatr Perinat Epidemiol. 2007 Nov;21(6):495–500.

316. Paul AK. Early identification of hearing loss and centralized newborn hearing screening facility-the Cochin experience. Indian Pediatr. 2011 May;48(5):355–9.

317. Tuli IP, Pal I, Sengupta S, Bhutia C, others. Role of early audiological screening and intervention. Indian J Otol. 2012;18(3):148.

318. Downs MP, Yoshinaga-Itano C. The efficacy of early identification and intervention for children with hearing impairment. Pediatr Clin North Am. 1999 Feb;46(1):79–87.

319. Volpe JJ. Encephalopathy of Prematurity Includes Neuronal Abnormalities. Pediatrics. 2005 Jan 7;116(1):221–5.

320. Deng W, Pleasure J, Pleasure D. Progress in Periventricular Leukomalacia. Arch Neurol. 2008 Oct;65(10):1291–5.

321. Khwaja O, Volpe JJ. Pathogenesis of cerebral white matter injury of prematurity. Arch Dis Child Fetal Neonatal Ed. 2008 Mar;93(2):F153–61.

322. Volpe JJ. Neurobiology of periventricular leukomalacia in the premature infant. Pediatr Res. 2001 Nov;50(5):553–62.

323. Volpe JJ. Brain injury in premature infants: a complex amalgam of destructive and developmental disturbances. Lancet Neurol. 2009 Jan;8(1):110–24.

324. Altman DI, Powers WJ, Perlman JM, Herscovitch P, Volpe SL, Volpe JJ. Cerebral blood flow requirement for brain viability in newborn infants is lower than in adults. Ann Neurol. 1988 Aug;24(2):218–26.

325. Ferriero DM. Neonatal brain injury. N Engl J Med. 2004 Nov 4;351(19):1985–95.

326. Volpe JJ, Kinney HC, Jensen F E, Rosenberg PA. The developing oligodendrocyte: key cellular target in brain injury in the premature infant. Int J Dev Neurosci Off J Int Soc Dev Neurosci. 2011 Jun;29(4):423–40.

327. Leviton A. Preterm birth and cerebral palsy: is tumor necrosis factor the missing link? Dev Med Child Neurol. 1993 Jun;35(6):553–8.

328. Wu YW, Escobar GJ, Grether JK, Croen LA, Greene JD, Newman TB. Chorioamnionitis and cerebral palsy in term and near-term infants. JAMA J Am Med Assoc. 2003 Nov 26;290(20):2677–84.

329. Perlman JM, Risser R, Broyles RS. Bilateral cystic periventricular leukomalacia in the premature infant: associated risk factors. Pediatrics. 1996 Jun;97(6 Pt 1):822–7.

330. De Vries LS, Van Haastert I-LC, Rademaker KJ, Koopman C, Groenendaal F. Ultrasound abnormalities preceding cerebral palsy in high-risk preterm infants. J Pediatr. 2004 Jun;144(6):815–20.

331. Krägeloh-Mann I, Petersen D, Hagberg G, Vollmer B, Hagberg B, Michaelis R. Bilateral Spastic Cerebral Palsy-Mri Pathology and Origin. Analysis from a Representative Series of 56 Cases. Dev Med Child Neurol. 1995;37(5):379–97.

332. Jacobson LK, Dutton GN. Periventricular leukomalacia: an important cause of visual and ocular motility dysfunction in children. Surv Ophthalmol. 2000 Aug;45(1):1–13.

333. Resić B, Tomasović M, Kuzmanić-Samija R, Lozić M, Resić J, Solak M. Neurodevelopmental outcome in children with periventricular leukomalacia. Coll Antropol. 2008 Jan;32 Suppl 1:143–7.

334. Bax M, Tydeman C, Flodmark O. Clinical and mri correlates of cerebral palsy: The european cerebral palsy study. JAMA. 2006 Oct 4;296(13):1602–8.

335. Ligam P, Haynes RL, Folkerth RD, Liu L, Yang M, Volpe JJ, *et al*. Thalamic Damage in Periventricular Leukomalacia: Novel Pathologic Observations Relevant to Cognitive Deficits in Survivors of Prematurity. Pediatr Res. 2009 May;65(5):524–9.

336. Zubiaurre-Elorza L, Soria-Pastor S, Junqué C, Fernandez-Espejo D, Segarra D, Bargalló N, *et al*. Thalamic changes in a preterm sample with periventricular leukomalacia: correlation with white-matter integrity and cognitive outcome at school age. Pediatr Res. 2012 Apr;71(4-1):354–60.

337. Isaacs EB, Edmonds CJ, Chong WK, Lucas A, Morley R, Gadian DG. Brain morphometry and IQ measurements in preterm children. Brain. 2004 Dec 1;127(12):2595–607.

338. Hoon AH, Stashinko EE, Nagae LM, Lin DDM, Keller J, Bastian A, *et al*. Sensory and motor deficits in children with cerebral palsy born preterm correlate with diffusion tensor imaging abnormalities in thalamocortical pathways. Dev Med Child Neurol. 2009 Sep;51(9):697–704.

339. Luque MJ, Tapia JL, Villarroel L, Marshall G, Musante G, Carlo W, *et al*. A risk prediction model for severe intraventricular hemorrhage in very low birth weight infants and the effect of prophylactic indomethacin. J Perinatol. 2014 Jan;34(1):43–8.

340. Hambleton G, Wigglesworth JS. Origin of intraventricular haemorrhage in the preterm infant. Arch Dis Child. 1976 Sep;51(9):651–9.

341. Taylor GA. New concepts in the pathogenesis of germinal matrix intraparenchymal hemorrhage in premature infants. Am J Neuroradiol. 1997 Jan 2;18(2):231–2.

342. Whitelaw A. Intraventricular haemorrhage and posthaemorrhagic hydrocephalus: pathogenesis, prevention and future interventions. Semin Neonatol. 2001 Apr;6(2):135–46.

343. Murphy BP, Inder TE, Rooks V, Taylor GA, Anderson NJ, Mogridge N, *et al*. Posthaemorrhagic ventricular dilatation in the premature infant: natural history and predictors of outcome. Arch Dis Child Fetal Neonatal Ed. 2002 Jul;87(1):F37–41.

344. McCrea HJ, Ment LR. The diagnosis, management, and postnatal prevention of intraventricular hemorrhage in the preterm neonate. Clin Perinatol. 2008 Dec;35(4):777–92, vii.

345. Pinto-Martin JA, Whitaker AH, Feldman JF, Van Rossem R, Paneth N. Relation of cranial ultrasound abnormalities in low-birthweight infants to motor or cognitive performance at ages 2, 6, and 9 years. Dev Med Child Neurol. 1999 Dec;41(12):826–33.

346. Morris BH, Smith KE, Swank PR, Denson SE, Landry SH. Patterns of physical and neurologic development in preterm children. J Perinatol Off J Calif Perinat Assoc. 2002 Jan;22(1):31–6.

347. Vollmer B, Roth S, Baudin J, Stewart AL, Neville BGR, Wyatt JS. Predictors of long-term outcome in very preterm infants: gestational age versus neonatal cranial ultrasound. Pediatrics. 2003 Nov;112(5):1108–14.

348. Bax M, Goldstein M, Rosenbaum P, Leviton A, Paneth N, Dan B, *et al*. Proposed definition and classification of cerebral palsy, April 2005. Dev Med Child Neurol. 2005 Aug;47(8):571–6.

349. Prevalence and characteristics of children with cerebral palsy in Europe. Dev Med Child Neurol. 2002 Sep;44(9):633–40.

350. Yeargin-Allsopp M, Van Naarden Braun K, Doernberg NS, Benedict RE, Kirby RS, Durkin MS. Prevalence of cerebral palsy in 8-year-old children in three areas of the United States in 2002: a multisite collaboration. Pediatrics. 2008 Mar;121(3):547–54.

351. Platt MJ, Cans C, Johnson A, Surman G, Topp M, Torrioli MG, *et al*. Trends in cerebral palsy among infants of very low birthweight (<1500 g) or born prematurely (<32 weeks) in 16 European centres: a database study. The Lancet. 2007 Jan 12;369(9555):43–50.

352. Nelson KB. Can We Prevent Cerebral Palsy? N Engl J Med. 2003 Oct 30;349(18):1765–9.

353. Strijbis EMM, Oudman I, van Essen P, MacLennan AH. Cerebral palsy and the application of the international criteria for acute intrapartum hypoxia. Obstet Gynecol. 2006 Jun;107(6):1357–65.

354. Grether JK, Nelson KB, Emery ES, Cummins SK. Prenatal and perinatal factors and cerebral palsy in very low birth weight infants. J Pediatr. 1996 Mar;128(3):407–14.

355. Weindling M. Periventricular haemorrhage and periventricular leukomalacia. BJOG Int J Obstet Gynaecol. 1995;102(4):278–81.

356. Leviton A, Paneth N. White matter damage in preterm newborns--an epidemiologic perspective. Early Hum Dev. 1990 Oct;24(1):1–22.

357. Hagberg B, Hagberg G, Olow I, von Wendt L. The changing panorama of cerebral palsy in Sweden. VII. Prevalence and origin in the birth year period 1987-90. Acta Paediatr Oslo Nor 1992. 1996 Aug;85(8):954–60.

358. Behrman RE, Butler AS, Outcomes I of M (US) C on UPB and AH. Neurodevelopmental, Health, and Family Outcomes for Infants Born Preterm. 2007 [cited 2014 Nov 24]; Available from: http://www.ncbi.nlm.nih.gov/books/NBK11356/

359. Vohr BR, Wright LL, Poole WK, McDonald SA. Neurodevelopmental outcomes of extremely low birth weight infants <32 weeks' gestation between 1993 and 1998. Pediatrics. 2005 Sep;116(3):635–43.

360. Mikkola K, Ritari N, Tommiska V, Salokorpi T, Lehtonen L, Tammela O, *et al*. Neurodevelopmental outcome at 5 years of age of a national cohort of extremely low birth weight infants who were born in 1996-1997. Pediatrics. 2005 Dec;116(6):1391–400.

361. Cummins SK, Nelson KB, Grether JK, Velie EM. Cerebral palsy in four northern California counties, births 1983 through 1985. J Pediatr. 1993 Aug;123(2):230–7.

362. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ. 2007 Oct 20;335(7624):806–8.

363. Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, *et al*. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. PLoS Med. 2007 Oct 16;4(10):e297.

364. Fenton TR. A new growth chart for preterm babies: Babson and Benda's chart updated with recent data and a new format. BMC Pediatr. 2003 Dec 16;3(1):13.

365. Amiel-Tison C, Stewart A. Follow up studies during the first five years of life: a pervasive assessment of neurological function. Arch Dis Child. 1989 Apr;64(4 Spec No):496–502.

366. Surveillance of Cerebral Palsy in Europe. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. Surveillance of Cerebral Palsy in Europe (SCPE). Dev Med Child Neurol. 2000 Dec;42(12):816–24.

367. Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. Dev Med Child Neurol. 1997 Apr;39(4):214–23.

368. Folio M., Fewell R. Peabody developmental motor scales 2nd edition. 2 nd. Austin, TX: Pro-Ed; 2000.

369. Tripathi R, Joshua AM, Kotian MS, Tedla JS. Normal motor development of Indian children on Peabody Developmental Motor Scales-2 (PDMS-2). Pediatr Phys Ther Off Publ Sect Pediatr Am Phys Ther Assoc. 2008;20(2):167–72.

370. Luiz D, Barnard A, Knosen N, Kotras N, Horrocks S, McAlinden P, *et al*. Griffiths Mental Development Scales - Extended Revised: 2 to 8 years (GMDS-ER 2-8) - Administration Manual. Hogrefe Ltd. Oxford, UK: The Association for Research in Infant and Child Development (ARICD); 2006.

371. Ivens J, Martin N. A common metric for the Griffiths Scales. Arch Dis Child. 2002 Aug;87(2):109–10.

372. Riley K, Roth S, Sellwood M, Wyatt JS. Survival and neurodevelopmental morbidity at 1 year of age following extremely preterm delivery over a 20-year period: a single centre cohort study. Acta Paediatr Oslo Nor 1992. 2008 Feb;97(2):159–65.

373. High Risk Follow-up Working Group (Kowloon Region). Neurodevelopmental outcomes of extreme-low-birth-weight infants born between 2001 and 2002. Hong Kong Med J Xianggang Yi Xue Za Zhi Hong Kong Acad Med. 2008 Feb;14(1):21–8.

374. Chacko J, Ford WD, Haslam R. Growth and neurodevelopmental outcome in extremely-low-birth-weight infants after laparotomy. Pediatr Surg Int. 1999;15(7):496–9.

375. Juneja M, Mohanty M, Jain R, Ramji S. Ages and Stages Questionnaire as a screening tool for developmental delay in Indian children. Indian Pediatr. 2012 Jun;49(6):457–61.

376. WHO: Geneva. WHO AnthroPlus for personal computers Manual: Software for assessing growth of the world's children and adolescents. 2009). [Internet]. 2009 [cited 2015 Jan 10]. Available from: www.who.int/growthref/tools/en/

377. Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. BMJ. 1988 Nov 19;297(6659):1304–8.

378. Mathai M, Jacob S, Karthikeyan NG. Birthweight standards for south Indian babies. Indian Pediatr. 1996 Mar;33(3):203–9.

379. Kandraju H, Agrawal S, Geetha K, Sujatha L, Subramanian S, Murki S. Gestational age-specific centile charts for anthropometry at birth for South Indian infants. Indian Pediatr. 2012 Mar;49(3):199–202.

380. Altman DG, Deeks JJ, Sackett DL. Odds ratios should be avoided when events are common. BMJ. 1998 Nov 7;317(7168):1318.

381. RICH JT, NEELY JG, PANIELLO RC, VOELKER CCJ, NUSSENBAUM B, WANG EW. A PRACTICAL GUIDE TO UNDERSTANDING KAPLAN-MEIER CURVES. Otolaryngol--Head Neck Surg Off J Am Acad Otolaryngol-Head Neck Surg. 2010 Sep;143(3):331–6.

382. Jeyaseelan L, Walter SD, Shankar V, John GT. Survival analysis: Cox proportional hazards model. Natl Med J India. 1999 Oct;12(5):230–3.

383. Spruance SL, Reid JE, Grace M, Samore M. Hazard Ratio in Clinical Trials. Antimicrob Agents Chemother. 2004 Jan 8;48(8):2787–92.

384. Sainani KL. Dealing with non-normal data. PM R. 2012 Dec;4(12):1001–5.

385. Yoon JJ, Kohl S, Harper RG. The relationship between maternal hypertensive disease of pregnancy and the incidence of idiopathic respiratory distress syndrome. Pediatrics. 1980 Apr;65(4):735–9.

386. Fanaroff AA, Hack M, Walsh MC. The NICHD neonatal research network: changes in practice and outcomes during the first 15 years. Semin Perinatol. 2003 Aug;27(4):281–7.

387. Ho JJ, Amar HS, Mohan AJ, Hon TH. Neurodevelopmental outcome of very low birth weight babies admitted to a Malaysian nursery. J Paediatr Child Health. 1999 Apr;35(2):175–80.

388. Aylward GP, Pfeiffer SI, Wright A, Verhulst SJ. Outcome studies of low birth weight infants published in the last decade: A metaanalysis. J Pediatr. 1989 Oct;115(4):515–20.

389. Braitman LE. Confidence intervals assess both clinical significance and statistical significance. Ann Intern Med. 1991 Mar 15;114(6):515–7.

390. Sainani KL. A closer look at confidence intervals. PM R. 2011 Dec;3(12):1134–41.

391. High Risk Follow-up Working Group (Kowloon Region). Neurodevelopmental outcomes of extreme-low-birth-weight infants born between 2001 and 2002. Hong Kong Med J Xianggang Yi Xue Za Zhi Hong Kong Acad Med. 2008 Feb;14(1):21–8.

392. Ghosh S, Bhargava SK, Madhavan S, Taskar AD, Bhargava V, Nigam SK. Intra-Uterine Growth of North Indian Babies. Pediatrics. 1971 Jan 5;47(5):826–30.

393. Mohan M, Prasad SR, Chellani HK, Kapani V. Intrauterine growth curves in north Indian babies: weight, length, head circumference and ponderal index. Indian Pediatr. 1990 Jan;27(1):43–51.

394. Bhatia J. Growth Curves: How to Best Measure Growth of the Preterm Infant. J Pediatr. 2013 Mar;162(3, Supplement):S2–6.

395. Katz J, Wu LA, Mullany LC, Coles CL, Lee ACC, Kozuki N, *et al*. Prevalence of small-for-gestational-age and its mortality risk varies by choice of birth-weight-for-gestation reference population. PloS One. 2014;9(3):e92074.

396. Niklasson A, Ericson A, Fryer JG, Karlberg J, Lawrence C, Karlberg P. An update of the Swedish reference standards for weight, length and head circumference at birth for given gestational age (1977-1981). Acta Paediatr Scand. 1991 Sep;80(8-9):756–62.

397. Kramer MS, Platt RW, Wen SW, Joseph KS, Allen A, Abrahamowicz M, *et al*. A new and improved population-based Canadian reference for birth weight for gestational age. Pediatrics. 2001 Aug;108(2):E35.

398. Beeby PJ, Bhutap T, Taylor LK. New South Wales population-based birthweight percentile charts. J Paediatr Child Health. 1996 Dec;32(6):512–8.

399. Kuczmarski RJ, Ogden CL, Guo SS, Grummer-Strawn LM, Flegal KM, Mei Z, *et al*. 2000 CDC Growth Charts for the United States: methods and development. Vital Health Stat 11. 2002 May;(246):1–190.

400. Rao SC, Tompkins J. Growth curves for preterm infants. Early Hum Dev. 2007 Oct;83(10):643–51.

401. International Institute for Population Sciences (IIPS), Macro International. 2008. National Family Health Survey (NFHS-3), India, 2005-06: Tamil Nadu. 2008.

402. Sehgal A, Telang S, Passah SM, Jyothi MC. Maternal and neonatal profile and immediate outcome in extremely low birth weight babies in Delhi. Trop Doct. 2004 Jul;34(3):165–8.

403. Roy KK, Baruah J, Kumar S, Malhotra N, Deorari AK, Sharma JB. Maternal antenatal profile and immediate neonatal outcome in VLBW and ELBW babies. Indian J Pediatr. 2006 Aug;73(8):669–73.

404. Levy A, Fraser D, Katz M, Mazor M, Sheiner E. Maternal anemia during pregnancy is an independent risk factor for low birthweight and preterm delivery. Eur J Obstet Gynecol Reprod Biol. 2005 Oct 1;122(2):182–6.

405. Backes CH, Markham K, Moorehead P, Cordero L, Nankervis CA, Giannone PJ. Maternal Preeclampsia and Neonatal Outcomes. J Pregnancy [Internet]. 2011 [cited 2014 Dec 30];2011. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3087144/

406. Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol. 2009 Jun;33(3):130–7.

407. Rugolo LMS de S, Bentlin MR, Trindade CEP. Preeclampsia: Effect on the Fetus and Newborn. NeoReviews. 2011 Jan 4;12(4):e198–206.

408. Leitner Y, Harel S, Geva R, Eshel R, Yaffo A, Many A. The neurocognitive outcome of IUGR children born to mothers with and without preeclampsia. J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet. 2012 Nov;25(11):2206–8.

409. Gray PH, O'Callaghan MJ, Mohay HA, Burns YR, King JF. Maternal hypertension and neurodevelopmental outcome in very preterm infants. Arch Dis Child Fetal Neonatal Ed. 1998 Sep;79(2):F88–93.

410. Silveira RC, Procianoy RS, Koch MS, Benjamin ACW, Schlindwein CF. Growth and neurodevelopment outcome of very low birth weight infants delivered by preeclamptic mothers. Acta Paediatr Oslo Nor 1992. 2007 Dec;96(12):1738–42.

411. Kronenberg ME, Raz S, Sander CJ. Neurodevelopmental outcome in children born to mothers with hypertension in pregnancy: the significance of suboptimal intrauterine growth. Dev Med Child Neurol. 2006 Mar;48(3):200–6.

412. Blondel B, Kogan MD, Alexander GR, Dattani N, Kramer MS, Macfarlane A, *et al*. The impact of the increasing number of multiple births on the rates of preterm birth and low birthweight: an international study. Am J Public Health. 2002 Aug;92(8):1323–30.

413. Garite TJ, Clark RH, Elliott JP, Thorp JA, the Pediatrix/Obstetrix Perinatal Research Group. Twins and triplets: The effect of plurality and growth on neonatal outcome compared with singleton infants. Am J Obstet Gynecol. 2004 Sep;191(3):700–7.

414. Sherer DM. Adverse perinatal outcome of twin pregnancies according to chorionicity: review of the literature. Am J Perinatol. 2001;18(1):23–37.

415. Hack KEA, Derks JB, Elias SG, Franx A, Roos EJ, Voerman SK, *et al*. Increased perinatal mortality and morbidity in monochorionic versus dichorionic twin pregnancies: clinical implications of a large Dutch cohort study. BJOG Int J Obstet Gynaecol. 2008 Jan;115(1):58–67.

416. Mathews TJ, Menacker F, MacDorman MF. Infant mortality statistics from the 2000 period linked birth/infant death data set. Natl Vital Stat Rep Cent Dis Control Prev Natl Cent Health Stat Natl Vital Stat Syst. 2002 Aug 28;50(12):1–28.

417. Donovan EF, Ehrenkranz RA, Shankaran S, Stevenson DK, Wright LL, Younes N, *et al*. Outcomes of very low birth weight twins cared for in the National Institute of Child Health and Human Development Neonatal Research Network's intensive care units. Am J Obstet Gynecol. 1998 Sep;179(3 Pt 1):742–9.

418. Morley R, Cole TJ, Powell R, Lucas A. Growth and development in premature twins. Arch Dis Child. 1989 Jul;64(7):1042–5.

419. Chaudhari S, Bhalerao MR, Vaidya U, Pandit A, Nene U. Growth and development of twins compared with singletons at ages one and four years. Indian Pediatr. 1997 Dec;34(12):1081–6.

420. Kyriakidou M, Karagianni P, Iliodromiti Z, Chatziioannidis I, Papaioannou E, Exadaktilou S, *et al*. Comparison of 24 months neurodevelopmental outcome in twins and singletons ≤ 34 weeks gestation at birth. J Pediatr Neonatal Individ Med JPNIM. 2013 Jan 15;2(1):48–54.

421. Wadhawan R, Oh W, Perritt RL, McDonald SA, Das A, Poole WK, *et al*. Twin gestation and neurodevelopmental outcome in extremely low birth weight infants. Pediatrics. 2009 Feb;123(2):e220–7.

422. Wadhawan R, Oh W, Vohr BR, Wrage L, Das A, Bell EF, *et al*. Neurodevelopmental outcomes of triplets or higher-order extremely low birth weight infants. Pediatrics. 2011 Mar;127(3):e654–60.

423. Allen VM, Wilson RD, Cheung A, Genetics Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC), Reproductive Endocrinology Infertility Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC). Pregnancy outcomes after assisted reproductive technology. J Obstet Gynaecol Can JOGC J Obstétrique Gynécologie Can JOGC. 2006 Mar;28(3):220–50.

424. Helmerhorst FM, Perquin DAM, Donker D, Keirse MJNC. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. BMJ. 2004 Jan 31;328(7434):261.

425. Bay B, Mortensen EL, Kesmodel US. Assisted reproduction and child neurodevelopmental outcomes: a systematic review. Fertil Steril. 2013 Sep;100(3):844–53.

426. Abdel-Latif ME, Bajuk B, Ward M, Oei JL, Badawi N. Neurodevelopmental outcomes of extremely premature infants conceived after assisted conception: a population based cohort study. Arch Dis Child - Fetal Neonatal Ed. 2013 Jan 5;98(3):F205–11.

427. Seshiah V, Balaji V, Balaji MS, Paneerselvam A, Arthi T, Thamizharasi M, *et al*. Prevalence of gestational diabetes mellitus in South India (Tamil Nadu)--a community based study. J Assoc Physicians India. 2008 May;56:329–33.

428. Ferrara A. Increasing Prevalence of Gestational Diabetes Mellitus: A public health perspective. Diabetes Care. 2007 Jul 1;30(Supplement 2):S141–6.

429. Thomas N, Chinta AJ, Sridhar S, Kumar M, Kuruvilla KA, Jana AK. Perinatal outcome of infants born to diabetic mothers in a developing country--comparison of insulin and oral hypoglycemic agents. Indian Pediatr. 2013 Mar;50(3):289–93.

430. Cordero L, Treuer SH, Landon MB, Gabbe SG. Management of infants of diabetic mothers. Arch Pediatr Adolesc Med. 1998 Mar;152(3):249–54.

431. Michael Weindling A. Offspring of diabetic pregnancy: short-term outcomes. Semin Fetal Neonatal Med. 2009 Apr;14(2):111–8.

432. Nold JL, Georgieff MK. Infants of diabetic mothers. Pediatr Clin. 2004 Jun 1;51(3):619–37.

433. Ornoy A, Wolf A, Ratzon N, Greenbaum C, Dulitzky M. Neurodevelopmental outcome at early school age of children born to mothers with gestational diabetes. Arch Dis Child - Fetal Neonatal Ed. 1999 Jan 7;81(1):F10–4.

434. Petersen MB, Pedersen SA, Greisen G, Pedersen JF, Mølsted-Pedersen L. Early growth delay in diabetic pregnancy: relation to psychomotor development at age 4. BMJ. 1988 Feb 27;296(6622):598–600.

435. Rizzo TA, Dooley SL, Metzger BE, Cho NH, Ogata ES, Silverman BL. Prenatal and perinatal influences on long-term psychomotor development in offspring of diabetic mothers. Am J Obstet Gynecol. 1995 Dec;173(6):1753–8.

436. Wright LL, Verter J, Younes N, Stevenson D, Fanaroff AA, Shankaran S, *et al*. Antenatal corticosteroid administration and neonatal outcome in very low birth weight infants: The NICHD neonatal research network. Am J Obstet Gynecol. 1995 Jul;173(1):269–74.

437. Woythaler MA, McCormick MC, Smith VC. Late preterm infants have worse 24-month neurodevelopmental outcomes than term infants. Pediatrics. 2011 Mar;127(3):e622–9.

438. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KS. Cognitive and behavioral outcomes of school-aged children who were born preterm: A meta-analysis. JAMA. 2002 Aug 14;288(6):728–37.

439. Kapellou O, Counsell SJ, Kennea N, Dyet L, Saeed N, Stark J, *et al*. Abnormal Cortical Development after Premature Birth Shown by Altered Allometric Scaling of Brain Growth. PLoS Med. 2006 Aug 1;3(8):e265.

440. Bhutta AT, Anand KJ. Abnormal cognition and behavior in preterm neonates linked to smaller brain volumes. Trends Neurosci. 2001 Mar;24(3):129–30; discussion 131–2.

441. Stevenson DK, Verter J, Fanaroff AA, Oh W, Ehrenkranz RA, Shankaran S, *et al*. Sex differences in outcomes of very low birthweight infants: the newborn male disadvantage. Arch Dis Child - Fetal Neonatal Ed. 2000 Jan 11;83(3):F182–5.

442. Van Marter LJ, Leviton A, Kuban KC, Pagano M, Allred EN. Maternal glucocorticoid therapy and reduced risk of bronchopulmonary dysplasia. Pediatrics. 1990 Sep;86(3):331–6.

443. Perelman RH, Palta M, Kirby R, Farrell PM. Discordance between male and female deaths due to the respiratory distress syndrome. Pediatrics. 1986 Aug;78(2):238–44.

444. Mohamed MA, Aly H. Male Gender Is Associated With Intraventricular Hemorrhage. Pediatrics. 2010 Jan 2;125(2):e333–9.

445. Kilbride HW, Daily DK. Survival and subsequent outcome to five years of age for infants with birth weights less than 801 grams born from 1983 to 1989. J Perinatol Off J Calif Perinat Assoc. 1998 Apr;18(2):102–6.

446. Hoffman EL, Bennett FC. Birth weight less than 800 grams: changing outcomes and influences of gender and gestation number. Pediatrics. 1990 Jul;86(1):27–34.

447. Elsmén E, Källén K, Marsál K, Hellström-Westas L. Fetal gender and gestational-age-related incidence of pre-eclampsia. Acta Obstet Gynecol Scand. 2006;85(11):1285–91.

448. Randolph DA, Nolen TL, Ambalavanan N, Carlo WA, Peralta-Carcelen M, Das A, *et al*. Outcomes of extremely low birthweight infants with acidosis at birth. Arch Dis Child Fetal Neonatal Ed. 2014 Jul;99(4):F263–8.

449. Gane B, Bhat BV, Adhisivam B, Joy R, Prasadkumar P, Femitha P, *et al*. Risk Factors and Outcome in Neonatal Necrotising Enterocolitis. Indian J Pediatr. 2014 May 1;81(5):425–8.

450. Singh M, Deorari AK, Aggarwal R, Paul VK. Assisted ventilation for hyaline membrane disease. Indian Pediatr. 1995 Dec;32(12):1267–74.

451. Murki S, Deorari A, Vidyasagar D. Use of CPAP and surfactant therapy in newborns with respiratory distress syndrome. Indian J Pediatr. 2014 May;81(5):481–8.

452. Barros FC, Bhutta ZA, Batra M, Hansen TN, Victora CG, Rubens CE. Global report on preterm birth and stillbirth (3 of 7): evidence for effectiveness of interventions. BMC Pregnancy Childbirth. 2010 Feb 23;10(Suppl 1):S3.

453. Bajwa NM, Berner M, Worley S, Pfister RE, Swiss Neonatal Network. Population based age stratified morbidities of premature infants in Switzerland. Swiss Med Wkly. 2011;141:w13212.

454. Davis AS, Hintz SR, Goldstein RF, Ambalavanan N, Bann CM, Stoll BJ, *et al*. Outcomes of extremely preterm infants following severe intracranial hemorrhage. J Perinatol Off J Calif Perinat Assoc. 2014 Mar;34(3):203–8.

455. Adams-Chapman I, Hansen NI, Stoll BJ, Higgins R, NICHD Research Network. Neurodevelopmental outcome of extremely low birth weight infants with posthemorrhagic hydrocephalus requiring shunt insertion. Pediatrics. 2008 May;121(5):e1167–77.

456. Gera T, Ramji S. Early predictors of mortality in very low birth weight neonates. Indian Pediatr. 2001 Jun;38(6):596–602.

457. Zakariya BP, Bhat V, Harish BN, Arun Babu T, Joseph NM. Neonatal sepsis in a tertiary care hospital in South India: bacteriological profile and antibiotic sensitivity pattern. Indian J Pediatr. 2011 Apr;78(4):413–7.

458. Boo NY, Ong LC, Lye MS, Chandran V, Teoh SL, Zamratol S, *et al*. Comparison of morbidities in very low birthweight and normal birthweight infants during the first year of life in a developing country. J Paediatr Child Health. 1996 Oct;32(5):439–44.

459. Adams-Chapman I, Stoll BJ. Neonatal infection and long-term neurodevelopmental outcome in the preterm infant. Curr Opin Infect Dis. 2006 Jun;19(3):290–7.

460. Shane AL, Stoll BJ. Neonatal sepsis: progress towards improved outcomes. J Infect. 2014 Jan;68 Suppl 1:S24–32.

461. Volpe JJ. Postnatal Sepsis, Necrotizing Entercolitis, and the Critical Role of Systemic Inflammation in White Matter Injury in Premature Infants. J Pediatr. 2008 Aug;153(2):160–3.

462. Pharoah PO, Cooke T. Cerebral palsy and multiple births. Arch Dis Child Fetal Neonatal Ed. 1996 Nov;75(3):F174–7.

463. Bonellie SR, Currie D, Chalmers J. Comparison of risk factors for cerebral palsy in twins and singletons. Dev Med Child Neurol. 2005 Sep;47(9):587–91.

464. Petterson B, Nelson KB, Watson L, Stanley F. Twins, triplets, and cerebral palsy in births in Western Australia in the 1980s. BMJ. 1993 Nov 13;307(6914):1239–43.

465. Bejar R, Vigliocco G, Gramajo H, Solana C, Benirschke K, Berry C, *et al*. Antenatal origin of neurologic damage in newborn infants. II. Multiple gestations. Am J Obstet Gynecol. 1990 May;162(5):1230–6.

466. Baker LL, Stevenson DK, Enzmann DR. End-stage periventricular leukomalacia: MR evaluation. Radiology. 1988 Sep 1;168(3):809–15.

467. Leppänen M, Ekholm E, Palo P, Maunu J, Munck P, Parkkola R, *et al*. Abnormal antenatal Doppler velocimetry and cognitive outcome in very-low-birth-weight infants at 2 years of age. Ultrasound Obstet Gynecol Off J Int Soc Ultrasound Obstet Gynecol. 2010 Aug;36(2):178–85.

468. Valcamonico A, Danti L, Frusca T, Soregaroli M, Zucca S, Abrami F, *et al*. Absent end-diastolic velocity in umbilical artery: Risk of neonatal morbidity and brain damage. Am J Obstet Gynecol. 1994 Mar;170(3):796–801.

469. Voßbeck S, Camargo OK de, Grab D, Bode H, Pohlandt F. Neonatal and neurodevelopmental outcome in infants born before 30 weeks of gestation with absent or reversed end-diastolic flow velocities in the umbilical artery. Eur J Pediatr. 2001 Jan 1;160(2):128–34.

470. Vinet É, Pineau CA, Clarke AE, Fombonne É, Platt RW, Bernatsky S. Neurodevelopmental disorders in children born to mothers with systemic lupus erythematosus. Lupus. 2014 Oct;23(11):1099–104.

471. Nelson KB. Perinatal Ischemic. Stroke. 2007 Jan 2;38(2):742–5.

472. Pharoah PO, Cooke T, Rosenbloom L. Acquired cerebral palsy. Arch Dis Child. 1989 Jul;64(7):1013–6.

473. Reddihough DS, Collins KJ. The epidemiology and causes of cerebral palsy. Aust J Physiother. 2003;49(1):7–12.

474. Kuban KCK, Leviton A. Cerebral Palsy. N Engl J Med. 1994 Jan 20;330(3):188–95.

475. Wilkins RH, Brody IA. Little's disease. Arch Neurol. 1969 Feb;20(2):217–24.

476. Pharoah POD, Cooke T, Johnson MA, King R, Mutch L. Epidemiology of cerebral palsy in England and Scotland, 1984–9. Arch Dis Child - Fetal Neonatal Ed. 1998 Jan 7;79(1):F21–5.

477. Badawi N, Watson L, Petterson B, Blair E, Slee J, Haan E, *et al*. What constitutes cerebral palsy? Dev Med Child Neurol. 1998;40(8):520–7.

478. Blair E, Stanley FJ. Issues in the classification and epidemiology of cerebral palsy. Ment Retard Dev Disabil Res Rev. 1997;3(2):184–93.

479. Venkateswaran S, Shevell MI. Comorbidities and clinical determinants of outcome in children with spastic quadriplegic cerebral palsy. Dev Med Child Neurol. 2008;50(3):216–22.

480. Laptook AR, O'Shea TM, Shankaran S, Bhaskar B, NICHD Neonatal Network. Adverse neurodevelopmental outcomes among extremely low birth weight infants with a normal head ultrasound: prevalence and antecedents. Pediatrics. 2005 Mar;115(3):673–80.

481. Marlow N, Wolke D, Bracewell MA, Samara M, EPICure Study Group. Neurologic and developmental disability at six years of age after extremely preterm birth. N Engl J Med. 2005 Jan 6;352(1):9–19.

482. Yliherva A, Olsén P, Mäki-Torkko E, Koiranen M, Järvelin MR. Linguistic and motor abilities of low-birthweight children as assessed by parents and teachers at 8 years of age. Acta Paediatr Oslo Nor 1992. 2001 Dec;90(12):1440–9.

483. Hindmarsh GJ, O'Callaghan MJ, Mohay HA, Rogers YM. Gender differences in cognitive abilities at 2 years in ELBW infants. Early Hum Dev. 2000 Dec;60(2):115–22.

484. Reiss AL, Kesler SR, Vohr B, Duncan CC, Katz KH, Pajot S, *et al*. Sex differences in cerebral volumes of 8-year-olds born preterm. J Pediatr. 2004 Aug;145(2):242–9.

485. Sandberg AD, Nydén A, Gillberg C, Hjelmquist E. The cognitive profile in infantile autism--a study of 70 children and adolescents using the Griffiths Mental Development Scale. Br J Psychol Lond Engl 1953. 1993 Aug;84 (Pt 3):365–73.

486. Fombonne E. Epidemiology of Pervasive Developmental Disorders. Pediatr Res. 2009 Jun;65(6):591–8.

487. Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Autism spectrum disorders in extremely preterm children. J Pediatr. 2010 Apr;156(4):525–31.e2.

488. Groote ID, Roeyers H, Warreyn P. Social-Communicative Abilities in Young High-Risk Preterm Children. J Dev Phys Disabil. 2006 Jun 1;18(2):183–200.

489. Kuban KCK, O'Shea TM, Allred EN, Tager-Flusberg H, Goldstein DJ, Leviton A. Positive screening on the Modified Checklist for Autism in Toddlers (M-CHAT) in extremely low gestational age newborns. J Pediatr. 2009 Apr;154(4):535–40.e1.

490. Indredavik MS, Vik T, Heyerdahl S, Kulseng S, Fayers P, Brubakk A-M. Psychiatric symptoms and disorders in adolescents with low birth weight. Arch Dis Child Fetal Neonatal Ed. 2004 Sep;89(5):F445–50.

491. Johnson S, Hollis C, Kochhar P, Hennessy E, Wolke D, Marlow N. Psychiatric disorders in extremely preterm children: longitudinal finding at age 11 years in the EPICure study. J Am Acad Child Adolesc Psychiatry. 2010 May;49(5):453–63.e1.

492. Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A. Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. The Vermont Oxford Network. Am J Obstet Gynecol. 2000 Jan;182(1 Pt 1):198–206.

493. Kok JH, den Ouden AL, Verloove-Vanhorick SP, Brand R. Outcome of very preterm small for gestational age infants: the first nine years of life. Br J Obstet Gynaecol. 1998 Feb;105(2):162–8.

494. Zeitlin J, El Ayoubi M, Jarreau P-H, Draper ES, Blondel B, Künzel W, *et al*. Impact of fetal growth restriction on mortality and morbidity in a very preterm birth cohort. J Pediatr. 2010 Nov;157(5):733–9.e1.

495. Guellec I, Lapillonne A, Renolleau S, Charlaluk M-L, Roze J-C, Marret S, *et al*. Neurologic outcomes at school age in very preterm infants born with severe or mild growth restriction. Pediatrics. 2011 Apr;127(4):e883–91.

496. Van Wassenaer A. Neurodevelopmental consequences of being born SGA. Pediatr Endocrinol Rev PER. 2005 Mar;2(3):372–7.

497. Mukhopadhyay K, Louis D, Mahajan G, Mahajan R. Longitudinal growth and post-discharge mortality and morbidity among extremely low birth weight neonates. Indian Pediatr. 2014 Sep;51(9):723–6.

498. Sharma PK, Sankar MJ, Sapra S, Saxena R, Karthikeyan CV, Deorari A, *et al*. Growth and neurosensory outcomes of preterm very low birth weight infants at 18 months of corrected age. Indian J Pediatr. 2011 Dec;78(12):1485–90.

499. Paz I, Seidman DS, Danon YL, Laor A, Stevenson DK, Gale R. Are children born small for gestational age at increased risk of short stature? Am J Dis Child 1960. 1993 Mar;147(3):337–9.

500. Latal-Hajnal B, von Siebenthal K, Kovari H, Bucher HU, Largo RH. Postnatal growth in VLBW infants: significant association with neurodevelopmental outcome. J Pediatr. 2003 Aug;143(2):163–70.

501. Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Growth in the neonatal intensive care unit influences neurodevelopmental and growth outcomes of extremely low birth weight infants. Pediatrics. 2006 Apr;117(4):1253–61.

502. Hay WW, Jr MD, Lucas A, Heird WC, Ziegler E, Levin E, *et al*. Workshop Summary: Nutrition of the Extremely Low Birth Weight Infant. Pediatrics. 1999 Jan 12;104(6):1360–8.

503. Batista RFL, Silva AAM, Barbieri MA, Simões VMF, Bettiol H. Factors Associated with Height Catch-Up and Catch-Down Growth Among Schoolchildren. PLoS ONE. 2012 Mar 12;7(3):e32903.

504. Darendeliler F, Coban A, Baş F, Bundak R, Dişçi R, Sükür M, *et al*. Catch-up growth in appropriate- or small-for-gestational age preterm infants. Turk J Pediatr. 2008 Jun;50(3):207–13.

505. Bartholomeusz HH, Courchesne E, Karns CM. Relationship between head circumference and brain volume in healthy normal toddlers, children, and adults. Neuropediatrics. 2002 Oct;33(5):239–41.

506. Lindley AA, Benson JE, Grimes C, Cole TM, Herman AA. The relationship in neonates between clinically measured head circumference and brain volume estimated from head CT-scans. Early Hum Dev. 1999 Sep;56(1):17–29.

507. Peterson J, Taylor HG, Minich N, Klein N, Hack M. Subnormal head circumference in very low birth weight children: neonatal correlates and school-age consequences. Early Hum Dev. 2006 May;82(5):325–34.

508. Cheong JLY, Hunt RW, Anderson PJ, Howard K, Thompson DK, Wang HX, *et al*. Head growth in preterm infants: correlation with magnetic resonance imaging and neurodevelopmental outcome. Pediatrics. 2008 Jun;121(6):e1534–40.

509. Schum RL. Language screening in the pediatric office setting. Pediatr Clin North Am. 2007 Jun;54(3):425–36, v.

510. Nelson HD, Nygren P, Walker M, Panoscha R. Screening for Speech and Language Delay in Preschool Children: Systematic Evidence Review for the US Preventive Services Task Force. Pediatrics. 2006 Jan 2;117(2):e298–319.

511. Barre N, Morgan A, Doyle LW, Anderson PJ. Language abilities in children who were very preterm and/or very low birth weight: a meta-analysis. J Pediatr. 2011 May;158(5):766–74.e1.

512. Foster-Cohen S, Edgin JO, Champion PR, Woodward LJ. Early delayed language development in very preterm infants: evidence from the MacArthur-Bates CDI. J Child Lang. 2007 Aug;34(3):655–75.

513. Wolke D, Meyer R. Cognitive status, language attainment, and prereading skills of 6-year-old very preterm children and their peers: the Bavarian Longitudinal Study. Dev Med Child Neurol. 1999 Feb;41(2):94–109.

514. Howard K, Roberts G, Lim J, Lee KJ, Barre N, Treyvaud K, *et al*. Biological and environmental factors as predictors of language skills in very preterm children at 5 years of age. J Dev Behav Pediatr JDBP. 2011 Apr;32(3):239–49.

515. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. The Lancet. 2008 Jan 25;371(9608):261–9.

516. Singer LT, Siegel AC, Lewis B, Hawkins S, Yamashita T, Baley J. Preschool language outcomes of children with history of bronchopulmonary dysplasia and very low birth weight. J Dev Behav Pediatr JDBP. 2001 Feb;22(1):19–26.

517. McAllister L, Masel C, Tudehope D, O'Callaghan M, Mohay H, Rogers Y. Speech and language outcomes in preschool-aged survivors of neonatal intensive care. Eur J Disord Commun J Coll Speech Lang Ther Lond. 1993;28(4):383–94.

518. Janowsky JS, Nass R. Early language development in infants with cortical and subcortical perinatal brain injury. J Dev Behav Pediatr JDBP. 1987 Feb;8(1):3–7.

519. D'Souza SW, McCartney E, Nolan M, Taylor IG. Hearing, speech, and language in survivors of severe perinatal asphyxia. Arch Dis Child. 1981 Apr;56(4):245–52.

520. Gonzalez FF, Miller SP. Does perinatal asphyxia impair cognitive function without cerebral palsy? Arch Dis Child Fetal Neonatal Ed. 2006 Nov;91(6):F454–9.

521. Weisglas-Kuperus N, Baerts W, Sauer PJ. Early assessment and neurodevelopmental outcome in very low-birth-weight infants: implications for pediatric practice. Acta Paediatr Oslo Nor 1992. 1993 May;82(5):449–53.

522. Escalona SK. Babies at double hazard: early development of infants at biologic and social risk. Pediatrics. 1982 Nov;70(5):670–6.

523. Broman SH, Nichols PL, Kenndy WA. Preschool IQ: Prenatal and Early Developmental Correlates. Hillsdale, NJ: Lawrence Erlbaum; 1975.

524. Silvestrin S, Silva CH da, Hirakata VN, Goldani AAS, Silveira PP, Goldani MZ. Maternal education level and low birth weight: a meta-analysis. J Pediatr (Rio J). 2013 Aug;89(4):339–45.

525. Msall ME, Sullivan MC, Park J. Pathways of risk and resiliency after prematurity: role of socioeconomic status. In: Nosarti C, Murray RM, Hack M, editors. Neurodevelopmental Outcomes of Preterm Birth. Cambridge: Cambridge University Press; 2010.

526. Hunt JV, Cooper BA, Tooley WH. Very low birth weight infants at 8 and 11 years of age: role of neonatal illness and family status. Pediatrics. 1988 Oct;82(4):596–603.

527. Parker S, Greer S, Zuckerman B. Double jeopardy: the impact of poverty on early child development. Pediatr Clin North Am. 1988 Dec;35(6):1227–40.

528. Navaneetham K, Dharmalingam A. Utilization of maternal health care services in Southern India. Soc Sci Med. 2002 Nov;55(10):1849–69.

529. Feldman HM. Using the Language Characteristics of Clinical Populations to Understand Normal Language Development. Pediatr Clin North Am. 2007 Jun;54(3):585–607.

530. Dollaghan CA, Campbell TF, Paradise JL, Feldman HM, Janosky JE, Pitcairn DN, *et al*. Maternal education and measures of early speech and language. J Speech Lang Hear Res JSLHR. 1999 Dec;42(6):1432–43.

531. Siegel LS. Reproductive, perinatal, and environmental factors as predictors of the cognitive and language development of preterm and full-term infants. Child Dev. 1982 Aug;53(4):963–73.

532. Spittle A, Orton J, Anderson P, Boyd R, Doyle LW. Early developmental intervention programmes post-hospital discharge to prevent motor and cognitive impairments in preterm infants. Cochrane Database Syst Rev. 2012;12:CD005495.

533. Kuppala VS, Tabangin M, Haberman B, Steichen J, Yolton K. Current state of high-risk infant follow-up care in the United States: results of a national survey of academic follow-up programs. J Perinatol Off J Calif Perinat Assoc. 2012 Apr;32(4):293–8.

APPENDICES AND ACKNOWLEDGMENTS

Ms. Rafiya and Ms. Meenakshi entering the data
(Each child had a file, some of them can be
seen in the cupboard in the background)

LIST OF THE APPENDICES

***The posters which are attached in Appendix 6 are based on studies done on the study cohort of VLBW babies, but are not directly related to the study.**

In addition to looking at the Neurodevelopmental outcomes of VLBW we also looked at the prognostic significance of General Motor Assessment (Prechtl's movements). We were interested in knowing if these movements at 3 months could predict the neuro-developmental outcomes of the infants. These studies are still ongoing.

CHRISTIAN MEDICAL COLLEGE
VELLORE - 632 002, INDIA.
INSTITUTIONAL REVIEW BOARD (IRB)

Dr. George Thomas, D.Orth
Editor Indian Journal of Medical Ethics
Chairman, Ethics Committee

Dr. Shuba Kumar, PhD
Deputy Chairman, Ethics Committee

Dr. L. Jeyaseelan, MSc,PhD
Secretary, IRB

Dr. George Mathew, MS,MD,FCAMS
Chairman, Research Committee &
Principal

Dr. Gagandeep Kang, MD,PhD,FRCPath
Deputy Chairman, IRB &
Additional Vice Principal (Research)

May 1, 2010

Dr. Samuel P Oommen
Assistant Professor
Department of Developmental Pediatrics
Christian Medical College
Vellore 632 004

Sub: **FLUID Research grant project NEW PROPOSAL:**
Neurodevelopmental outcomes of Very Low birth weight infant born in a tertiary health Centre.
Dr. Samuel P Oommen, Assistant Professor, Developmental Pediatrics Unit, Dr. MC Mathew, Professor of Developmental Pediatrics, Dr. AK Jana, Dr. S. Sridhar, Neonatology , Dr. L. Jeyaseelan , Biostatistics.

Ref: IRB Min. No. 7134 dated 21.04.2010

Dear Dr. Oommen,

The Institutional Review Board (Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project entitled "Neurodevelopmental outcomes of Very Low birth weight infant born in a tertiary health Centre" on April 21, 2010.

The Committees reviewed the following documents:

1. Format for application to IRB submission
2. Patient Information Sheet and Informed Consent Form (English and Tamil)
3. Cvs of Drs. Samuel P Oommen, S. Sridhar, L. Jeyaseelan.
4. A CD containing document 1 – 3.

The following Ethics Committee members were present at the meeting held on April 21, 2010 at 10:00 am in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

Name	Qualification	Designation	Other Affiliati
Dr. George Thomas	MBBS, D.Ortho	Chairperson (IRB) & Orthopaedic Surgeon, St. Isabel Hospital, Chennai &	Non-CMC Staf

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788
e-mail : research@cmcvellore.ac.in

CHRISTIAN MEDICAL COLLEGE
VELLORE - 632 002, INDIA.
INSTITUTIONAL REVIEW BOARD (IRB)

Dr. George Thomas, D.Orth
Editor Indian Journal of Medical Ethics
Chairman, Ethics Committee

Dr. Shuba Kumar, PhD
Deputy Chairman, Ethics Committee

Dr. L. Jeyaseelan, MSc,PhD
Secretary, IRB

Dr. George Mathew, MS,MD,FCAMS
Chairman, Research Committee &
Principal

Dr. Gagandeep Kang, MD,PhD,FRCPath
Deputy Chairman, IRB &
Additional Vice Principal (Research)

		Editor, Indian Journal of Medical Ethics	
Dr. Shuba Kumar	MA, MSc, Ph.D.	Dy. Chairperson (IRB) & Social Scientist, SAMRATH, Chennai.	Non-CMC Staf
Mrs. Mary Johnson (on behalf of Mrs. Sundari Edwin)	M.Sc. (Nursing)	Nursing Superintendent, CMC.	
Mrs. Shirley David (or behalf of Mrs. Bharath Jacob)	M.Sc. (Nursing), R RM	Dean, College of Nursing, CMC.	
Dr. Jayaprakash Muliy	BSC, MBBS, MD, DrPH(Epid), DMH	Academic Officer, CMC	
Dr. P. Zachariah	MBBS, MD	Retired Professor	Non-CMC Staf
Mr. Harikrishnan	BL.	Lawyer	Non-CMC Staf
Dr. Sujith Chandy	MBBS, MD	Professor, Pharmacology Dept. CMC.	
Dr. Denny Fleming	MBBS, MD	Professor, Pharmacology Dept. CMC.	
Dr. Srinivas Babu	MSc, Ph.D.	Sr. Scientist, Neurological Sciences, CMC.	
Mrs. S. Pattabiraman	BSc, DSSA	Social Worker, Vellore	Non-CMC-Staf

We approve the project to be conducted in its presented form.

The Institutional Ethics Committee / Independent Ethics Committee expects to be informed about the progress of the project, any SAE occurring in the course of the project, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

A sum of Rs. 3, 96, 120/- is sanctioned for 2 years out of which a maximum of Rs. 1,500/- can be spent for stationery, printing, Xeroxing and computer charges (if computers used are within the institution).

Yours sincerely,

Gagandeep Kang, MD, PhD, FRCPath
Secretary, IRB

Secretary
Institutional Review Board
(Ethics Committee)
Christian Medical College
Vellore - 632 002, Tamil Nadu, India

TEL : 0416 - 2284294, 2284202 FAX : 0416 - 2262788
e-mail : research@cmcvellore.ac.in

DEFINITIONS OF THE VARIOUS CONDITIONS

FACTOR/CONDITION	DEFINITION
MATERNAL	
Gestational hypertension	BP ≥ 140/90 mmHg first detected during pregnancy, No proteinuria, postpartum (within 12 weeks) BP becomes normal
Pre-eclampsia	*Minimum criteria:* BP ≥ 140/90 mmHg after 20 weeks gestation; Proteinuria ≥ 300 mg/24 or ≥ 1+ dipstick *Increased certainty of pre-eclampsia:* BP≥ 160/110 mmg Hg Proteinuria 2g/24hours or ≥ 2+ dipstick Serum creatinine >1.2 mg/dL , Platelets < 100,000/mm^3, Microangiopathic hemolysis (increased LDH), Elevated ALT or AST, Persistent headache or other cerebral or visual disturbance Persistent epigastric pain
Eclampsia	Seizures that cannot be attributed to other causes in a woman with preeclampsia
Pre-gestational hypertension (chronic/essential/secondary)	BP ≥ 140/90 mmHg before pregnancy or Hypertension
Pre-gestational /overt Diabetes	Diabetes existing before pregnancy Overt diabetes — A diagnosis of overt diabetes can be made in women who meet any of the following criteria at their initial prenatal visit: • Fasting plasma glucose ≥126 mg/dL [7.0 mmol/L], or • HbA1C ≥6.5 percent using a standardized assay, or • Random plasma glucose ≥200 mg/dL [11.1 mmol/] that is subsequently confirmed by elevated fasting plasma glucose or A1C, as noted above
Gestational Diabetes Mellitus	Diabetes not known to be present before pregnancy Fasting plasma glucose ≥92 mg/dL [5.1 mmol/L], but <126 mg/dL [7.0 mmol/L] at any gestational age At 24 to 28 weeks of gestation: 75 gram two hour oral glucose tolerance test (GTT) with at least one abnormal result: fasting plasma glucose ≥92 mg/dL [5.1 mmol/L], but <126 mg/dL [7.0 mmol/L] or one hour ≥180 mg/dL (10.0 mmol/L) or two hour ≥153 mg/dL (8.5 mmol/L)
Preterm premature rupture of membranes (PPROM)	Rupture of membranes when the pregnancy is less than 37 completed weeks of gestation
Antepartum hemorrhage	Uterine bleeding after 20 weeks of gestation that is unrelated to labor

	and delivery
Stillbirths/ Intra-uterine death (IUD)	Fetal death after 20 weeks of gestation prior to expulsion or extraction from the mother Early still birth: death between 20 to 27 weeks gestation or late still birth ≥28 weeks gestation.
Neonatal death	Infant death after birth before 28 days of age. Early neonatal deaths occur within the first 7 days of birth, Late neonatal deaths occur between 8 and 27 days of age
Post-neonatal death	Death of infant between 28 to 365 days of age
Abortion	Termination of pregnancy, spontaneously or by intervention prior to 20 weeks of gestation or less than 500 grams birth weight
Threatened abortion	Bloody vaginal discharge or bleeding appearing through a closed cervical os during the first half of pregnancy
Induced abortion	Medical or surgical termination of pregnancy before the time of fetal viability
Anemia	Anemia in pregnant women: Hemoglobin less than11 g/dL or hematocrit < 33 percent) Severe anemia in pregnancy : Hb <7 g/dL Very severe anaemia: Hemoglobin <4 g/dL. (WHO definition)
HELLP syndrome	The diagnosis is established by the presence of preeclampsia and the following criteria: • Microangiopathic hemolytic anemia with characteristic schistocytes on blood smear • Platelet count <100,000 cells/µL • Serum lactate dehydrogenase >600 IU/L or total bilirubin >1.2 mg/dL • Serum aspartate aminotransferase (AST) >70 IU/L
Chorioamnionitis	Fever > 38^{o}C or 101.4^{o}F with accompanying ruptured membranes (*additional features*: uterine tenderness, fetal tachycardia and malodorous amniotic fluid)
Oligohydramnios	Amniotic fluid index [AFI] <5 on ultrasound examination
Polyhydramnios	Amniotic fluid index greater than 25 cm on ultrasound examination
Abrutio placenta	Premature separation of a normally implanted placenta prior to delivery of the infant confirmed by ultrasound

NEONATAL CONDITIONS – DEFINITIONS

Respiratory distress syndrome	• RR > 60, grunting expiration, in-drawing of sternum, intercostal spaces and lower ribs during inspiration, cyanosis without added oxygen, • CXR characteristic of RDS, • Surfactant used (help in corroborating not diagnosing the condition) • ABG – hypoxemia, mixed metabolic and respiratory acidosis, hypercarbia
Acidosis	Respiratory Acidosis: (pCO2 >= 60 mmHg, pH < 7.25) Metabolic Acidosis: (HCO3 < 17 mmol/L or B.E. < minus 6.0 mEq/L, pH < 7.30) {Source: Neonatal handbook}
Alkalosis	Metabolic Alkalosis: (e.g. HCO3 > 28 mmol/L or B.E. > plus 4.0 mEq/L, pH > 7.40) Respiratory alkalosis: (e.g. pCO2 < 35 mmHg, pH > 7.40) {Source: Neonatal handbook}
Hypercapnia	$PaCO_2$ > 60 mmHg (Avery)
Hypocapnia	$PaCO_2$ < 30 mmHg (Avery p.968)
Shock	• Mean BP (diastolic pressure + 1/3 systolic pressure) less than 10^{th} percentile for gestational age and postnatal age • Capillary refill time of > 3 seconds • Other signs which may help – increased heart rate (>120/min), pallor, cool peripheries, lethargy, low urine output, acidosis
Sepsis/bacterial sepsis/septicemia	• Systemic signs of infection (fever, lethargy, jitteriness, poor perfusion, accompanied by bacteremia (blood culture positive)
Risk of sepsis	Any of the following: • Prolonged rupture of membranes (>24 hours) • Prematurity (especially in association with PROM) • Preterm labour with no adequate explanation • Fetal distress without adequate explanation (fetal heart rate abnormalities especially fetal tachycardia, passage of meconium) • Maternal fever during labour (100.4^{o}F)or other evidence of infection • Foul smelling amniotic fluid (Chorioamnionitis) or malodorous baby • GBS colonization not give prophylaxis during labour, previous baby with GBS sepsis • Multiple vaginal examinations (>3) after ROM

	• Indwelling vascular catheter
Probable sepsis	Systemic signs of infection with sterile blood culture and any 2 of the following: • CRP >10 • Total WBC count <5,000/mm^3 • Absolute Neutrophil count < 1500/mm^3 • I:T ratio >0.2 • CRP >10
Fever	Rectal or axillary temperature > 100.1^{0}F or 37.8^{0}C for more than one hour
Pneumonia	Respiratory rate > 60 and signs of respiratory distress (dyspnea, grunting, coughing, nasal flaring, irregular respirations, cyanosis, intercostal and subcostal retractions, rales and decreased breath sounds with • Fever • Associated signs of sepsis • Radiologic features: hyper expansion, atelectasis, parahilar peribronchial infiltrate, consolidation, air bronchograms, pneumatoceles, pleural effusion • Tracheal aspirates or other sites (blood, CSF, urine) culture positive
Meningitis	• CRP >10 or bacteremia along with CSF findings (CSF Protein > 100 mg% and/or WBC > 20/ mm^3) • Gold std: Organism isolated from the CSF
UTI	Positive urine culture in a urine specimen obtained by suprapubic culture In the absence of bacteriuria then • Any bacterial colony count in a SPC sample with features of sepsis or failure to thrive • Colony count of 10^3/ml in a catheter sample with features of sepsis • Bacteriuria in a catheter obtained sample with features of sepsis
Renal failure	Creatinine > 1.5 g% regardless of rate of urine output
Hypoglycemia (symptomatic, asymptomatic, persistent)	Plasma glucose level < 46 mg% Persistent hypoglycemia when dextrose infusion of > 10 mg/kg/min is used
Hypocalcemia (early,late)	Calcium levels < 7 mg% .Early hypocalcemia if within less than 48 hours. Late hypocalcemia if > 48 hours
Hyponatremia	At least one reading of S. sodium less than 130 mEq/L

Hypokalemia	Serum potassium less than 3.5 mEq/l
Hyperglycemia	Plasma glucose concentration >145 mg%
Hypercalcemia	Serum calcium >11 mg%
Hypomagnesemia	Serum magnesium <1.4 mg %
Hypernatremia	At least one reading of S. Sodium more than 150 mEq/L
Hyperkalemia	Serum potassium > 6 mEq/L
Small for gestational age	Infants whose birth weight are more than 2SD below the mean or less than the 10^{th} percentile of the mean for the gestational age (using AIIMS growth charts).
Very low birth weight infants	Less than 1500 grams at birth
Extremely low birth weight infants	Less than 1000 grams at birth
Prematurity	Infant whose birth occurs before 37 completed weeks (before 260^{th} day) following onset of the last menstrual period
Fetal distress/ Non reassuring fetal status	Three tier diagnosis based on the ACOG guidelines published by Macones et al in **OBSTETRICS & GYNECOLOGY** VOL. 112, NO. 3, SEPTEMBER 2008 p.661-68
Apnea of prematurity	Cessation of breathing for more than 20 seconds with accompanying bradycardia (HR<100/min)in infants born before 37 weeks
Diaphragmatic hernia	Prenatal diagnosis by antenatal ultrasounds Postnatal – Respiratory distress, decreased breath sounds, scaphoid abdomen, signs of mediastinal shift X-ray features of diaphragmatic hernia
Transient tachypnea of newborn	• Radiologic features: streaky, perihilar opacities, lung over inflation • Respiratory distress – grunting, nasal flaring, retractions, tachypnea (>60/min) within few hours after birth in term or near term infant. Requirement of oxygen of FiO_2 of <40% • Clinical and radiologic features resolve within 72 hours • All other causes of respiratory distress have been ruled out
Persistent pulmonary hypertension or Persistent fetal circulation	• Respiratory distress and cyanosis within 12 hours • Clinical features: RV impulse, single second heart sound and/or systolic murmur consistent with tricuspid regurgitation • A 10% or greater difference in oxygen saturation between the preductal (right upper extremity) and postductal(lower limbs) in the absence of structural heart disease suggests PPHN • ECHO findings Chest X-ray may be normal • Exclude all other causes of respiratory distress

Pneumothorax	• Sudden onset of respiratory distress with or without signs of circulatory compromise • Radiologic features of pneumothorax
Chronic lung disease of prematurity or Bronchopulmonary dysplasia	Treatment with FiO_2 greater than 0.21 for at least 28 days PLUS failure of room air challenge test at 36 weeks post-menstrual age Radiologic features of BPD on chest X-ray
Patent ductus arteriosus	• Systolic murmur • Hyperdynamic precordium • Wide pulse pressure, bounding pulse • Worsening respiratory status • ECHO- Diameter of LA : Aortic root > 1.4
Osteopenia of prematurity	• Serum phosphorus < 4 mg% • Alkaline phosphatase > 800 IU • Radiologic features: decreased lucency of bones with or without epiphyseal changes • Clinical features: failure to wean from ventilator, hypotonia, decreased linear growth with sustained head growth, widened cranial sutures, frontal bossing, craniotables, large anterior fontanel, rachitic rosary, enlarged wrists/ knees/ ankles, Harrison's groove
Late onset metabolic acidosis	Metabolic acidosis after 4 days

Perinatal asphyxia	• Umbilical cord ABG or or peripheral ABG within 1 hour: pH ≤ 7.0 or ABE ≥ -12
	• APGAR ≤ 5 at 5 minutes
	• History of acute perinatal event
	  ▪ Intrapartum fetal distress
	  ▪ Cord prolapsed
	  ▪ Placental abruption
	  ▪ Uterine rupture/dehiscence
	• If outborn – resuscitated for >10 mins/did not cry at birth with signs of encephalopathy

HIE (1,2,3)	Features of Perinatal asphyxia plus encephalopathy as defined by Sarnat and Sarnat staging (see table below)
Intraventricular hemorrhage (1,2,3,4)	Using Papile's grading using Ultrasound findings
Periventricular leukomalacia	Infarction of deep white matter adjacent to the trigones and frontal horns of the lateral ventricles Staged using de Vries classification based on the ultrasound findings
Retinopathy of prematurity	Vasoproliferative disorder of the retina in premature babies caused due to interruption in normal vasculogenesis and due to abnormal neo-vascularization in extra-retinal tissues, finally resulting in retinal

	detachment and scarring of the macula, and significant visual loss. Graded using International Classification of ROP
NEC (1,2,3)	Using modified Bell's criteria
Recurrent feed intolerance (without NEC)	Feed intolerance - (abdominal distension, large aspirate - >50% of feeds in the previous 6 hours, vomiting) necessitating discontinuing feeds and starting anti-reflux medications
Anemia	Hb < 9 g% any time during the nursery stay
Polycythemia	Hct > 65% or Hb > 22 g%
Thrombocytopenia	Platelet count < 150,000/mm^3
Hyperbilirubinemia (physiologic or pathologic)	• Clinical jaundice in the first 24 hours of life • Serum TB conc. Increasing more than 0.2 mg%/hour or 5mg%/day • S. TB exceeding the 95^{th} percentile for age in hours • Direct bilirubin exceeding 1.5-2 mg% • Clinical jaundice persisting for more than 2 weeks in full term infant • Total bilirubin more than 15 mg%
Meconium aspiration syndrome	Respiratory distress in a infant born through meconium stained amniotic fluid Radiologic signs of air trapping, atelecasis, patchy opacities

Sarnat Clinical Stages of Perinatal Hypoxic Ischemic Brain Injury

	State 1	**Stage 2**	**Stage 3**
Level of Consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Neuromuscular Control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex Reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong; low threshold	Weak; incomplete; high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic Function	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable; often unequal; poor light reflex
Heart Rate	Tachycardia	Bradycardia	Variable
Bronchial and Salivary Secretions	Sparse	Profuse	Variable
GI Motility	Normal or decreased	Increased; diarrhea	Variable
Seizures	None	Common; focal or multifocal	Uncommon (excluding decerebration)
EEG Findings	Normal (awake)	Early: low-voltage continuous delta and theta Later: periodic pattern (awake) Seizures: focal 1-to 1-Hz spike-and-wave	Early: periodic pattern with Isopotential phases Later: totally isopotential
Duration	1-3 days	2-14	Hours to weeks

Classification of periventricular leukomalacia, according to de Vries

Grade	Definition
I	Transient periventricular echodensities persisting for 7 days or longer
II	Periventricular echodensities evolving into small localized frontoparietal cystic lesions
III	Periventricular densities, evolving into extensive periventricular cystic lesions
IV	Densities extending into the deep white matter evolving into extensive cystic lesions

Grading of the severity of germinal matrix-intraventricular haemorrhages from US scan, adapted from Volpe

Grade	Extension of haemorrhage
I	Germinal matrix haemorrhage with minimal or no intraventricular haemorrhage (<10% of ventricular area in parasagittal view)
II	Intraventricular haemorrhage (10–50% of ventricular area in parasagittal view)
III	Intraventricular haemorrhage (>50% of ventricular area in parasagittal view; usually distends lateral ventricle)
Separate notion	Periventricular echodensity (location and extent)

Bell clinical staging of NEC:

Stage I: Suspect: Infant with suggestive clinical signs but Xray non-diagnostic.
Stage II: Definite: Infant with pneumatosis intestinalis. (IIA: mildly ill - IIB: moderately ill (acidosis, thrombocytopenia or ascites))
Stage III: Advanced. (IIIA: Critical with impending perforation - IIIB: Critical with proven perforation)

REFERENCES

1. Remington JS. Infectious Diseases of the Fetus and Newborn Infant. Elsevier Saunders; 2006. 1313 p.

2. Rennie JM. Rennie & Roberton's Textbook of Neonatology. Elsevier Health Sciences; 2012. 5294 p.

3. Taeusch HW, Ballard RA, Gleason CA, Avery ME. Avery's Diseases of the Newborn. Elsevier Health Sciences; 2005. 1675 p.

4. Cloherty JP, Eichenwald EC, Stark AR. Manual of Neonatal Care. Lippincott Williams & Wilkins; 2008. 792 p.

5. Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycaemia. BMJ. 1988 Nov 19;297(6659):1304–8.

6. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: A clinical and electroencephalographic study. Arch Neurol. 1976 Oct 1;33(10):696–705.

7. Kliegman RM, Walsh MC. Neonatal necrotizing enterocolitis: Pathogenesis, classification, and spectrum of illness. Curr Probl Pediatr. 1987 Apr;17(4):219–88.

8. Papile LA, Burstein J, Burstein R, Koffler H. Incidence and evolution of subependymal and intraventricular hemorrhage: a study of infants with birth weights less than 1,500 gm. J Pediatr. 1978 Apr;92(4):529–34.

9. Bell MJ, Ternberg JL, Feigin RD, Keating JP, Marshall R, Barton L, et al. Neonatal necrotizing enterocolitis. Therapeutic decisions based upon clinical staging. Ann Surg. 1978 Jan;187(1):1–7.

10. De Vries LS, Eken P, Dubowitz LM. The spectrum of leukomalacia using cranial ultrasound. Behav Brain Res. 1992 Jul 31;49(1):1–6.

11. International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. Arch Ophthalmol. 2005 Jul;123(7):991–9.

12. American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 106: Intrapartum fetal heart rate monitoring: nomenclature, interpretation, and general management principles. Obstet Gynecol. 2009 Jul;114(1):192–202.

13. Cunningham F, Leveno K, Bloom S, Hauth J, Gilstrap L, Wenstrom K. Williams Obstetrics: 22nd Edition: 22nd Edition. McGraw Hill Professional; 2005. 1457 p.

14. Volpe JJ. Neurology of the Newborn. Elsevier Health Sciences; 2008. 1109 p.

INFORMATION BROCHURE AND CONSENT FORM

Dear parents of _____

As you know, your baby was born preterm (born before the due date) and therefore required to be in the Nursery for many weeks. Now that your baby is stable, putting on weight and is feeding well, he/she is being discharged. However babies who are born prematurely (especially those who have a birth weight of less than 1.5 k.g) will need special care during their first 2 years and constant monitoring after that.

What are the problems which premature babies can have after leaving Nursery?

Although many preterm babies grow to be normal children, some preterm infants can have complications.

The usual complications which premature babies can have:

1. The development of a preterm infant can be slower than children who are born with normal birth weight. Some of these children will require help in walking, speaking, and understanding.
2. Hearing problems: Hearing can be affected in babies who are born with a low birth weight. When your baby was in the nursery his/ her hearing would have been checked. However if you feel that your child is not responding to sounds or to your voice please show the child to the doctors.
3. Eye problems: Some preterm babies can have eye problems. If detected early, this can be treated. All preterm babies have eye check up in the Nursery. If the baby's eyes were not checked, he will have to be shown to the Ophthalmologist at Schell eye hospital, Vellore.
4. Some premature infants can have seizures and will require medicine.
5. In some preterm infants brain may be affected and they may develop cerebral palsy which will require long term treatment.

How can you help your baby's development?

Even in those who seem to be standing and walking normally, there may be minor impairments in their language, understanding and other functions. Regularly showing your baby to the doctors can help in early detection and immediate treatment of complications.

How can I help my child develop to his best potential?

In order to regularly follow up and help infants who are born with a low birth weight we have a special clinic for Very Low Birth weight babies on Wednesday mornings in the Developmental Pediatrics Unit. We will see these babies till they are 2 years old. When problems are detected, your child will then receive help from a dedicated team of doctors, psychologists and occupational therapists in the Very Low birth Infants Clinic and the Developmental Pediatrics Unit.

When your child is discharged from the Nursery, the doctors will inform when you have to bring the child to the Very Low Birth weight infant clinic. You will be seen by Dr. Sridhar or Dr. Niranjan Thomas (Neonatologists), Dr. Samuel P Oommen (Developmental specialist) and the Occupational therapist Ms. Hima in the clinic. Your child's development will be monitored and appropriate help will be given. Sometimes you may require to see a specialist (if he has any hearing or eye problems, if there are seizures), in which case the doctors will refer you to the concerned specialist.

How frequently should I bring my child?

This depends on your child's developmental progress. For the first 3 months it is advisable to bring your child at least once a month and after that, once in 2 months will be sufficient. However please ask the doctors about the date of your next visit. At one year of age and at 1 ½ years of age we will check the child's complete development using a test called the Griffith Mental Developmental Scales. This will tell us how the child is developing as compared to other children of the same age.

Will my child require any special blood tests or brain scans?

All preterm babies will require ultrasound scans of the brain at 6 weeks of age. After that if your child is developing normally there is no need for any tests. However if the doctor feels that there is some problem with your child's development, he will require special blood tests and brain scans.

If you would like to take part in this regular follow up program as mentioned above for the next **1 ½ years** kindly sign in attached form. You are welcome to stop coming at any time, but for reasons mentioned above, we would encourage you to come regularly.

If you have clarifications you can contact any one of the following doctors:

1. Dr. Samuel P Oommen, Developmental Pediatrics Unit (above the Well baby clinic) Phone: 0416 228 3260
2. Dr. Sridhar, Neonatology, Phone: 0416 228 3311
3. Dr. Niranjan Thomas, Neonatology, Phone: 0416 228 3311
4. Ms. Hima, Occupational Therapist, Neonatology
   Phone: 0416 228 3311

Details about your appointment are written in the blue colour card (Very Low Birth weight clinic card) which is given at the time of discharge from the nursery.

CONSENT FORM

I, _____

(printed name of parent/guardian signing the form)

- confirm that I have read (or the information has been read to me) and understood the written informed consent form for the parent/guardian for study. Study conduct and purpose has been explained to me.
- confirm that I have been given enough of time to consider participation in the study, I have had the opportunity to ask questions and I have been provided with satisfactory answers.

By signing this consent form I voluntarily agree to bring my child for regular developmental monitoring and take part in the early intervention programme as advised, during the study period.

I understand that I can withdraw my consent at any time without having to give any reason. This will not have any impact on my child's right to receive the medical care he/she is entitled to.

Child's name: _____

Hospital Number: _____

Signature of parent/guardian: _____

Date:_____

Note: only the signature of a legal guardian is valid.

Person obtaining consent:

Dr. Samuel P Oommen, Developmental Pediatrics Unit
(or) Dr. S. Sridhar (or) Dr. Niranjan Thomas (or) Ms. Hima (Neonatology)

Signature: _____

Date: _____
CMC Hospital, Vellore

நீங்கள் எப்பொழுது வேண்டுமானாலும் வருவதை நிறுத்திக் கொள்ளலாம், ஆனால் மேலே குறிப்பிட்ட காரணங்களினால் நீங்கள் தொடர்ந்து வர நாங்கள் உங்களை ஊக்கப்படுத்துகிறோம்.

உங்களுக்கு ஏதாவது சந்தேகம் இருந்தால், நீங்கள் கீழே கொடுக்கப் பட்டுள்ள ஏதாவது ஒரு மருத்துவரை அனுகலாம்:-

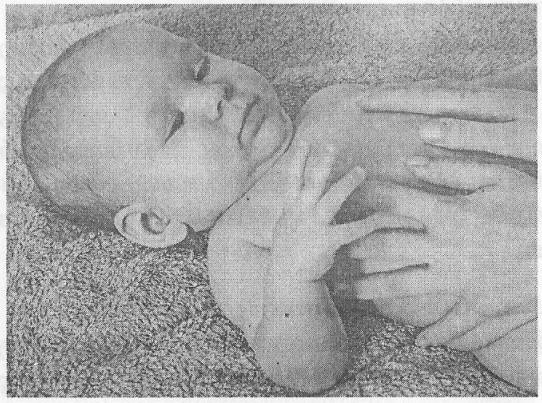
1. டாக்டர் சாமுவேல் பி.உம்மன், மனவளர்ச்சிப் பிரிவு (குழந்தைகள் நல் வாழ்வு மற்றும் நோய் தடுப்பு ஊசி பிரிவிற்கு மேல் தளத்தில் உள்ளது)
   தொலைபேசி : 0416 - 2283260

2. டாக்டர் ஸ்ரீதர், பச்சிளம் குழந்தைகள் பிரிவு
   தொலைபேசி : 0416 - 2283311

3. டாக்டர் நிரஞ்சன், பச்சிளம் குழந்தைகள் பிரிவு
   தொலைபேசி : 0416 - 2283311

4. திருமதி ஹீமா, பயிற்சியாளர், பச்சிளம் குழந்தைகள் பிரிவு
   தொலைபேசி : 0416 - 2283311

நீங்கள் இளம் குழந்தைகள் பிரிவிலிருந்து வீடு திரும்பும் முன் கொடுக்கப் பட்டுள்ள நீல அட்டையில் எப்பொழுது (மிகவும் எடை குறைவுள்ள கிளினிக்கின் அட்டை) வரவேண்டும் என்கிற விவரம் எழுதப்பட்டுள்ளது.



தகவல் குறிப்பு மற்றும் ஒப்புதல் படிவம்

அன்புள்ள் பெற்றோராகிய _____

உங்கள் குழந்தை குறை பிரசவத்தில் பிறந்ததினால் இளம் குழந்தைகளுக்கான பிரிவில் பலவாரங்கள் மருத்துவமனையில் சேர்க்கப் பட்டிருந்ததை நீங்கள் அறிவீர்கள். உங்கள் குழந்தை திடமாக, எடை கூடி மற்றும் நன்றாக பால் குடித்த பிறகு வீட்டிற்கு அனுப்புவார்கள். இது போன்று குறை பிரசவத்தில் பிறந்த குழந்தைகளுக்கு (அதிலும் பிறந்த எடை 1.5 கிலோவுக்கும் கீழ் இருக்கும் குழந்தைகளை)முதல் இரண்டு வருடங்கள் தொடர்ந்து அதிக கவனத்தோடு கவனித்து மேலும் அதற்கு பிறகும் கண்காணித்து வரவேண்டும்.

இதுபோன்று குறை பிரசவத்தில் பிறந்த அநேக குழந்தைகள் மற்ற குழந்தைகள் போல் இயல்பு நிலையுடன் வளரும், ஆனாலும் சில குழந்தைகள் சில விளைவுகளை சந்திக்க நேரிடும்.

வழக்கமாக இது போன்ற குழந்தைகளுக்கு ஏற்படும் விளைவுகள்:-

1. குறை பிரசவத்தில் பிறந்த குழந்தைகளின் வளர்ச்சி மற்ற சரியான எடையுடன் பிறந்த குழந்தைகளின் வளர்ச்சியைப் போல் இல்லாமல் மெதுவாக காணப்படும். இது போன்ற சில குழந்தைகளுக்கு, நடப்பதிற்கும், பேசுவதிற்கும் மற்றும் புரிந்து கொள்ளுவதற்கும் உதவி தேவைப்படுகிறது

2. கேட்பதில் பிரச்சனை : எடை குறைவாக பிறக்கும் குழந்தைகளுக்கு, கேட்பதில் பாதிப்பு ஏற்பட வாய்ப்பு உள்ளது. உங்கள் குழந்தை, இளம் குழந்தைகளுக்கான பிரிவில் சேர்க்கப்பட்டிருக்கும் பொழுது அவன்/அவளுடைய கேட்கும் தன்மையை பரிசோதித்திருப்பார்கள். எனினும், உங்கள் குழந்தை சத்தத்திற்கு செவி கொடுக்கவில்லை என்றாலோ அல்லது உங்களுடைய குரலுக்கு பதில் கொடுக்கவில்லை என்றாலோ, தயவு செய்து மருத்துவரிடம் காண்பிக்கவும்.

3. கண்ணில் பிரச்சனை : சில குழந்தைகளுக்கு கண்ணில் பிரச்சனை ஏற்படும், சீக்கிரமாக கண்டுபிடித்தால் இதற்கு சிகிச்சை அளிக்கலாம்.

இளம் குழந்தைகளுக்கான பிரிவில் சேர்க்கப்பட்டிருக்கும், குறை பிரசவத்தில் பிறந்த எல்லா குழந்தைகளுக்கும் கண் பரிசோதனை செய்யப்படும். அப்படி குழந்தையின் கண் பரிசோதிக்கப் படவில்லை என்றால், சி.எம்.சி., வேலூர் மருத்துவ மனையைச் சேர்ந்த கண் டாக்டரிடம் காண்பிக்க வேண்டும்.

4. சில குறைபிரசவத்தில் பிறந்த குழந்தைகளுக்கு வலிப்பு வரும், அதற்கு மருத்து கொடுப்பது அவசியம்.

5. குறை பிரசவத்தில் பிறந்த சில குழந்தைகளுக்கு மூளையில் பாதிப்பு ஏற்படுவதால் அவர்களுக்கு மூளை வாதம் ஏற்படும் அதற்கு நீண்டகால சிகிச்சை தேவைப்படுகிறது.

உங்கள் குழந்தையின் வளர்ச்சிக்கு நீங்கள் எவ்வாறு உதவ முடியும்?

சாதாரணமாக நன்றாக நின்று மற்றும் நடக்கும் குழந்தைகளுக்கு புரிந்து கொள்ளுதல், மொழி மற்றும் வேறு செயல்களில் சில குறைபாடுகள் ஏற்பட வாய்ப்புள்ளது. தொடர்ந்து மருத்துவரிடம் காண்பிப்பதன் மூலம் சீக்கிரமாக இக்குறைகளை கண்டுபிடித்து அதற்கு சிகிச்சை அளித்து அதனால் வரும் விளைவுகளை தடுக்கலாம்.

நான் என்னுடைய குழந்தையை சிறந்த திறமையுடன் வளர்க்க எவ்வாறு உதவ முடியும்?

எடை குறைவாக பிறந்த குழந்தைகளை தொடர்ந்து கண்காணித்து உதவ ஒரு சிறப்பு கிளினிக் ஒவ்வொரு புதன்கிழமையும் காலையில் குழந்தைகள் மனவளர்ச்சிப் பிரிவில் நடைபெறும். இந்த குழந்தைகளுக்கு இரண்டு வயது ஆகும் வரை நாங்கள் பார்ப்போம். குழந்தைகளுக்கு பிரச்சனை ஏதாவது இருக்கிறது என்று கண்டுபிடித்தால், மருத்துவர்கள், மனோதத்துவ நிபுணர்கள் மற்றும் பயிற்சியாளர்கள் மூலம் மிகவும் எடை குறையுடன் பிறந்த குழந்தைகளின் கிளினிக்கில், குழந்தைகள் மன வளர்ச்சிப் பிரிவில் உதவி அளிக்கப்படும்.

உங்கள் குழந்தை இளம் குழந்தைகளுக்கான பிரிவிலிருந்து வீடு திரும்பும் முன் மருத்துவர்கள், நீங்கள் எப்பொழுது, மிகவும் எடை குறைவுடன் பிறந்த குழந்தைகளின் கிளினிக்குக்கு கொண்டுவர

வேண்டும் என்று கூறுவார்கள். இந்த கிளினிக்கில் டாக்டர் ஸ்ரீதர் அல்லது டாக்டர். நிரஞ்சன் தாமஸ் (இளம் குழந்தைகளுக்கான டாக்டர்), டாக்டர் சாமுவேல் உம்மன் (மன வளர்ச்சி நிபுணர்) மற்றும் ஹீமா (பயிற்சியாளர்) ஆகியோர் பார்ப்பார்கள். உங்கள் குழந்தையின் வளர்ச்சி கண் காணிக்கப்பட்டு அதற்கேற்ப உதவி அளிக்கப்படும். சில நேரங்களில் சிறப்பு மருத்துவரை காண நேரிடும் (அதாவது உங்கள் குழந்தைக்கு கேட்பதிலோ, பார்ப்பதிலோ பிரச்சனை இருந்தால் மற்றும் இழுப்பு ஏற்பட்டால்). அப்பொழுது மருத்துவர்கள் அந்த பிரச்சனைக்கு ஏற்ற சிறப்பு மருத்துவரைக்காண ஆலோசனை கொடுப்பார்கள்.

நான் என் குழந்தையை அடிக்கடி கூட்டிக் கொண்டு வர வேண்டுமா?

இது உங்கள் குழந்தையின் வளர்ச்சியைப் பொருத்தது. முதல் 3 மாதத்திற்கு, மாதம் ஒரு முறையாவது கூட்டிக்கொண்டு வருவது நல்லது, பிறகு இரண்டு மாதத்திற்கு ஒரு முறை வந்தால் போதும். ஆனாலும், நீங்கள் திரும்பி வரவேண்டிய நாளை டாக்டரிடம் கேட்டுச் செல்லவும். ஒன்று மற்றும் ஒன்றரை வயதில் குழந்தையின் வளர்ச்சியை ஒரு சோதனை மூலம் அறிவோம். இந்த பரிசோதனையின் மூலம், அதே வயதைச் சார்ந்த சாதாரணமாக உள்ள குழந்தைகளுக்கும் மற்ற குழந்தைகளுக்கும் உள்ள வளர்ச்சியை ஒப்பிட முடியும்.

என் குழந்தைக்கு சிறப்பு இரத்தப் பரிசோதனை அல்லது மூளைக்கு ஸ்கேன் எதாவது எடுக்க அவசியப்படுமா?

குறை பிரசவத்தில் பிறந்த எல்லா குழந்தைகளுக்கும் ஆறுவாரத்தில் மூளைக்கு ஸ்கேன் எடுக்கப்படும். அதற்கு பிறகு உங்கள் குழந்தையின் வளர்ச்சி மற்ற சராசரி குழந்தையின் வளர்ச்சியைப் போல் இருந்தால் மற்ற எந்த சோதனையும் தேவைப்படாது. ஆனால் மருத்துவர், உங்கள் குழந்தையின் வளர்ச்சியில் ஏதாவது பிரச்சனை என்று நினைத்தால், குழந்தைக்கு சிறப்பு இரத்தப் பரிசோதனை மற்றும் மூளை ஸ்கேன் எடுக்க அவசியப்படும்.

மேலே குறிப்பிட்ட வண்ணம், உங்கள் குழந்தை ஒன்றரை ஆண்டுக்கு இங்கு தொடர்ந்து கண்காணிக்கப்பட நீங்கள் விரும்பினால், இதனுடன் இணைக்கப்பட்டுள்ள ஒப்புதல் படிவத்தில் கையெழுத்திடவும்.

ஒப்புதல் படிவம்

நான் _____
(பெற்றோர் அல்லது பாதுகாப்பாளரின் பெயர் அச்சடிக்கப்பட்ட கையெழுத்துப் படிவம்)

- நான் இந்த ஒப்புதல் படிவத்தில் எழுதியுள்ள பரிசோதனை தகவலை நன்றாக படித்து புரிந்து கொண்டேன் (அல்லது இதில் எழுதியுள்ள தகவல் எனக்கு வாசித்து காண்பிக்கப் பட்டது) என்று உறுதி அளிக்கிறேன். இந்த பரிசோதனைக்கான குறிக்கோளும் நடத்துதலும் எனக்கு விளக்கப்பட்டது.

- எனக்கு இந்த பரிசோதனையில் பங்கு பெற தீர்மானம் செய்வதற்கு போதிய நேரம் அளிக்கப்பட்டது, மேலும் இதைப் பற்றி நான் கேள்விகள் கேட்க வாய்ப்பும் அதற்கு திருப்தி அளிக்கிற வகையில் பதிலும் அளிக்கப்பட்டது.

நான் எந்த விளக்கமும் தராமல் இந்த பரிசோதனையிலிருந்து எப்பொழுது வேண்டுமானாலும் விலகிக் கொள்ளலாம் என் அறிகிறேன். இதனால், என் குழந்தைக்கு கிடைக்க வேண்டிய மருத்துவ உதவியில் எந்த பாதிப்பும் இல்லை என அறிகிறேன்.

குழந்தையின் பெயர் : _____

சி.எம்.சி. அட்டை எண் : _____

பெற்றோர்/பாதுகாப்பாளரின் கையொப்பம் : _____

தேதி : _____

குறிப்பு : குழந்தையின் சட்டப்படியான பாதுகாப்பாளரின்கையொப்பமே செல்லும்

ஒப்புதல் படிவத்தின் உரிமையாளர்:
டாக்டர் சாமுவேல் பி.உம்மன், மன வளர்ச்சிப் பரிவு (அல்லது)
டாக்டர் ஸ்ரீதர் (அ) டாக்டர் நிரஞ்சன் தாமஸ் (அ) திருமதி. ஹீமா, பச்சிளம் குழந்தைகள் பிரிவு.

கையொப்பம்: _____

தேதி: _____
சி.எம்.சி, மருத்துவமனை, வேலூர்.

PROTOCOL FOR LBW STUDY
NICU PHASE

PERSONAL DETAILS

	Name	Hosp. No	Age	Occupation	Literacy : (illit/ <5/5-8/9-10/+2/grad or PG/prof)
Mother					
Father					

Address:

Phone Nos.:

Baby's H. No:

Date of Birth:

SEX: B/G

PAST OBSTETRIC HISTORY

Years of Marriage:

Consanguinity: Y/N

Gravida: 1/2/3/>3
Para: 0/1/2/3/>3
Living: 0/1/2/3/>3
Neo/END: 0/1/2/3/>3

Abortions: 0/1/2/>2
Still births: 0/1/2/>2
IUDs: 0/1/2/>2

	Year	Sex	GA	Delivery (n/I/C)	Weight	ANC	Neonatal	Currently
1.								
2.								
3.								
4.								
5.								
6.								
				N-normal I-Instrum C-Cesar				

Maternal Risk Factors (previous pregnancy):

Second stage complications:

Family History

PRESENT PREGNANCY.

AN visits: <3 / >3 (booked)

LMP Not known **Gest. Age (Weeks)**

MATERNAL RISK FACTORS (PRESENT PREGNANCY)

Elderly/Teenaged primi: Y/N **Grand Multipara: Y/N** **Height <140: Y/N**

Threatened abortion/Spotting: Y/N

Infertility treated: Y/N

Pregestational Thyroid disorder: Y/N **Thyroid disorder during pregnancy: Y/N**

Max. TSH **Treatment**

Multifetal pregnancy: Y/N **Amnion** **Chorion**

Drugs: Y/N **Details:**

Infections: Y/N **Details:**

Pregestational Hypertension: Y/N

PIH: Y/N **Max. BP:** **Complications: Y/N**

Albuminuria (≥3+) y/N **Seizures: Y/N** **Bleeding: Y/N** **HELLP: Y/N**

Diabetes: Pregestational DM: Y/N **GDM: Y/N**

HbA1C:<7/>7 **Treatment for GDM : Diet/OHA/Insulin**

Fetal Movements:

Ultrasound scans:

Date	GA	ANOMALY	AFI	DOPPLER	IUGR

Summary of above:

Fetal anomaly: Y/N **if yes then Head (size, structure): N/AbN** **Limbs: Y/N** **Viscera: Y/N**
Growth: N/AbN
AFI: N/AbN

Antepartum Bleeding: Y/N Details:

Antepartum steroids: 0/1/2

Drugs during pregnancy: Y/N Details:

INVESTIGATIONS

Hb <10/>10	Blood Group	Rh	ICT at
HIV: Y/N	Urine alb	VDRL : Y/N	HBsAg:Y/N
GTT: N/abN	AC/PC	HbA_1C	Uric acid
Creat	UTI Urine c/s – organism: Y/N		
LFT			
Other obst.comp Y/N			

LABOUR		
Duration of labour : <6 /6-12 />12		
Spontaneous Induced – Indication	Oxytocin + -	Others
Vaginal examinations after ROM:		
Membranes ruptured: Spontaneously Artificially: Hrs before delivery : <12 />12h		
Amniotic Meconium stained: Nil/Gr 1/Gr 2/Gr 3 Foul smelling Chorioamnionitis (fever)		
Sedation in previous 6 hrs before delivery: Y/N Sedative:		
Drugs in labour (specify): Antibiotics/ Tocolytics/Mg		
CTG record: Nature of foetal distress : N/NRFS/FD/Nd		
DELIVERY **Type: Normal/CS/ Breech/Forceps/Suction** **Indication (if abnormal):**		
Placenta: N/AbN **If Abn:** Anatomic defect: Retroplacental clot Infarction; Calcification: **Umbilical** Blood vessels:		
Maternal Complications during labour and delivery: Y/N If yes give details:		
BABY		
Born (time and day) **Inborn/Outborn**		
Birth weight (checked within 4 hours):		
Length	Head circumference after 48 hours	

Gestational age:	LMP:	Dubowitz /clinical:	
APGAR SCORE: 1 min	5 min.	10 min	20 min
Umbilical Cord pH:	**bicarb:**	**Base ex:**	

RESUSCITATION DETAILS

IPPV: Y/N

Chest compression

Drugs: NS/adrenalin/naloxone **Ventilation**: Y/N

EXAMINATION

AF	Ears	Eyes
Mouth	Throat	Heart
Abdomen	Femorals	Skin
Hips	Anus	Genitalia
Scalp	Summary: Normal examination: Y/N (Abnormality in any of above)	

NEONATAL MORBIDITY

Respiratory distress (Tachypnoea, Grunting, Retractions,apnea): Yes/No
Time of onset:
Diagnosis: Treatment:
X-ray:
ABG at onset:
Duration:
VENTILATION: Y/N Duration: Type
Surfactant therapy; PIP: PEEP:
Diagnosis: RDS/TTN/Pneumothorax/ Pneumothorax/MAS

Shock: Y/N
Time of onset:
Diagnosis:
Duration

Septicemia: Y/N Onset of first symptom: Poor feeding Length Y / N
Fever Y / N clinical features Y / N DURATION OF ABX
Organism
Duration:
Diagnosis: CRP pos/neg
Dx: SEPSIS/MENINGITIS/SEPTIC ARTHRITIS/OTHERS

Renal failure : Y / N
Maximum creatinine
Dialysis
Diagnosis :

Anemia/Polycythemia

Thrombocytosis/Thrombocytopenia

Seizures : Y/N

Diagnosis:

EEG

Jaundice (>8 mg%): Y/N
If yes:
Highest bilirubin:
Treatment: Phototherapy/Exchange transfusion:

Hypoglycemia: Y/N
If yes
Seizure: Y/N **Onset:**
Duration: <24 h? **Max dextrose reqd. g/kg/d:**

Hypocalcemia: Y/N
If yes:
Seizures: Y/N **Onset:**
Duration: < 24 h

Electrolyte imbalances:
Hypernatremia: Y/N **Hyponatremia: Y/N**

Hyperkalemia: Y/N **Hypokalemia: Y/N**

PDA: Y/N
If yes:
CCF: Y/N
Day of Onset
Treatment: Indo/Ibupr./Ligation

Necrotising enterocolitis: Y/N
If yes:
Stage: 0/1/2/3
Surgery: Y/N

NEUROSONOGRAM :Normal/ ICH/ PVL

1.
2.
3.

IF ICH then Grade: 1/2/3/4
If PVL : Flare/Cystic/ Non cystic
VP shunt : Y/N

CNS infection: Y/N
If yes:
Onset:
CSF cells CSF sugar CSF protein
CSF culture
Treatment given

Other complications: Y/N
Onset
Duration
Treatment

Eye Involved: Y/N
Etiology: ROP/ Cataract/ Others

Hearing difficulty: Passed/Referred

NEUROLOGIC EXAMINATION (ATNAT): Normal or mild/moderate/severe

AT DISCHARGE: Duration of stay:
Discharge Weight:
Discharge length:
Discharge HC:

Feeding at discharge:
DBF/ others

AMIEL TISON NEUROLOGICAL EXAMINATION SHEET (0 - 18+ months)

NAME:	Hosp. No:	DOB:	Notes:
Mother's Name:	EDC:	B wt. Gest. Age:	
Father's Name:	Sex:	Contact no.:	

Visit	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
Exmn. Date															
Corrected Gest. Age															
Chron. Age															

1. GROWTH (N ± 2SD (0); <2SD (2); >2SD (2)

GROWTH	A	B	C	D	E	F	G	H	I	J	K	L	M	N	F
Head circumference															
Weight															
Height															
HC : Ht: Y/N															
VP Shunt															
A.F: Open=0 Closed =2 Closed >9m=0															

CRANIOFACIAL EXAMINATION															
SUTURES **Edge- edge:0** **Overlapping:1** **Squamous:** **Frontal:** **Coronal:** **Sagittal:** **Occipital**	**A**														
SKULL SHAPE **Normal(0):** **Abnormal (1):** **Describe**															
PALATE **Flat (0):** **High arched-1**															

2. SOCIAL INTERACTIONS & NEUROSENSORY EXAMINATION

SEIZURES: Absent-0, Focal/Short:1 Prolonged -2, Febrile –X	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
ALERTNESS & ATTENTION Normal age: 0 Mod. Deficit:1 Sev. Deficit: 2															
HYPER-EXCITABILITY No signs: 0 Compatible: 1 Uncontrolled:2															

NEUROSENSORY EXAMINATION

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
HEARING (Normal:0. Mod. HL:1; Severe HL:2)															
VISION - Fix & Track: Easy to obtain: 0 Difficult: 1 No response: 2															
NYSTAGMUS Absent : 0 Present: 2															
EYE MOVEMENTS Synchrnous: 0 Erratic: 2															
STRABISMUS - Absent : 0: Present : 1															
SUNSET SIGN - Absent : 0 Present: 2															

Diagnostic tests:
Hearing (Audiogram, BERA, Tympanogram):
Vision (VEP)

MOTOR DEVELOPMENTAL MILESTONES

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
Head Control: **<4 months: 0** **5-6 months: 1** **After 6 m: 2**															
SITTING: **< 9 m: 0** **10-12 m: 1** **>12m: 2**															
WALKING: **<18 m : 0** **18-24 m: 1** **>24m :2**															
CUBE in CUP: **<10 m: 0** **11-14 m: 1** **>14m: 2**															
Grasp pellet **<12 m: 0** **13-15 m: 1** **>15m: 2**															
3-cube tower: **<21 m: 0** **22-24 m: 1** **>24m: 2**															
Turns over															
Reach & Mouth															
Knee-hand															

3. PASSIVE MUSCLE TONE

		A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
ADDUCTOR ANGLE																
Asymmetry (R>L/R<L) Present: X																
POPLITEAL ANGLE	R															
	L															
Slow Dorsi-Flexion	R															
	L															
Rapid Dorsiflex.	R															
	L															

		0-3 m	4-6 months	7-9 months	10-18 months	19-24 months
Adductor angle	**0**	≥40	≥70	≥100	≥110	≥110
	1	≤30	≤60	80-90	80-100	80-100
	2	**No resistance** (NR)	NR	≤70 **or** NR	≤70	≤70 or **NR = 2**
	X				NR	
Popliteal angle (Left or right)	**0**	≥80	≥90	≥110	≥110	≥110
	1	≤70	≤80	90-100	90-100	90-100
	2	NR	NR	≤80 **or** NR	≤80	≤80 or **NR = 2**
	X				NR	
Slow dorsiflexion (R or L)	**0**	NOT SCORED	≤80	≤80	≤80	≤80
	1		90-100	90-100	90-100	90-100
	2		≥110	≥110	≥110	≥110
Rapid dorsiflexion	**0**	NOT SCORED	Identical **(I)**	Identical	Identical	Identical
	1		Phasic stretch **(P)**	Phasic stretch	Phasic stretch	Phasic stretch
	2		Tonic stretch **(T)**	Tonic stretch	Tonic stretch	Tonic stretch
SCARF SIGN	**0**	EBM,ECM	ECM, EPM	ECM, EPM	ECM, EPM	ECM, EPM
	1		EBM			
	2	EPM, NR	NR	EBM, NR	EBM	EBM, NR
	X				NR	

EBM: elbow before midline; ECM: elbow crosses midline; EPM: Elbow well past midline No resistance - NR

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
Candlestick Absent:0 Present:X															
FINGERS MOVE: 0 CLOSED: 1 Thumb Inactive/ Cortical :2	R														
	L														
SCARF Sign (See above for score)	R														
	L														

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O
Dorsal extension Absent to moderate: **0** Opisthoton:**2**															
Ventral flexion Moderate to absent: **0** Excessive: **2**															
Comparison of curvature Flex≥Extn:0 Flex<Extn:1 Ragdoll: 2															
RIGID diffusely None: 0 Lead pipe:2															
Asymmetry of tone Absent:0 R>L or R<L: 1															

4. MOTOR ACTIVITY															
FACIAL EXPRESSIONS Symmetrical.(0) Insufficient (1)	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
DROOLING Absent::0; 0-1y:X Present:1 > 1yr															
FACIAL PARALYSIS Absent (0) Present (2)															
TONGUE FASCICULATIONS Absent (0) Present (2)															
LIMBS															
SPONTANEOUS MOVEMENTS Coordinated and varied (0) Insuff/uncoord/ stereotypic(1) Absent/uncoordinated (2)															
INVOLUNTARY MOVEM. Absent (0) Present (2) Describe:															
Dystonia - Absent (0) Present (2)															

DEEP TENDON & CUTANEOUS REFLEXES															
BICIPITAL REFLEX Normal:0 Brisk:1 Clonus/Absent:2	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
PATELLAR JERK Normal:0 Brisk:1 Clonus/Absent:2															
PLANTAR REFLEX Flexion: 0 Extension < 1Yr.:X Extension > 1 yr:2															

5. PRIMITIVE REFLEXES - Except ATNR, rest not scored after 9 months (*DNS> 9m*)

SUCKING:***DNS>9m*** Present (0) Insufficient(1) Absent (2)															
MORO- ***DNS>9m*** **0:Presnt<3&Absnt>6** **2:Absnt<3&Presnt>6** **X:Prsnt or absnt 3-6**															
GRASP- ***DNS>9m*** **0:Presnt<3&Absnt>6** **2:Absnt<3&Presnt>6** **X:Prsnt or absnt 3-6**															
WALKING ***DNS>9m*** **0:Presnt<3&Absnt>6** **2:Absnt<3&Presnt>6** **X:Prsnt or absnt 3-6**															
ATNR **0: Absent > 6 months** **2: Present > 6 mnths** **X:Prsnt or absnt 0-6**															
R/L asymmetry (which side)															

Moro, Grasp, Walking reflex score 2 only if other signs of CNS depression are present.

POSTURAL REACTIONS (Scored after 6 months)															
Lateral Propping# **0: Present > 6 m** **1:Incomplete > 9 m** **2:Absent>9 m** **X: Incom/Absnt 6-9m**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**	**K**	**L**	**M**	**N**	**O**
	R														
	L														
PARACHUTE **0: Present > 6 m** **1:Incomplete > 9 m** **2:Absent>9 m** **X: Incom/Absnt 6-9m**	**R**														
	L														

#Lateral propping done while baby is sitting

Qualitative Abnormalities in Gross Motor Function and Acquired Deformities															
Holding head behind axis Abnormal. Absent: 0 Abnormal. Present: X															
Poor head control Abnormal. Absent: 0 Abnormal. present X															
Sitting (score >6m)* Normally: 0 Falls forward/back (**1**:6-12/, **2:** 12-18)															
Standing position Normal standing:0 Opisthotonos(2)															
Lower limb Deformity absent (0) Scissoring (2)															

*** Falls forward (global hypotonia); Falls backward (hypertonia of extensor muscles)**

ROP Screening (Schell)	
6 weeks Neuro-sonogram (Radiology)	
Others (Hearing etc.)	
Any significant medical concerns,	

INTERPRETATION OF ATNA (0 - 6 MONTHS)

(Severe: score of 2 in ≥ four of five sections / Moderate: mostly 1, some scores of 2 are acceptable)

Date of visit									
Corrected Gest. Age									
1. Head growth (HC, growth profile, fontanels, sutures) (Severe 2; Mod. 1)									
2. Social interactions (alertness & attention, visual tracing, excitability)									
3. Passive muscle tone (limbs and trunk) (Severe 2; Mod. 1)									
4. Motor activity (quality and quantity) (Severe 2; Mod. 1)									
5. Primitive reflexes (absent /insufficient, especially sucking) (Severe 2; Mod. 1)									
FINAL INTERPRETATION OF NEUROLOGIC STATUS (Normal/moderate/Severe)									

INTERPRETATION OF ATNA (7 - 9 MONTHS)

(Severe: score of 2 in ≥ four of six sections
Moderate: Scores of 1 in at least 4 of six sections, some scores of 2 are acceptable)

Date of visit					
Corrected Gest. Age					
1. Head growth (HC, growth profile, fontanels, sutures) (Severe 2; Moderate 1)					
2. Social interactions (alertness & attention, visual tracing, excitability) (Severe 2; Moderate 1)					
3. Passive muscle tone (limbs and trunk) (Severe 2; Moderate 1)					
4. Motor activity (quality and quantity) (Severe 2; Moderate 1)					
5. Head control (scored according to age of acquisition) (Severe 2; Moderate 1)					
6. Evident ATNR (Severe 2; Moderate 0)					
FINAL INTERPRETATION OF NEUROLOGIC STATUS (Normal/moderate/Severe)					

INTERPRETATION OF ATNA (10 - 24 MONTHS)

Severe deficit: a score of 2 in at least 6 of 7 sections, including inability to walk.

Moderate abnormality: a score of 1 in at least 5 of 7 sections, some scores of 2 are acceptable.

Minor abnormality: a score of 1 in at least 3 of 7 sections

Date of visit									
Corrected Gest. Age									
1. Head growth (insufficient HC, all structures abnormal or an isolated abnormality with squamous sutures) (Severe - 2; Moderate - 1 or 2; Minor - 0 or 1)									
2. Social interactions (alertness & attention, visual tracing, excitability) (Severe - 2; Moderate - 1 ; Minor - 0)									
3. Passive muscle tone **Trunk Imbalance (Sev:2, Mod:1, Minor:1)** **Stretch reflex in limbs (Sev:2, Mod:1/2, Minor:1)** **Hypotonia or rigidity (Severe:2, Mod &, Minor:0)**									
4. Involuntary movements (Severe - 2; Moderate & Minor - 0)									
5. Parachute reaction (scored according to age of acquisition) (Severe - 2; Moderate - 1 ; Minor - 0)									
6. Gross motor skills (scored according to age of acquisition) **Head control** **Sitting position** **(Severe - 2; Moderate - 1 ; Minor - 0)**									
7. Independent walking (Severe - 1; Moderate - 1 ; Minor - 0/1)									
FINAL INTERPRETATION OF NEUROLOGIC STATUS									

GRIFFITHS MENTAL DEVELOPMENT SCALES – EXTENDED REVISED (GMDS-ER)

for testing babies and young children from birth to eight years

RECORD BOOK

Child's name: [redacted] Gender: M/F FEMALE

Address: 17, [illegible] STREET

[illegible]

Telephone: [illegible]

Examiner: MRS. HANNAH GRACE

Referral source: NOVEL STUDY

Date of first assessment:	2012	year	APRIL (4)	month	20	day
Date of birth:	2010	year	9	month	4	day
Chronological age:	1	year	07	month	16	day

CORRECTED GESTATIONAL AGE - 18 MONTHS, 2 DAYS.

Age at first testing: 19 months 16 days

..... months

Published by HOGREFE – THE TEST AGENCY, 4630 Burgner House, Kingsgate, Oxford Business Park South, Oxford, UK.

HOGREFE
THE TEST AGENCY

Child's name: ..... Date of birth: 4/9/10

Gestation: 33+5 weeks Birth weight: 1.16 kg Delivery: CESAREAN SECTION

Position in family: FIRST CHILD Age of siblings: –

Mother's name: Mrs. **Father's name:** MR.

Age: 22 Nationality: INDIAN Age: 29 Nationality: INDIAN

Occupation: 12TH STD. / HOUSEWIFE Occupation: MTECH / PROFESSOR

Relevant history: PRIMI GRAVIDA. MOTHER HAD GESTATIONAL DIABETES,
HAD EARLY ONSET IUGR. DATE OF BIRTH: 4/9/10
ABNORMAL DOPPLER - S/D RATIO - 6 DATE OF ASSESSMENT - 20/4/12

Reason for referral: NOVEL STUDY ASSESSMENT AT 18 MONTHS
PARENTS HAVE NO CONCERN.

Vision: NORMAL Hearing: NORMAL

Summary of test results

Subscales	A	B	C	D	E	F
Section I (months)*	12	12	12	12	12	
Section II (months)*	9.4	6.78	6.34	4.57	8.84	
Section III (items x 2)*						
Section IV (items x 2)*	21.4	18.78	18.31	16.57	20.84	
TOTAL RAW SCORE† for subscales	21.4	18.78	18.31	16.57	20.84	
Percentile score	92	45	77	45	87	
Confidence range (RAW SCORE)	92	45	43	45	49	
z-score (SUB QUOTIENT)	123	98	112	98	118	
Age equivalent score (months)	21	19	18	17	21	
Date of test						
Chronological age	19 MONTHS 20 DAYS					
Corrected age	18 MONTHS 2 DAYS					

GQ#	108

*Use MA in months for Sections I and II; items x 2 for Sections III and IV.
†Add 'months' of MA for Sections I and II to 'items x 2' for Sections III and IV.
#Obtain the GQ raw score by taking the ***average*** of the ***raw scores*** for the six subscales.

Clinical observations/behaviour/diagnosis: .....
Pleasant child
Cooperative even though slightly apprehensive
Parents were very motivated

SECTION I:

Year 1 Months of age (approx.)		Subscale A Locomotor	Response		Subscale B Personal-Social	Response		Subscale C Hearing and Language	Response
1	1	Lifts chin when prone		1	Regards person – fleeting glance		1	Startled by sound R	
	2	Pushes with feet against examiner's hands		2	Quieted when picked up R		2	Listens to bell	
	3	Holds head erect for few seconds		3	Enjoys bath R		3	Vocalisation other than crying	
	4	Kicks vigorously		4	Visually recognises mother		4	Cooing – one syllable R	
	5	Lifts head up when prone		5	Follows moving persons with eyes		5	Makes two different sounds	
	6	Active in bath – kicks R		6	Smiles		6	Listens to music	
	7	Rolls from side to back		7	Vocalises when talked to		7	Searches for sound with eyes	
2	8	Back firm when held in sitting position		8	Returns examiner's glance with smiling or cooing		8	Searches for sound with head movements	
	9	Lifts head when in dorsal position		9	Friendly to strangers R		9	Laughs aloud R	
	10	Lifts head, shoulders and chest when prone		10	Expresses 2 or more recognisable emotions, e.g. pleasure, fear, sadness, distress or anger		10	Talks (babbles) to persons	
3	11	Holds head erect continuously		11	Stops crying when talked to R		11	Coos or stops crying on hearing music	
	12	Lifts head and shoulders, dorsal		12	Frolics when played with		12	Turns head deliberately to bell	
4	13	Crawling reaction 1: draws up knees, etc		13	Regards mirror image 1: looks at		13	Makes 4 different sounds	
	14	Rolls from side to side via dorsal position		14	Resists adult who tries playfully to take ring		14	Listens to tuning fork	
	15	Sits with slight support		15	Turns head to person talking or singing		15	Responds when called	
	16	Plays with own toes R		16	Holds a spoon		16	Manipulates bell	
5	17	Stepping reaction 1: dancing movements		17	Anticipatory movements when about to be lifted		17	Shouts for attention R	
	18	Sits alone for a short time		18	Knows strangers from familiar friends		18	2-syllable babble	
	19	Crawling reaction 2: can turn around when left on floor (pivoting)		19	Prompt reaction to situation, e.g. at table, waiting to be fed		19	Listens to conversations	
6	20	Crawling reaction 3: tries vigorously to crawl		20	Manipulates cup or spoon in play		20	Rings bell	
	21	Can roll from stomach to back (or from back to stomach)		21	Displeased if toy is taken		21	Looks at pictures for a few seconds	
	22	Crawling reaction 4: makes some progress forwards or backwards		22	Holds and bites biscuits, rusks, ice-cream wafers, etc		22	Singing tones R	
7	23	Stepping reaction 2: one foot in front of the other		23	Interested in small children other than own siblings R		23	One word (mama, dada, etc) definite and meaningful	
	24	Can be left sitting on floor R		24	Helps to hold cup or mug for drinking		24	Babbled phrase: 4+ syllables R	
	25	'Stands' when held up		25	Pulls off hat		25	Likes rhymes and jingles	
8	26	Sits well in a chair		26	Drinks from any open cup or mug if held to lips		26	Knows own name	
	27	Crawling reaction 5: creeps on hands and knees, etc		27	Stretches to be taken up		27	Babbled monologue when alone	
9	28	Pulls self up by furniture	✓	28	Finger feeds (thumb and forefinger), e.g. sultanas, 'Smarties', etc R		28	Shakes head for 'No'	
	29	Can stand holding on to furniture	✓	29	Picks up and drinks from lidded and closed feeder-cup unaided R	✓	29	Uses 2 definite words	✓
10	30	Side-steps round inside of cot or playpen holding rails	✓	30	Responds socially to mirror image 2: smiles at or plays with	✓	30	Reacts to music vocally	✓
	31	Climbs on a low ledge or step	✓	31	Gives affection R	✓	31	Short babbled sentences	✓
11	32	Can walk when led	✓	32	Plays very simple interactive games with others R	✓	32	Uses 3 words	✓
	33	Climbs stairs (up)	✓	33	Plays with cup, spoon and saucer	✓	33	Identifies objects (1)	✓
	34	Likes pushing pram, toy, horse, etc R	✓	34	Waves bye-bye R	✓	34	Tries definitely to sing R	✓
12	35	Stands alone	✓	35	Shows an interest in the activities of others R	✓	35	Identifies objects (2)	✓
		SECTION I: A Total items = ... Months credit: (35/35) × 12 = 12			SECTION I: B Total items = ... Months credit: (35/35) × 12 = 12			SECTION I: C Total items = ... Months credit: (35/35) × 12 = 12	

FIRST YEAR

Subscale D Eye and Hand Co-ordination		Response	Subscale E Performance		Response	Notes and Comments
1	Follows moving light with eyes		1	Reflex grasp of examiner's finger		
2	Looks at bell-ring or toy momentarily		2	Reacts to paper 1: generalised physical movements		
3	Looks steadily at bell-ring held still		3	Energetic arm movements		
4	Follows moving bell-ring horizontally		4	Hand goes to mouth R		
5	Follows moving bell-ring vertically		5	Holds rod		
6	Glances from one object to another		6	Plays with own fingers R		
7	Follows moving bell-ring in a circle		7	Reacts to paper 2: vigorous head-turning		
8	Watches objects pulled along by string		8	Resists withdrawal of rod		
9	Grasps ring when given		9	Looks at yellow box on table		
10	Visually explores new environment		10	Clasps cube put in hand and holds it		
11	Reaches for ring and grasps		11	Shows interest in box		
12	Carries ring to mouth		12	Drops first cube for second		
13	Clutches at dangling ring		13	Reacts to paper 3: pulls it away		
14	Secures dangling ring		14	Takes cube or toy from table		
15	Hands explore table surface		15	Holds 2 cubes		
16	Plays with ring – shaking, banging, etc		16	Manipulates cube or toy		
17	Reaches for and picks up string		17	Grasps box		
18	Looks for fallen object		18	Passes toy or cube from hand to hand		
19	Strikes one object with another		19	Reacts to paper 4: reaches for and takes		
20	Secures ring by means of string		20	Manipulates 2 objects at once		
21	Watches examiner scribble		21	Reacts to paper 5: plays with – tears, crumples		
22	Forefinger and thumb partly specialised		22	Lifts cup inverted over toy		
23	Dangles ring by string		23	Drops one cube for third		
24	Fine prehension		24	Rattles box		
25	Interested in motor car R		25	Lifts lid off box		
26	Likes holding little toys		26	Finds toy under cup		
27	Throws objects (record how child throws)		27	Tries to take cubes out of box		
28	Thumb opposition complete		28	Holds third cube		
29	Can hold pencil as if to mark on paper		29	Clicks 2 bricks together (in imitation) TX2		
30	Can point with index finger	✓	30	Manipulates box, lid and both cubes	✓	
31	Plays pulling ring or toy by string	✓	31	Removes both cubes from box	✓	
32	Uses pencil on paper a little	✓	32	Unwraps and finds toy or cube	✓	
33	Preference for one hand R	✓	33	One-circle board TX2	✓	
34	Plays pushing little cars along	✓	34	Removes lids and both bricks from the other 2 boxes	✓	
35	Can hold 4 cubes in hands at once	✓	35	Puts 2 bricks back into any one box when encouraged to do so	✓	
	SECTION I: D Total items = ... Months credit: (35/35) × 12 = 12			SECTION I: E Total items = ... Months credit: (35/35) × 12 = 12		

SECTION II:

Year 2 Months of age (approx.)		Subscale A Locomotor	Response		Subscale B Personal-Social	Response		Subscale C Hearing and Language	Response
	1	Climbs into low chair	✓	1	Claps hands in imitation	✓	1	Uses 4 words	✓
13	2	Walks alone	✓	2	Puts small objects in and out of cup in play	✓	2	Uses 5 words	✓
	3	Kneels on floor or chair	✓	3	Tries to help dressing – arms into coat, etc R	✓	3	Identifies objects (3)	✓
14	4	Stoops	✓	4	Obeys simple requests – 'give me the cup' R	✓	4	Uses 6 or 7 words	✓
	5	Trots about well	✓	5	Can hold open cup for drinking R	✓	5	Enjoys picture book	✓
15	6	Can walk backwards	✓	6	Tries to turn doorknob or handle R	✓	6	Identifies objects (4)	✓
	7	Climbs to stand on a chair	✓	7	Shows shoes	✓	7	Uses 9 words	✓
16	8	Climbs stairs – up and down R	✓	8	Uses spoon himself: spills some R	X	8	Names objects (1)	
	9	Walks backwards pulling toy on string	✓	9	Likes adult to show book	✓	9	Long babbled sentences – some words clear	X
17	10	Can seat self at table	✓	10	Parts of doll's body (1) – hands, hair, feet, eyes, nose and mouth	✓	10	Names objects (2)	X
18	11	Walks upstairs	✓	11	Cleanliness – indicates when wet or dirty	✓	11	Uses 12 words	X
19	12	Runs	✓	12	Uses spoon well	X	12	Uses 20+ words	X
	13	Can kick a ball (tennis ball size)	✓	13	Manages cup well – half full	X	13	Identifies objects (5 or 6)	X
20	14	Goes alone on stairs	✓	14	Can open a door	✓	14	Uses word combinations	✓
21	15	Walks up and down stairs	✓	15	Can take off shoes and socks	✓	15	Identifies objects (7)	X
22	16	Jumps	X	16	Parts of doll's body (2) – hands, hair, feet, eyes, nose and mouth	✓	16	Listens to stories	X
23	17	Can jump off a step	X	17	Parts of doll's body (3) – hands, hair, feet, eyes, nose and mouth	✓	17	Names objects (3)	X
24	18	Jumps off one step – both feet together and land together	X	18	Helps actively to dress or undress R	X	18	Identifies objects (8)	X
	19	Walks upstairs – one foot on each step, adult manner *	X	19	Parts of doll's body (4) – hands, hair, feet, eyes, nose and mouth	X	19	Names objects (4)	X
				20	Puts away toys or objects when encouraged to do so R	X	20	Names objects (5)	X
				21	Asks for things at table by name – at least 2 articles of food or drink R	X	21	Uses sentences of 4+ syllables	
				22	Begins to co-operate in play with other children R	X			
				23	At table uses spoon and fork together without help *R	X			
		SECTION II: A Total items = 15 Months credit: (15/19) × 12 = 9.47			*SECTION II: B Total items = 13 Months credit: (13/23) × 12 = 6.78			SECTION II: C Total items = 8 Months credit: 8 /21) × 12 = 4.57	

*Note: Please refer to the revised instructions which provide the administration instructions for items AII.19, BII.23 and EII.18 (see Administration Manual, page 24).

SECOND YEAR

	Subscale D Eye and Hand Co-ordination	Response		Subscale E Performance	Response
1	Plays at rolling a ball	✓	1	Two-circle board (1 in)	✓
2	Places one lid, box or brick upon another	✓	2	Puts bricks in and out of boxes in play	✓
3	Pulls cloth to get toy	X	3	Square board Tx2	✓
4	Scribbles more freely	✓	4	Two-circle board (2 in)	✓
5	Constructive play with boxes or other materials	✓	5	Can put lid back on box	✓
6	Can throw a ball towards person	✓	6	Three-hole board (1 in) Tx2	✓
7	Tower of 3 bricks	✓	7	Circle and square board together Tx2	✓
8	Tower of 4 bricks	X	8	Three-hole board (2 in)	✓
9	Enjoys vigorous straight scribble	✓	9	Puts 2 bricks into one box, and the lid on; all complete	✓
10	Can transfer cube from one container to another	✓	10	Three-hole board (3 in)	✓
11	Can pour water from one container to another	✓	11	Circle and square boards rotated	X
12	Tower of 5 bricks	X	12	Two-circle board rotated	✓
13	Makes a brick or toy 'walk'	X	13	Puts 2 bricks in each box	✓
14	Circular scribble (in imitation)	✓	14	Three-hole board rotated (2 in)	✓
15	Tower of 6 bricks	X	15	Three-hole board rotated (3 in)	X
16	Throws ball into basket	X	16	Puts lids on all 3 filled boxes	X
17	Train of 3 (bricks)	X	17	Can open screw toy	X
18	Perpendicular stroke	X	18	Reassembles screw toy *	X
19	Horizontal stroke	X	19	Returns 9 bricks to box and replaces lid within 60 secs (Time ..... secs)	X
	SECTION II: D Total items = 10 Months credit: (10/19) × 12 = 7.89			SECTION II: E Total items = 14 Months credit: (14/19) × 12 = 8.84	

Objects	IDENTIFIED	NAMED
Ball	✓	
Spoon	✓	
Brush	✓	
Car	✓	
Doll	✓	✓
Cup	X	
Sock	X	
Brick	X	
TOTAL	5	1

Toileting questions (unscored Subscale B)

A: Bowel control complete
Is this child usually quite bowel-continent and reliable as regards this function, except for an occasional mishap?
YES/NO

B: Bladder control by day
Is this child usually reliably dry by day in regard to bladder function, but not necessarily at night?
YES/NO

Total months credit: SECTION II
(Total items passed / 101) × 12 = months

ARE WE OVERESTIMATING THE INCIDENCE OF RETINOPATHY OF PREMATURITY ?
RESULTS OF A LONGITUDINAL COHORT OF VLBW BABIES

Saban Horo[1], Samuel P Oommen[2], Santhanam Sridhar[3], Niranjan Thomas[3], Manish Kumar[3], Atanu Kumar Jana[3]
Departments of Ophthalmology[1], Developmental Pediatrics[2] & Neonatology[3], Christian Medical College, Vellore, India.

BACKGROUND

▪Retinopathy of prematurity is a potential cause of blindness in preterms and low birth weight infants

▪Wide variation in incidence of ROP reported across different centers in India

▪ There are multiple risk factors associated with ROP.

AIMS AND OBJECTIVES

- To estimate the incidence of ROP in a cohort of premature, VLBW babies
- To identify risk factors that are significantly associated with ROP

METHODOLOGY

▪ **Study design:** Prospective, follow up of a cohort of VLBW babies

▪ **Setting:** Tertiary Neonatal center in South India

▪ **Period:** September 2010- March 2013

▪ **Inclusion Criteria:** Infants ≤34 weeks GA and/or ≤ 1500 g birth weight.

Statistical Analysis:

▪ Antenatal and perinatal factors and morbidities were collected prospectively

▪ Association between the variables/ risk factors and the outcome (ROP) were calculated.

▪ Univariate analysis was done using Chi-square and Odds ratio.

▪ Risk factors that were significant on univariate analysis were entered into logistic regression to assess their independent effect.

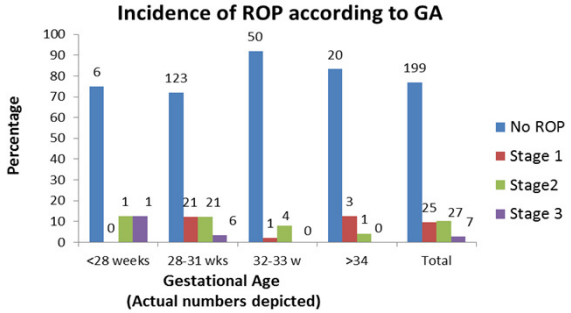
▪ Analyses were done using SPSS 16.0

RESULTS

- **258** infants were examined as per the protocol
- Mean Birth weight was **1190g (SD±184)**
- Mean Gestational age was **31 weeks (SD± 2.14)**
- **59 (22.9%)** infants had ROP
  32 (54.4%) were boys and
  27 (45.7%) were girls
- **Stage 1 ROP**: 25 babies (42.7%)

  Stage 2 ROP: 27 babies (45.7%)

  Stage 3 ROP: 7 babies (11.9%) of ***which 3 babies required Laser photocoagulation.***
- In the other babies ROP regressed spontaneously.
- In Univariate analysis (table below) the following variables showed significant association with ROP – Gestational age, Birth weight, Septicemia, Respiratory complications, Hypotension and Low sodium
- On Multivariate analysis septicemia alone was independently associated with ROP. There was a trend to develop ROP with decreasing birth weight and gestational age.



HIGHLIGHT OF THE STUDY

▪ **Incidence of ROP requiring treatment is only 3/59 (5%) which is much less than the incidence from other centers in India** [1-4]

CONCLUSIONS

▪ **This cohort was predominantly inborn and therefore incidence of ROP is likely to differ with quality of neonatal care**

▪ **The etiology and risk factors for developing ROP may be heterogeneous in various parts of country.**

Variable	Univariate analysis		Multivariate analysis	
	p-Value	Unadjusted odds (95% CI)	p-Value	Adjusted odds (95% CI)
Gestational Age	**0.004**	**0.81 (0.69-0.94)**	**0.028**	**0.813 (0.676-0.978)**
Birth weight	**0.001**	**0.997 (0.996-0.999)**	**0.088**	**0.998 (0.996-1.000)**
Septicemia	**0.001**	**3.097 (1.52-6.31)**	**0.004**	**3.12 (1.45-6.69)**
Respiratory Compl.	**0.057**	1.766 (0.97-3.18)	**0.14**	**1.65 (0.85-7.405)**
Hypotension	0.003	2.797 (1.407-5.58)	**0.29**	**1.53 (0.7-7.35)**
Abnormal sodium	0.003	2.57 (1.36-4.8)	**0.47**	**1.32 (0.64-2.74)**
Sex	0.489	1.229 (**0.685-2.20**)	**0.67**	**1.15 (0.61-2.21)**

REFERENCES

1.. Chaudhari S, Patwardhan V, Vaidya U, Kadam S, Kamat A. Retinopathy of prematurity in a tertiary care center--incidence, risk factors and outcome. Indian Pediatr. 2009 Mar;46(3):219–24.
2. Vinekar A, Dogra MR, Sangtam T, Narang A, Gupta A. Retinopathy of prematurity in Asian Indian babies weighing greater than 1250 grams at birth: ten year data from a tertiary care center in a developing country. Indian J Ophthalmol. 2007 Oct;55(5):331–6.
3. Gupta VP, Dhaliwal U, Sharma R, Gupta P, Rohatgi J. Retinopathy of prematurity--risk factors. Indian J Pediatr. 2004 Oct;71(10):887–92.
4. Kumar P, Sankar MJ, Deorari A, Azad R, Chandra P, Agarwal R, et al. Risk factors for severe retinopathy of prematurity in preterm low birth weight neonates. Indian J Pediatr. 2011 Jul;78(7):812–6.

GENERAL MOVEMENT ASSESSMENT IN VERY LOW BIRTH WEIGHT INFANTS IN SOUTH INDIA AND MOTOR OUTCOMES AT ONE YEAR

Hima B John*, Lars Adde***, Samuel P Oommen**, Toril Fjørtoft***, Ragnhild Støen*** Niranjan Thomas* *Department of Neonatology,**Developmental Paediatrics Unit, Christian Medical College, Vellore, ***Department of Laboratory Medicine, Women's and Trondheim and St. Olavs University Hospital, Trondheim, Norway.

BACKGROUND

- Very Low Birth weight infants are at risk of adverse neurodevelopmental outcomes[1]
- Early identification is important to offer intervention programs to minimize the functional consequences of cerebral palsy (CP)[2]
- Assessment of general movements (GMA) appears to have the potential for predicting the development of CP with a high degree of certainty at an early stage[3,4]
- There are no studies which have looked at GMs in Indian infants

AIMS AND OBJECTIVES

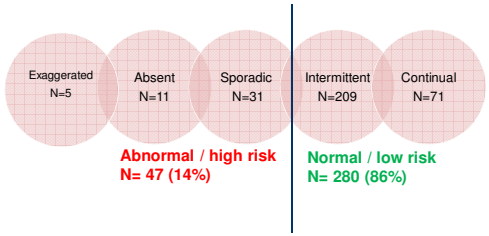
- To evaluate the applicability of GMA in Indian infants
- To evaluate the association between GMA and motor function at one year.

METHODOLOGY

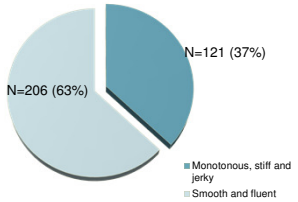
- **Design:** Prospective, observational cohort study
- **Setting:** Tertiary care neonatal unit in south India.
- **Participants and Methods:**
- Video recordings of a cohort of 327 VLBW babies born in Christian Medical College, Vellore was taken between 9-15 weeks post term age (The Fidgety movements period) and analyzed according to Assessment of Motor Repertoire (AMR) by two observers masked for the infants' medical history.
- Fidgety movements (FMs) were classified as abnormal if absent, sporadic or exaggerated and as normal if continuously or intermittently present. Movement character was classified as normal if smooth and fluent and abnormal if monotonous, stiff or jerky. Motor function at 1 year corrected age was assessed using the Peabody Developmental Motor Scales (PDMS-2)
- **Statistical Analysis:** The variables Gross Motor Quotient (GMQ), Fine Motor Quotient (FMQ) and Total Motor Quotient (TMQ) were transformed using logarithmic transformation in parallel with reversing the data due to zero or below zero values. Hence, to get mean values, statistics were performed using a General linear model and the GMQ, FMQ and TMQ Reversed lg10 were used to get p- values.

RESULTS

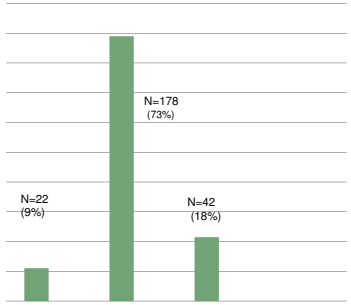
General Movement Assessment



Global Movement Character



PDMS-2 Total Motor Quotient



- There was a significant correlation between normal and abnormal FMs and the Gross Motor Quotient of the PDMS-2 (p=0.006)
- Presence of FMs and presence of smooth and fluent movement character when compared to abnormal FMs and monotonous, jerky and stiff movement character was significantly associated with higher scores in the Fine Motor and Total Motor Quotient (p=0.007)
- When FMs were present, smooth and fluent movement character was significantly associated with a higher score on Gross Motor Quotient of the PDMS-2 (p=0.005).
- The sensitivity of the test was calculated to be 22.7% and the specificity is 88.2%. The positive predictive value is 16% and the negative predictive value is 92%.

CONCLUSION

❖This study documents applicability of General Movement Assessment in a low-resource setting in south India and contributes to GMA validity.
❖There is a significant association between general movements and motor function assessed by the PDMS-2 at one year.
❖ Longer follow-up studies are needed to evaluate the neurodevelopmental outcomes and relationship to GMA in this population.

REFERENCES

1. Escobar GJ, Littenberg B, Pettiti DB. Outcome among surviving very low birth weight infants: a metaanalysis. Arch Dis Child 1991; 66: 204-211
2. O'Brien F, Roth S, Stewart A, Rifkin L, Rushe T, Wyatt J. The Neurodevelopmental progress of infants less than 33 weeks into adolescence. Arch Dis Child 2004; 89: 207-211
3. Prechtl HF, Einspieler C, Cioni G, Bos AF, Ferrari F, Sontheimer D. An early marker for neurological deficits after perinatal brain lesions. Lancet. 1997;349(9062):1361-3.
4. Darsaklis V, Snider LM, Majnemer A, Mazer B. Predictive validity of Prechtl's Method on the Qualitative Assessment of General Movements: a systematic review of the evidence. Dev Med Child Neurol. 2011;53(10):896-906.

General movement assessment (GMA) in very low birth weight infants in south India

Lars Adde, Niranjan Thomas, Hima B John,
Samuel P Oommen, Toril Fjørtoft, Ragnhild Støen

Christian Medical College, Vellore, India
Norwegian University of Science and Technology, Trondheim, Norway
St. Olavs University Hospital, Trondheim, Norway

Quality of general movements are associated with cerebral palsy (1,2)

Cerebral palsy status: yes/no

GMA needs higher quality evidence (3)

- Larger, heterogeneous and representative samples
- Studies originated outside Europe to expand generalizability to other parts of the world

AND

The fact that GMA is done purely through observation of video recordings should make it feasible for clinical use in low resource settings

The aim of this study

To evaluate the applicability of GMA during the fidgety movement's period in India

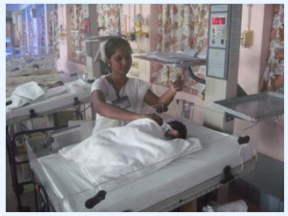
And to describe fidgety movements and movement character in a cohort of Very Low Birth Weight (VLBW) infants in India

The study site

Christian Medical College, Vellore, India (Tamil Nadu)

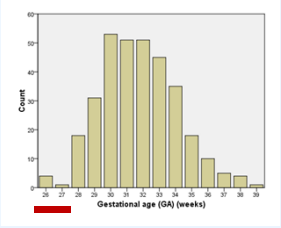
Participants

345 VLBW infants (<1500 g) (170 boys and 157 girls) from a two year cohort were included from the NICU

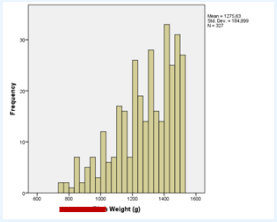


Participants

- 327 out of 345 had corresponding video recordings
- Mean gestational age 32 (range 26-39) weeks
- Mean birth weight 1275 grams (range 760-1500)



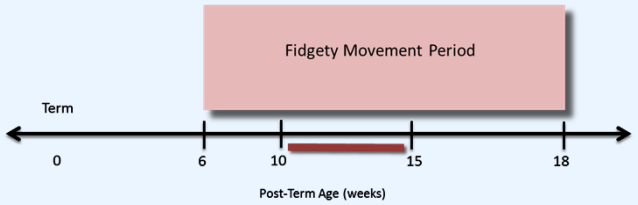
N=5



N=29

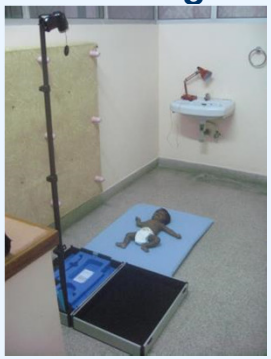
Methods – video recordings

All participants (n=327) were video recorded during the fidgety movement's period



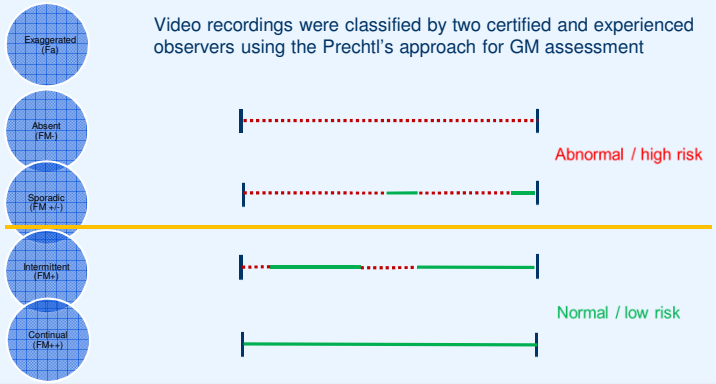
Methods – video recordings

Video recordings were performed using a standard mobile set-up



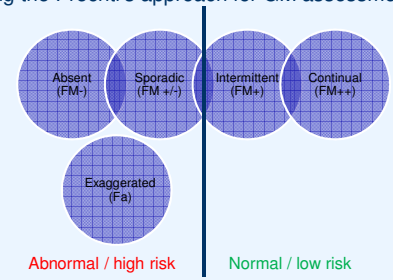
Methods – FMs classification

Video recordings were classified by two certified and experienced observers using the Prechtl's approach for GM assessment



Methods – FMs classification

Video recordings were classified by two certified and experienced observers using the Prechtl's approach for GM assessment

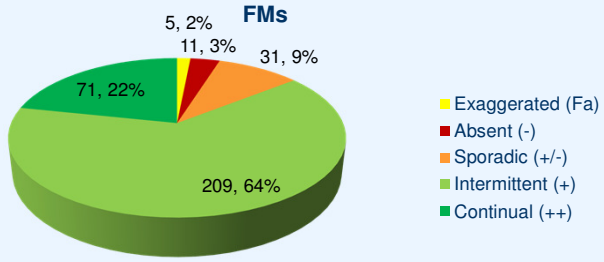


Results

Fidgety movements

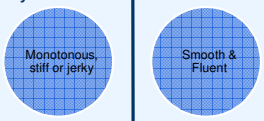
FMs	N (%)	Risk for adverse development
Exaggerated (Fa)	5 (2)	High risk
Absent (-)	11 (3)	High risk
Sporadic (+/-)	31 (9)	High risk
Intermittent (+)	209 (65)	Low risk
Continual (++)	71 (22)	Low risk
Total	327	

Results



Methods – movement character classification

The global movement character were classified as smooth & fluent or as monotonous, stiff or jerky

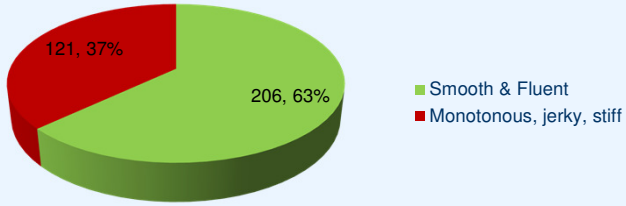


Abnormal / at risk

Normal / low risk

Results

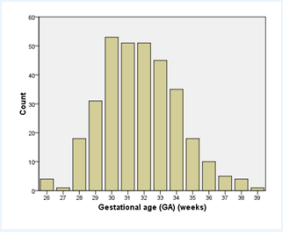
Global movement character



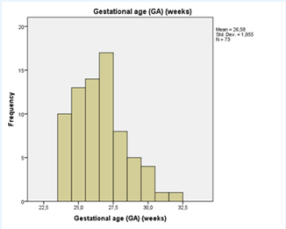
Discussion: participants

- Vellore, India: VLBW (Mean gestational age 32 weeks)
- Norway: ELBW (Mean gestational age 26 weeks)

Vellore, India



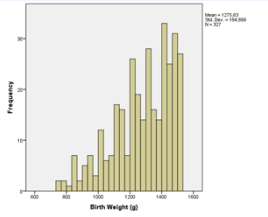
Norway



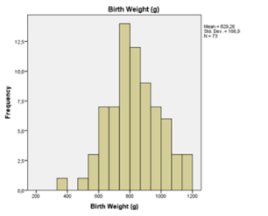
Discussion: participants

- Vellore, India: VLBW (Mean birth weight 1275 grams)
- Norway: ELBW (Mean birth weight 816 grams)

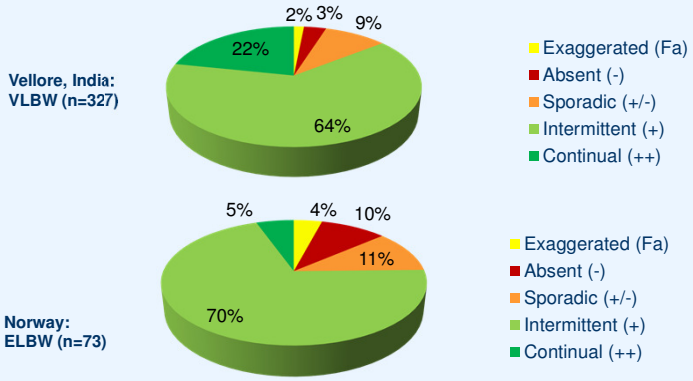
Vellore, India



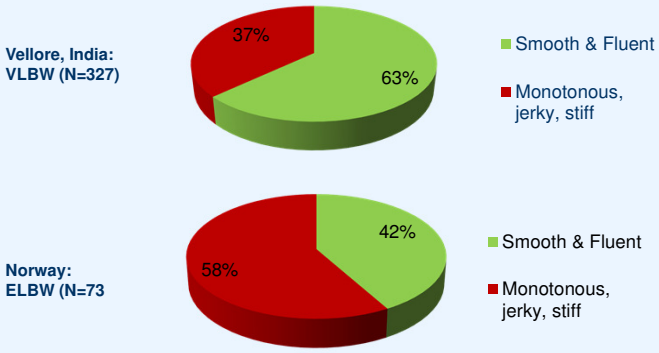
Norway



Discussion: FMs classifications



Discussion: Global movement character



References

1) *Prechtl HF, Einspieler C, Cioni G, Bos AF, Ferrari F, Sontheimer D. An early marker for neurological deficits after perinatal brain lesions. Lancet. 1997;349(9062):1361-3.*
2) *Einspieler C, Prechtl HF, Bos A, Ferrari F, Cioni G. Prechtl's method on the qualitative assessment of general movements in preterm, term and young infants. New York: Mac Keith Press; 2004.*
3) *Darsaklis V, Snider LM, Majnemer A, Mazer B. Predictive validity of Prechtl's Method on the Qualitative Assessment of General Movements: a systematic review of the evidence. Dev Med Child Neurol. 2011;53(10):896-906.*

With utmost gratitude …

I thank **the Lord Jesus** for His grace which has sustained me thus far.

I would like to place on record my immense gratitude to the following people:

Dr. MC Mathew (Professor and former Head of Developmental Pediatrics Unit, CMC Vellore), the guide for this thesis, for his patient support and unstinting belief in me.

Dr.AK Jana (Professor and former Head of Neonatalogy Department, CMC Vellore), the co- guide for his encouragement and his valuable advice.

Dr. S. Sridhar and Dr. Niranjan Thomas (Professors of Neonatology, CMC) for the numerous brainstorming sessions and for their help.

Ms. Hima John (Occupational therapist), whose untiring efforts and multi-tasking has resulted in the recruitment of this large cohort. She was also responsible for the interim motor assessment at one year of age and for providing therapy for the children who had developmental needs.

Mrs. Caroline Padankatti, Mrs. Reeba Roshan, Mrs. Hannah Grace, Ms. Rainu Miriam and Ms. Rachel Beulah (Psychologists), my wonderful colleagues, who despite their numerous appointments always accommodated the study children for the neurodevelopmental assessments.

A special thanks to **Ms. Premila John** who, notwithstanding her very busy schedule was still willing to find an " appointment slot for the study children".

I will always remain grateful to **Mr. Shekar, Mrs. Mary Pramila and Mrs. Viji** who were always at my beck and call, for their loving support.

Ms. Meenakshi Papanasam (Social worker), **Ms. Rafiya** (Data entry operator) who liaised with the parents, constantly encouraging them to bring their children for the assessments and for the entry of the data.

My colleagues in the Developmental Pediatrics Unit – **Drs. Beena, Susan, Dorothy and Murugan** who uncomplainingly bore the additional clinical responsibilities, so that I could devote my time to this thesis.

My other colleagues in the Unit, **Lincy, Ruth, Merlin, Varalakshmi, Anita, Shari, Diji, Renugopal, Meena and Uma** for their support

The **Dr. Anil Kuruvilla** and the Staff of the Department of Neonatology for their help.

Dr. Jeyaseelan, Mr. Bijesh Yadav, Dr. Visalakshi, Ms. Tunny and Ms. Grace (Department of Biostatistics) for their help in the analysis.

My friends **Dr. Santosh Varughese, Dr. Parimala Bai and Dr. John Viswnath** for their constant encouragement

To my parents **Drs. Ashok and Molly Oommen** who are immensely proud of this effort

To my family members **Vinita, Abey, Anita, Sunil, Reena, Jobby, Sajany, Aby, Richie, Mercy and Pappa (Mr. Philip Mathew) mummy (Mrs. Aleyamma Mathew) and the kids,** a big thank you.

And finally my wife **Beena and my beloved children Rohan, Divya and Abhay** for preserving my sanity throughout this venture and for tolerating daddy's absences to do "his PhD"!

Dr. Samuel P Oommen.

I am grateful to all parents who gave permission for using the photographs and the MRIs of their children

Dr. Samuel P. Oommen


Turnitin Document Viewer - Windows Internet Explorer
https://www.turnitin.com/dv?o=507519661&u=1036428312&s=&student_user=1&lang=en_us
The Tamil Nadu Dr.M.G.R.Medical...
TNMGRMU EXAMINATIONS - DUE 15-A...
Originality
GradeMark
PeerMark
Neurodevelopmental Outcomes of Very
BY SAMUEL P OOMMEN
turnitin
9%
SIMILAR
--
OUT OF 0
NEURODEVELOPMENTAL OUTCOMES OF
VERY LOW BIRTH WEIGHT INFANTS
IN A TERTIARY HEALTH CARE CENTRE
THESIS SUBMITTED TO
THE TAMIL NADU DR. MGR MEDICAL UNIVERSITY,
CHENNAI
FOR THE AWARD OF DEGREE OF DOCTOR OF PHILOSOPHY
by
Dr. SAMUEL P. OOMMEN
DEPARTMENT OF PEDIATRICS
CHRISTIAN MEDICAL COLLEGE, VELLORE
JANUARY 2015
Match Overview
2 matches
1 pediatrics.aappublicati... 1%
Internet source
2 fisioterapianeonatal.co... <1%
Internet source
3 www.ncbi.nlm.nih.gov <1%
Internet source
4 archsix.com <1%
Internet source
5 Richard D. Semba. "Lo... <1%
Publication
6 phfi.org <1%
Internet source
7 www.science.gov <1%
Internet source
8 B. A. Darlow. "Prenatal... <1%
Publication
PAGE: 1 OF 253
Text-Only Report
Done
Internet | Protected Mode: Off
100%