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The High Risk Newborn

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Foreword

The accreditation process of Level-II care introduced by National Neonatology Forum (NNF) standardized and accelerated the growth of special care units for high risk neonates in our country. With the introduction of DM (Neonatology) training programme there has been a phenomenal growth of Neonatal Intensive Care Units (NICU) in India.

The ultimate determinant of the quality of care delivered by such units is the intact survival rates of the neonates treated by them. Survival rates alone cannot be the end point to assess NICU treatment protocols. Experiences of the western world have clearly shown the importance of simultaneously organizing early intervention programmes for high risk babies in order to reduce the potential burden of neurodevelopment disabilities. From survival to intact survival is a real challenge of modern neonatal intensive care. This book will go a long way in meeting that challenge. There has been a genuine need for an Indian book specifically focusing on the outcome of graduates of NICUs.

The major highlight of this book is the attempt to review the relationship of risk factors, the brain damage caused, and neurodevelopmental outcome and link the same to NICU management principles. This book focuses on the follow-up in the first two years of post-natal period. Details of specific neurodevelopment disabilities, available elsewhere, have been rightly omitted.

I am glad to see so many of my colleagues and former neonatology students contributing to this book. My special congratulations to Dr Naveen and Dr Srinivas for a job well done. Dr MKC Nair and Dr A Parthasarathy team has once again shown the same magic touch, as in the IAP Textbook of Pediatrics.

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Preface

In India, neonatal mortality has remained static over the last several years. Majority of mortality could be explained by infection (52%), asphyxia (20%) and low birth weight (17%), all of which are preventable. At the community level, we have made a conscious shift from “diagnosis based” approach to “illness based protocols” in the integrated management of neonatal and childhood illness (IMNCI), a concept endorsed by both National Neonatology Forum and the Indian Academy of Pediatrics. At the tertiary level health care, Neonatal Intensive Care Units (NICUs) across the country have definitely improved the survival chances of many high risk babies, who otherwise would have succumbed easily.

Now, the question asked more often is, whether we are increasing the incidence of developmental delay and disability by saving more and lower birth weight and other at-risk babies. Unfortunately we do not have hard data on this. Our understanding of risk factors for neurodevelopmental disabilities has made definite progress, yet we still cannot predict outcome in every individual case. But, we surely know that the answer probably lies in promoting “developmental friendly well baby clinic” concept and mother oriented early stimulation at home for all babies especially for preterm/ IUGR babies. Infact, it may be now considered unethical to have a level-II and level-III NICU, without having a neonatal follow-up and developmental stimulation program. The lack of a “standard-protocol” for neurodevelopmental follow-up and availability of trained personnel has been the major limiting factors. The one year Postgraduate Diploma in Developmental Neurology course for doctors and two years Master of Health Science (MHSc) in Clinical Child Development course for nurses, therapists and doctors, being conducted by Child Development Centre, in association with Institute of Distance Education, University of Kerala is a step in the right direction.

This book attempts to **organize currently available knowledge** on risk factors affecting neurodevelopment, best practices in modifying these risks and explains simple neurodevelopmental assessment techniques. It also discusses, in detail the early stimulation program that can be initiated in the neonatal period and management of developmental delay in the

first two years, with the ultimate **objective of minimizing child hood disability**. The emphasis in this book has been in organizing current evidence into **simple protocols that can be practiced at all levels of care**. We do hope that you would find this book useful and pardon us for inadequacies inevitable in the first edition of any book.

Editors

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Contents

SECTION 1: INTRODUCTION

- 1. Introduction to the High Risk Newborn 3**
MKC Nair, Babu George, Elsie Philip

SECTION 2: PREMATURITY AND LOW BIRTH WEIGHT

- 2. Preterm Brain Injury 13**
Naveen Jain, Neetu Gupta
- 3. Preterm/Low Birth Weight 29**
Rhishikesh Thakre

SECTION 3: NEONATAL ENCEPHALOPATHY

- 4. Perinatal Asphyxia 41**
Karthik Nagesh N
- 5. Neonatal Seizures 62**
Srinivas Murki

SECTION 4: METABOLIC PROBLEMS

- 6. Hypoglycemia 73**
Suman Rao PN
- 7. Neonatal Jaundice 82**
Srinivas Murki
- 8. Inborn Errors of Metabolism (IEM) 88**
Suvasini Sharma, Ramesh Agarwal

SECTION 5: RESPIRATORY PROBLEMS

- 9. Apnea 101**
Sanjay Wazir
- 10. Meconium Aspiration Syndrome (MAS) 117**
Amuchou Singh Soraisham
- 11. Persistent Pulmonary Hypertension of Newborn (PPHN) 126**
Amuchou Singh Soraisham, Abbas Hyderi

SECTION 6: PERFUSION PROBLEMS

- 12. Neonatal Shock** 143
Gurdev Chowdhary
- 13. Neonatal Sepsis** 157
John BM, Daljit Singh

SECTION 7: INTERVENTIONS

- 14. Pain and Analgesia** 175
Jaikrishan Mittal
- 15. Neonatal Transport** 186
Dinesh Kumar Chirla
- 16. Perinatal Steroids** 194
Ravishankar K
- 17. Mechanical Ventilation** 198
Ashish Mehta

SECTION 8: NEURODEVELOPMENTAL ASSESSMENT

- 18. Risk Stratification for Neurodevelopmental Disability** 207
Naveen Jain, MKC Nair
- 19. Clinical Examination Protocol**..... 209
Naveen Jain, MKC Nair
- 20. Screening Protocol** 216
Naveen Jain, MKC Nair

SECTION 9: NEURODEVELOPMENTAL FOLLOW-UP

- 21. Discharge Protocol** 225
Naveen Jain, MKC Nair
- 22. Follow-up Protocol** 230
Naveen Jain, MKC Nair
- 23. Organization of Neurodevelopmental Follow-up** 236
Naveen Jain, MKC Nair

SECTION 10: DEVELOPMENTAL EVALUATION

- 24. Developmental Evaluation** 243
Babu George, Narayanan Potti, MKC Nair

SECTION 11: EARLY DEVELOPMENTAL STIMULATION

- 25. Early Stimulation in NICU** 259
Prasanna GL, Rajeev K, MKC Nair

- 26. Early Stimulation after Discharge 264**
Sunitha RM, Lakshmi MA, Babu George
- 27. Early Stimulation Protocol 270**
Resmi VR, Latha S, MKC Nair

SECTION 12: DEVELOPMENTAL THERAPY

- 28. Motor Stimulation in Early Infancy 279**
Jyothi R, Deepa Jayaprasad, MKC Nair
- 29. Vision and Hearing Stimulation in Early Infancy 287**
Mini AO, Rekha S, MKC Nair

SECTION 13: PRENATAL STRATEGIES

- 30. Prenatal Risk Factors 295**
Archana P Bilagi, Ranjan Kumar Pejaver
- 31. Multiple Fetal Pregnancies 312**
Arvind Shenoj, Mohan BK
- 32. Assisted Reproductive Technique—Is It Safe?..... 319**
Sathy M Pillai

SECTION 14: UNEXPLORED TERRITORIES

- 33. Nutrition, Fluid and Electrolytes 329**
Pankaj Garg, Manoj Modi
- 34. Follow-up Research—Some Methodological Issues 338**
Rhishikesh Thakre, MKC Nair

SECTION 15: COUNSELING

- 35. Genetic Counseling—High Risk Pregnancy..... 347**
Sankar VH
- 36. Parent Counseling 356**
Meharban Singh

Index 363

Abbreviations

NICU	Neonatal Intensive Care Unit
CNS	Central Nervous System
NDD	Neurodevelopmental Disability
HIE	Hypoxic Ischemic Encephalopathy
IVH	Intraventricular Hemorrhage
PVL	Periventricular Leukomalacia
WMD	White Matter Disease
CP	Cerebral Palsy
MR	Mental Retardation
MSAF	Meconium Stained Amniotic Fluid
PPHN	Persistent Pulmonary Hypertension of Newborn
MAP	Mean Arterial Pressure
ELBW	Extremely Low Birth Weight
VLBW	Very Low Birth Weight
LBW	Low Birth Weight
SVC flow	Superior Vena Caval Flow
EEG	Electroencephalogram
CSF	Cerebrospinal Fluid
LP	Lumbar Puncture
CLD	Chronic Lung Disease
BPD	Bronchopulmonary Dysplasia
ROP	Retinopathy of Prematurity
NEC	Necrotizing Enterocolitis
PDA	Patent Ductus Arteriosus
ANS	Antenatal Steroids
nCPAP	Nasal Continuous Positive Airway Pressure
DDST	Denver Development Screening Test
BSID	Bayley Scale of Infant Development

Section 1 **Introduction**

- 1. Introduction to the High Risk Newborn**

Introduction to the High Risk Newborn

Sustained global initiatives and efforts of local governments have improved child survival in most parts of the world and hence, now the focus should shift to quality of survival. Although the infant mortality in India has fallen significantly, the neonatal mortality is remaining by and large static and we do know that low birth weight is the major contributor.¹ In the India CLEN multicentric neonatal health research initiative (NHRI) study, the causes of neonatal deaths as per verbal autopsy were respiratory distress syndrome (57%), low birth weight (51%), birth injury/asphyxia (42%), neonatal sepsis complex (36%), pre-maturity (29%), congenital malformations (13%), hypothermia (12%), jaundice (4%) neonatal tetanus (3%) and causes not known (3%).² Poverty, illiteracy and poor environmental hygiene are factors detrimental to child survival and development, especially so for the marginalized and vulnerable groups.³ Parenting practices do play an important role in child survival and development. In a recent study on parenting practices, early child-care practices were reaching high standards, even in tribal and economically backward areas, probably explaining the better indicators observed in Kerala.⁴

AT-RISK CONCEPT

Child development is a dynamic process of optimally utilizing the genetic potential of the baby, within the context of the environment made available, so as to enable him/her to achieve the full potential. Although a continuous process, the first one-year of life and pre-school years are the most critical period in the child's development. The difficult part is identifying babies at-risk for poor development. A risk factor is something that increases the likelihood of getting a disease or condition. The division of risk as mild, moderate and high is often arbitrary. Hence the concept of "at-

risk” newborns may be replaced by the concept of “optimality”. Newborns with a low “optimality score” are considered highly likely to develop neurodevelopmental disabilities later in life. Which ‘high risk’ newborns require periodic screening, ideally needs to be determined locally, keeping in mind the feasibility and cost-effectiveness of any neonatal follow-up program. It must, however, be remembered that many babies not considered “at-risk” may also manifest developmental problems as they grow. These babies would obviously not be seen during “at-risk” focused follow-up screening.⁵

Risk factors for developmental deficits may be grouped under four categories; biological risk, genetic and metabolic disorders, environmental risk, and no apparent risk.⁶ Low birth weight babies form the single largest group of easily identifiable babies at-risk for poor development. Around two out of three babies weighing less than a kilogram at birth will suffer some degree of disability, usually as a result of lack of oxygen or brain hemorrhage.⁷ Half of surviving very preterm babies, grow up to be mentally or physically disabled.⁸ Although developmental delay is more likely to be found among babies with risk factors (at-risk concept), the large majority born with a risk factor are likely to develop normally. On the other hand cerebral palsy and mental retardation are also observed among the large group of babies born normally without any apparent risk. The concept of “double vulnerability” means that a baby with a biological risk factor like low birth weight is more likely to fare poorly if born into a family with poor child rearing capabilities as compared to one with a positive environment. This is very relevant in the Indian context.

FOLLOW-UP AND EARLY INTERVENTION

In a follow-up study of graduates of level-II neonatal nursery, multiple regression analysis for Bayley scores at 1 and 2 years showed that after adjusting for the significant risk factors for development—birth weight, neonatal seizure, congenital anomaly, intrauterine infection, mother’s education, type of baby, occupation of father and residence—the babies who had intervention had significantly higher Bayley scores compared to control babies. Also, the observation that for increase of every 500 grams, there was a significant and consistent increase in mean values of neurodevelopmental outcome indicators at 1 and 2 years and that in every birth weight group, the mean values were higher for the intervention group, suggest that early intervention is effective across the birth weight groups.⁹ Developmental follow-up of at-risk babies supported by early intervention therapy is the answer, as shown in the experience of the developed countries.¹⁰ Meta-analysis of early intervention efficacy

studies done at Utah State University has shown that early intervention is effective in improving the developmental status, although there is still no uniform agreement as to whether the effects last long.¹¹

LOW BIRTH WEIGHT

A recent meta-analysis to review the effectiveness of early developmental intervention post-discharge from hospital for pre-term (less than 37 weeks) infants on motor or cognitive development concluded that intervention improved cognitive outcomes at infant age (0 to 2 years). However, there was significant heterogeneity between studies for cognitive outcomes at infant age.¹² It has been shown that 40% reduction in poor performance could be achieved among low birth weight babies, by CDC model early stimulation.^{13,14} By early “Infant Stimulation” we mean early interventional therapy for babies at-risk for developmental delay and periodic developmental assessment. A team of professionals consisting of developmental pediatrician, developmental tester, developmental therapist and developmental teacher chalk out programmes of various activities including play, passive exercises and also teach the same to the mother, to help her to do the therapy at home. Improvement in one functional area helps the child to improve functions in other areas.

In the Indian context, it appears that reduction of low birth weight should be the centre point of our thoughts and actions, whether it is for reduction of mortality, morbidity, childhood disability and poor scholastic performance. In order to reduce the burden of low birth weight with the resultant consequences, it is important to understand the community attributable risk factors for low birth weight. In a large community study in India, reporting a 29% LBW incidence had described the following population attributable risks for LBW: Socioeconomic status (41.4%), severe anemia in pregnancy (34.5%), maternal height (29.5%) and maternal pre-pregnant weight (22.9%), highlighting the importance of improving pre-adolescent and adolescent girls’ nutrition.¹⁵ However, it is to be appreciated that low birth weight has an intergenerational effect and interventions in one generation alone cannot address the issue fully.

NEWBORN ENCEPHALOPATHY

Newborn encephalopathy represents the neurological manifestations of central nervous system injury due to any cause obvious or not so obvious, that occurs in the first few hours or days of life. The importance of intra-uterine asphyxia in the genesis of hypoxic-ischemic brain injury is well known. In a retrospective survey of 100 infants with hypoxic-ischemic

encephalopathy there was evidence of intra-uterine hypoxia in 90% and only in 10% was the insult postnatal.¹⁶ Similarly, Brown et al in a series of 91 infants with hypoxic-ischemic encephalopathy reported intrauterine insult in 91% and postpartum insult in 9%.¹⁷ Two well conducted studies, a large prospective US national collaborative perinatal project (NCPP) and case control study in western Australia stand testimony to this.^{18,19}

Newborn encephalopathy as described by Sarnat and later by Fenichel, particularly with seizures and recurrent apnoea has been demonstrated to be an important predictor of subsequent motor and cognitive handicaps.^{20,21} Clinical presentation of birth asphyxia with severe newborn depression has demonstrated that most children who survived with sequelae had clinical signs of encephalopathy during the neonatal period.²² Hence prevention of perinatal asphyxia with better obstetric care, resuscitation using positive pressure ventilation, with or without oxygen and optimal brain protective immediate postnatal care would be the ideal solution. But in a vast country like India with extremes of perinatal care, abolishing post asphyxial encephalopathy would be a distant dream. Also it has been demonstrated that pyritinol, a widely used so-called neurotonic has no positive effect in improving the neurodevelopmental status of post asphyxial encephalopathy babies at one year of age and hence its use should be dissuaded.²³

INTRAUTERINE INFECTIONS.....

Severe forms of disability are not common and are often due to congenital, genetic, metabolic causes or intrauterine infections and need specific preventive strategies.²⁴ Recurrent pregnancy wastage due to maternal infections transmissible *in utero* at various stage of gestation can be caused by a wide array of organisms which include the TORCH complex (toxoplasma gondii, rubella virus, cytomegalovirus, herpes simplex virus) and other agents like *Chlamydia trachomatis*, *Treponema pallidum*, *Niesseria gonorrhoeae*, HIV etc. Toxoplasmosis acquired during pregnancy may cause damage to the fetus.²⁵ Seroepidemiological studies have shown that 10-20 percent of women in childbearing age in India are susceptible to Rubella infection.²⁶ Infection with Rubella during pregnancy may lead to congenital malformation in 10-54 percent of cases.²⁷ The infection caused by CMV in adult is usually asymptomatic but its significance is many times increased when it occurs during pregnancy. However, the rate of primary CMV infection is significantly higher for pregnant women from low socioeconomic group.²⁸ The mother is the usual source of transmission of HSV to the fetus or newborn. Primary HSV infection during first half of pregnancy is associated with increased frequency of spontaneous abortion, still birth, and congenital malformation.²⁹

ENVIRONMENTAL FACTORS

Poverty, environmental deprivation and inadequacy of early stimulation are much more common and therefore need an integrated program of nutrition and developmental stimulation. Developmental research has clearly shown that both socioeconomic status (SES) and aspects of the home environment account for a significant proportion of the variance in cognitive functioning of both healthy and pre-term children. In addition, researchers have also established that the home environment may serve as a protective factor for children.³⁰ It is suggested that early social environment plays a role in mediating establishment of neural networks that regulate a child's response to stress and capacity for self-control.³¹ Secure and stable relationships with caring adults assure that young children are adequately nourished and protected from dangerous illnesses, exposure to toxins, and hazards that can lead to preventable injuries. It also provides preventive health check-ups, protect from excessive stress and afford predictable daily routines that convey a sense of security. These influences contribute significantly to healthy brain development that depends upon the care and support provided by individuals in the community as well as in the family.³²

POLICY IMPLICATION

In those parts of the country, where maternal education is poor, one of the strategies would be providing family counseling by regularly visiting families having specially identified persons such as pregnant mothers, post natal mothers, 0-2 months old (neonatal) babies, and 2-24 months old babies, observing and monitoring their parenting behavior, until such desirable changes are evident.³³ Notwithstanding the isolated centers of excellence, the overall quality of institutional neonatal care and postnatal follow-up care at home, remains unsatisfactory in India. It is in this context that the Indian Academy of Pediatrics and the National Neonatology Forum had resolved as early as 2004, to consolidate their ongoing partnership by looking at newer objectives and methods to improve the existing status of neonatal and child health in India.³⁴ It is the same realization that necessitated provision of a group of community volunteers (ASHA) under national rural health mission (NRHM) and addition of the neonatal component in the integrated management of childhood illness (IMCI) in India.

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Section 2

Prematurity and Low Birth Weight

2. Preterm Brain Injury

3. Preterm/Low Birth Weight

Preterm Brain Injury

Very preterm babies (**gestation \leq 32 weeks**) are at increased risk of neurodevelopmental disability. Most neurodevelopmental impairments are likely to be the consequence of brain damage of perinatal origin. Majority of these lesions can be identified in the neonatal period with the use of cranial ultrasound. **IVH-PVH and (White matter damage) WMD (parenchymal echo-densities, cystic PVL, Ventriculomegaly) are the best recognized preterm brain injuries** associated with adverse neurodevelopmental outcomes.

Adverse neurodevelopmental outcome in very preterm babies depends primarily on the severity of the intracranial lesion, rather than on gestational age.

CURRENT UNDERSTANDING OF PATHOPHYSIOLOGY^{1,2}

The site of origin of PVH-IVH is the **sub-ependymal germinal matrix**. During fetal development, the sub-ependymal germinal matrix is a site of neuronal proliferation and glial cell proliferation until approximately 32 weeks' gestation. The **proliferating cells** of the germinal matrix are rich in mitochondria and, therefore, are quite **sensitive to ischemia**. Supplying this area of metabolically active differentiating cells is a primitive and **fragile rete like capillary network**. This fragile capillary network is the site at which PVH-IVH hemorrhage occurs.

Two major factors that contribute to the development of PVH-IVH are:

- Loss of **cerebral auto regulation** and
- Abrupt **alterations in cerebral blood flow** and pressure.

In the absence of autoregulation, the systemic blood pressure becomes the primary determinant of cerebral blood flow and pressure, a **pressure-**

passive situation. When a pressure-passive circulatory pattern is challenged with fluctuations of cerebral blood flow and pressure, hemorrhage can occur. The capillaries of the immature germinal matrix possess neither tight junctions between endothelial cells nor a strong basement membrane. Therefore, increased flow and pressure may rupture the delicate capillaries, leading to bleeding. IVH is considered to be a consequence of **ischemia-reperfusion** of the preterm/immature germinal matrix of the brain.

The significance of **alterations in cerebral blood flow** is perhaps not only in the generation of hemorrhage but in more **diffuse brain injury** as well. Two disorders that may coexist with IVH are **global hypoxic-ischemic injury (loss of cerebral volume-ventriculomegaly) and periventricular leukomalacia (PVL)**. Both significantly affect the neurologic outcome in infants.

It is alteration in cerebral blood flow that's the cause of concern in prophylactic use (rapid infusions) of indomethacin. Although, indomethacin might improve the risk of PVH-IVH, it may be increasing the risk of periventricular leukomalacia.

The pathogenesis of grade IVS hemorrhages/intra parenchymal hemorrhages (IPH) differs. IPH appears to result from **hemorrhagic venous infarctions** surrounding the terminal vein and its feeders. A peculiar anatomic arrangement is considered as reason for proneness to IPH. Following parenchymal hemorrhages, necrotic areas form cysts that may become contiguous with the ventricles (**porencephalic cysts**).

The other mechanism by which long-term neurological outcome can be altered is through the development of **post hemorrhagic hydrocephalus**. The mechanisms by which hydrocephalus develop include:

- a. Decreased absorption of cerebrospinal fluid (CSF) secondary to obstruction of arachnoid villi by blood and debris or the development of obliterative arachnoiditis (i.e. communicating hydrocephalus) and
- b. Obstruction to CSF circulation (i.e. obstructive hydrocephalus).

The major sequel of PVH-IVH relate to the **destruction of cerebral parenchyma-white matter damage** (Ventriculomegaly, periventricular cystic leukomalacia) and the development of post hemorrhagic hydrocephalus.

The white matter is arranged such that tracts **innervating the lower extremities** are nearest to the ventricles, followed by those innervating the trunk, the arm, and, finally, the face. This anatomical arrangement accounts for the greater degree of motor dysfunction of the extremities

as compared to the face (spastic hemiplegia in unilateral lesions and spastic diplegia or quadriplegia in bilateral lesions).

Evidence of antenatal insult: Chorioamnionitis has been considered as a serious risk factor for WMD. Histopathological evidence of acute inflammatory placental lesions is the best predictor of occurrence of neonatal IVH.

CLINICAL PRESENTATION OF PVH-IVH

Postnatally, most hemorrhages occur when the neonate is **younger than 72 hours**, with **50%** of hemorrhages occurring on the **first day of life**. Hence, most **preventive strategies are directed at perinatal care and cerebral perfusion on 1st day of life**. PVH-IVH can occur when the individual is older than 3 days, especially if a significant life-threatening illness arises.

Most infants are **asymptomatic** or demonstrate subtle signs that are easily overlooked. PVH-IVH subsequently is found on **surveillance sonography**. A catastrophic presentation is sudden and significant deterioration associated with anemia, metabolic acidosis, glucose instability, respiratory acidosis, apnea, hypotonia, and stupor. This is associated with high risk of death. Between the two extremes of presentation, infants might demonstrate varying degrees of **neurological and systemic signs**.

Currently it is recognized that **neurologic sequelae are better associated with WMD (parenchymal echodensities, cystic PVL, ventriculomegaly)**. Hence, a new practical approach to describing ultrasound findings is:

Classification of hemorrhagic and/or ischemic abnormalities detected by cranial ultrasound examinations

- Isolated GM and/or IVH
- Parenchymal echodensities and/or lucencies with or without GM and/or IVH
- Ventricular enlargement with or without GM and/or IVH

GM/IVH—Germinal matrix / intraventricular hemorrhage

Many of these ultrasound findings are noted late, around term gestational age or even later. 30% of children who developed (Cerebral palsy) CP after major ultrasound abnormalities **would have not been diagnosed if ultrasound scans had been restricted to the first 4 weeks after birth**.

IMPACT ON NEURODEVELOPMENT³⁻⁵

CP is the primary neurological disorder observed after PVH-IVH and WMD, though **mental retardation, language disorders, seizures** and others can ensue as well.

CEREBRAL PALSY

IVH-PVH and WMD are **major determinants** of neurodevelopmental outcomes in preterm born infants. In a review of 15 studies, Holling and Leviton showed that 59% of neonates with **periventricular echolucencies** developed CP. In EPIPAGE, a population based of nearly 3000 preterms from 9 centers in France, among 76 children with **cystic PVL**, 44 (58%) developed CP. As expected, the risk of CP is higher when cystic PVL is **bilateral and when the injury is in the parietal and occipital lobes**.

Incidence of CP increases with decreasing gestation—20% at < 27 weeks, 12% at 27 to 28 weeks, 8% at 29 to 31 weeks, and 4% at 32 weeks. Increased risk of CP with decreasing gestational age is **partly or may be wholly attributable to cerebral abnormalities**. 17% of children with isolated grade III IVH and 25% of children with white matter damage had CP, compared with only 4% of children with normal ultrasound scans.

Studies have shown that **only preterm infants with IVH differ from term infants in neurological examination findings**. The rates of **CP**, which were 20%–32% in group with IVH compared with only 5%–6% for the group without IVH. This finding represents a **4-to 5-fold** increase among children with IVH.

PVL is the most powerful independent predictor of CP in extremely preterm infants (27 weeks' gestation or less).

BEST PRACTICES - INTERVENTIONS TO PREVENT PRETERM BRAIN INJURY⁶

A. Prenatal

1. Prevention of prematurity
 - a. Timing of delivery
 - b. Tocolysis
2. Antenatal Steroids (ANS)
3. Antibiotics in prelabour rupture of membranes (pROM)
4. In utero transport
5. Mode of delivery of preterm

- B. Optimize Peripartum Management
 - 1. Resuscitation
 - a. Trained personnel for preterm delivery
 - b. Avoid unsafe practices
 - 2. Delay cord clamping
 - 3. Establish cardiorespiratory stability before surfactant administration
- C. Management of Preterm Baby
 - 1. Cerebral Perfusion
 - a. Optimize therapy for systemic hypoperfusion
 - b. Use postnatal indomethacin judiciously
 - c. Implement Measures to Minimize Pain and Stress Responses (fluctuations in cerebral perfusion)
 - 2. Optimize Respiratory Management
 - a. Synchronized ventilation
 - b. Avoid hypocapnea
 - c. Avoid routine chest physiotherapy
 - d. Avoid routine suctioning
 - e. Neuromuscular paralysis
 - f. Sedation
 - g. Use Postnatal Dexamethasone Judiciously
 - h. Limit Sodium Bicarbonate Use
 - 3. Correct coagulopathy
 - 4. Administrator Strategies in NIW
 - 5. Unproven therapies
 - a. Magnesium sulfate (antenatal)
 - b. Ethamsylate, vitamin E
- D. Screening and Diagnosis of Preterm Brain Injury
 - 1. Clinical examination
 - a. Head circumference
 - b. Popliteal angle
 - 2. Neurosonographic Screening for IVH–PVH and WMD.

PRENATAL

Prevention of Prematurity

There is an inverse relation between neurodevelopmental disability and gestation. The auto regulatory abilities of cerebral blood flow in neonates vary inversely to gestational age at birth. **Prevention of preterm birth should decrease the risk of brain injury.** (Some of the large population studies have observed that gestation ceases to be an independent risk factor if IVH-PVH and WMD are not present).

- **Timing of delivery: Risk of continuing pregnancy** with an unfavorable in utero environment must be **weighed against early delivery** and increased risk of IVH at borderline gestations. This is particularly important at gestations below 29 weeks where continuation of pregnancy must be preferred, if maternal safety permits.
- **Tocolysis:**⁷ Short delays in preterm birth can enable women to reach specialist care and receive antenatal steroids. When tocolysis is indicated for women in preterm labor, **calcium channel blockers** (usually nifedipine) are preferable to other tocolytic agents compared, mainly betamimetics. Twelve randomized controlled trials involving 1029 women were included. When compared with any other tocolytic agent (mainly betamimetics), calcium channel blockers reduced the number of women giving birth within seven days of receiving treatment (relative risk (RR) 0.76; 95% confidence interval (CI) 0.60 to 0.97) and prior to 34 weeks' gestation (RR 0.83; 95% CI 0.69 to 0.99). Calcium channel blockers also reduced the requirement for women to have treatment ceased for adverse drug reaction (RR 0.14; 95% CI 0.05 to 0.36), the frequency of neonatal respiratory distress syndrome (RR 0.63; 95% CI 0.46 to 0.88), necrotising enterocolitis (RR 0.21; 95% CI 0.05 to 0.96), **Intraventricular hemorrhage (RR 0.59, 95% CI 0.36 to 0.98)** and neonatal jaundice (RR 0.73; 95% CI 0.57 to 0.93). There is insufficient information on which to base decisions about the role of COX inhibition (Indomethacin) for women in preterm labor. Betamimetics help to delay delivery for women transferred to tertiary care or completed a course of antenatal corticosteroids. However, multiple adverse effects must be considered. The data are too few to support the use of any particular betamimetics.

Antenatal Steroids (ANS)⁸⁻¹²

The antenatal use of betamethasone improves intact survival and decreases the incidence of IVH and severe grades of IVH. (Level-1 evidence)

In babies born at or before 31 weeks gestation when mothers were administered antenatal steroids. (RR 0.54, 95% CI 0.43 to 0.69, 13 studies, 2872 infants). **Antenatal steroids (ANS) must be given to a mother in preterm labor, as it reduces brain injury of the preterm baby.**

- **Preferred dosing:** Betamethasone 12 mg 24 hours apart intramuscular. Try to deliver 24 hours after the course is completed.

- **Incomplete course of ANS**

Even an **incomplete course** of antenatal corticosteroids is associated with **reduction in the rate of Intraventricular hemorrhage.**

- **Alternate regimen**

Dosing betamethasone in **12-hour intervals** may result in similar neonatal outcomes compared to the standard 24-hour regimen when delivery is likely to occur within 48 hours of therapy initiation.

- **Chorioamnionitis and ANS**

A complete course of antenatal steroids appeared to **extinguish any association between in utero inflammation (chorioamnionitis) and adverse neurological outcome.**

- **Repeat doses of prenatal corticosteroids** for women at risk of preterm birth. If ANS was given for pretend preterm delivery and the baby is not delivered in a week the effect of ANS decreases and it is a practice in many units to repeat ANS for the anticipated loss of effect. Repeat dose(s) of prenatal corticosteroids reduce the occurrence and severity of neonatal lung disease and the risk of serious health problems in the first few weeks of life. These short-term **benefits for babies support the use of repeat dose(s) of prenatal corticosteroids for women at risk of preterm birth.** However, these benefits are associated with a reduction in some measures of weight, and head circumference at birth, and there is still insufficient evidence on the longer-term benefits and risks. No statistically significant differences were seen for periventricular hemorrhage and periventricular leukomalacia. (2000 women between 23 and 33 weeks' gestation).

- **Betamethasone vs dexamethasone**

Most studies favor use of Betamethasone. Some have noted better neonatal outcomes with dexamethasone.

Antibiotics in Pre labour Rupture of Membranes (pROM)¹³

The use of antibiotics for mother following pROM is associated with a statistically significant reduction in chorioamnionitis, preterm delivery and abnormal cerebral ultrasound scan prior to discharge from hospital (RR 0.82, 95% CI 0.68 to 0.98). The choice of antibiotic may have to be based on local culture reports. **Appropriate antibiotic therapy must be started for the mother having preterm rupture of membranes as it reduces preterm brain injury.**

In-utero Transport

Encourage delivery in a tertiary center with a NICU. If preterm labor is inevitable, babies must be transported to referral center in-utero (before delivery) rather than after birth. **Outborn or transported infants consistently have higher rates of IVH and cystic PVL.**

Mode of Delivery of Preterm¹⁵

Infants with **early IVH** (noted on first scan at less than 6 hours age) **were significantly more likely to be born by vaginal delivery** in nearly 250 very preterm babies born in two cohorts (1995–1996 adjusted odds ratios [OR]: 13.29; 1998–1999 adjusted OR: 18.15). But prospective studies have not been able to demonstrate benefit of caesarean (decreased risk for mortality or IVH).

There is an increased incidence of mortality and morbidity for the **VLBW breech infant delivered vaginally**.¹⁶ Caesarean delivery may improve outcome for these infants. (Higher incidence of grade III or grade IV IVH (18.8% vs. 3.5%, $P < 0.001$ in VLBW babies delivered by vaginal route).

OPTIMIZE PERI-PARTUM MANAGEMENT

Resuscitation

- a. **Resuscitation of preterm baby by trained personnel:** Maternal fetal medicine specialists and neonatologists should manage pre-term labor and delivery. No literature is available, but it was a prominent feature at the best-performing hospitals.
- b. **Avoid harmful practices:** Gentle handling—**avoid painful stimulation** to initiate breathing, the baby should **not be held in a head down (hanging) position**. Care should be taken to prevent over zealous ventilation and **hypocarbica**. Administer **bolus medications slowly** (like volume expanders) and **sodabarbonate is best avoided**.

Need for CPR in extreme preterm was associated with a clear increase in neurological morbidity, with **a three-time greater risk of brain damage**.¹⁷

Delay Cord Clamping¹⁸

Delaying cord clamping by 30 to 120 seconds, rather than early clamping, seems to be associated with less need for transfusion and less intraventricular hemorrhage. Seven studies (297 infants) were eligible for inclusion. Delayed cord clamping was associated with fewer transfusions for anemia (three trials, 111 infants; relative risk (RR) 2.01, 95% CI 1.24 to 3.27) or **fewer “low blood pressures”** (two trials, 58 infants; RR 2.58, 95% CI 1.17 to 5.67) and **less intraventricular hemorrhage** (five trials, 225 infants; RR 1.74, 95% CI 1.08 to 2.81) than early clamping.

Establish Cardiorespiratory Stability before Surfactant Administration

Most of the benchmark sites did not use prophylactic surfactant, but ample evidence supports this therapy. The benchmark sites were very good at stabilizing the infants before surfactant. One study indicates that giving surfactant 10 minutes after birth is better than immediate instillation.

MANAGEMENT OF PRETERM BABY

Cerebral Perfusion¹⁹

Superior vena caval flow is currently considered as best indicator of systemic and cerebral blood flow. Infants with low superior vena caval (SVC) flow after birth, in first few hours of life, have higher incidence of IVH when SVC flow normalizes (ischemia reperfusion) and CP in future. **Low SVC flow is associated with lower gestation, no antenatal steroids, severe RD (higher mean airway pressure), large PDA (>1.6 mm)**

- Optimize therapy for systemic hypoperfusion: **Treat only overt hypovolemia such as obvious blood loss from placenta previa, cord rupture, and so forth with fluid boluses.** Without overt hypovolemia, use maximum of 2 volume boluses. Give bolus infusions over >30 minutes.

Volume bolus – seems to be inferior to dopamine in increasing blood pressure in hypotensive preterms. No documented difference in cerebral flow, but increase in severe IVH (borderline significance). Dopamine/dobutamine—In preterm infants with low systemic blood flow, there is some evidence that **dobutamine is better than dopamine** at increasing and maintaining systemic blood flow although dopamine is better in increasing blood pressure.

- **Use postnatal indomethacin judiciously:** Decreases the incidence of IVH in VLBW and increases the risk of intestinal perforation and renal insufficiency. Recently, the trial of indomethacin prophylaxis in preterms study indicated that although infants who are **given indomethacin do have less severe hemorrhages, they do not have a better cognitive outcome at 18 months.** The expert suggested that perhaps **indomethacin be reserved** for certain at-risk infants, such as those for whom the mother had **not received antenatal betamethasone or had chorioamnionitis**, rather than giving it to all infants.
- implement measures to minimize pain and stress responses (fluctuations in cerebral perfusion)
 - Avoid early lumbar puncture, prevent pneumothorax, and control seizures.

- Provide developmental care, decrease noise, and minimize handling and lighting.
- Use narcotic sedation judiciously.
- Instillation of mydriatics, rapid colloid infusion (eg, exchange transfusion), changes in pH, PaCO₂, and PaO₂, apnoea and anemia are factors that can alter cerebral blood flow and are associated with IVH.
- Position of UAC²⁰-high UAC positioning is suggested as a possible cause for IVH. Surfactant causes sudden change in mean airway pressure and cerebral perfusion, although, there is no evidence that it increases risk of IVH.

Optimize Respiratory Management

- Synchronized ventilation**—Use either **SIMV** or **HF(O)V** with **optimal volume strategy**
- Avoid hypocapnia**—The consensus is to keep PCO₂ > 40 mm Hg.
- Avoid routine chest physiotherapy**—The procedure can be devastating, especially in the first 72 hours.
- Avoid routine suctioning**—It is well documented that changes occur in blood pressure, cerebral blood flow, and intracranial pressure during suctioning.
- Neuromuscular paralysis**—For ventilated preterm infants with evidence of **asynchronous respiratory efforts**, neuromuscular paralysis with pancuronium seems to have a favorable effect on intraventricular hemorrhage and possibly on air leak. Uncertainty remains, however, regarding the long-term pulmonary and neurologic effects, and regarding the safety of prolonged use of pancuronium in ventilated newborn infants. The routine use of pancuronium or any other neuromuscular blocking agent in ventilated newborn infants **cannot be recommended** based on current evidence.
- Sedation:** Morphine, Fentanyl, Midazolam²¹—Morphine infusions, although they cause hypotension, can be used safely for most preterm neonates but should be used cautiously for 23- to 26-week neonates and those **with preexisting hypotension**.
- Use Postnatal Dexamethasone Judiciously**
- Avoid early use** of postnatal dexamethasone. Early (before day 14 of life) postnatal dexamethasone is associated with a higher incidence of CP or significant neurodevelopmental handicap. Another study has shown increased risk of ICH. **Avoid prolonged courses** of postnatal dexamethasone.
- Limit Sodium Bicarbonate Use:** The American Heart Association recognizes **only 3 situations in which NaHCO₃ is useful:**

hyperkalemia, urinary bicarbonate loss, and prolonged cardiac arrest. There is substantial evidence that diluting the bicarbonate and infusing it slowly is preferable to rapid concentrated infusions. If sodabarbonate is actually indicated give over 30 minutes.

Correct Coagulopathy^{22,23}

The role of bleeding in producing neurological deficit is now being considered **lesser in importance in IVH-PVH and WMD than to the global ischemia** that follows. Studies have demonstrated coagulation defects (platelet count, function, PT, APTT) in babies who eventually had IVH. Also, in thrombocytopenic VLBW babies incidence of IVH, severe IVH and neurological deficits was higher. But, platelet transfusions did not seem to reduce IVH rates in very preterm babies. The development of IVH in a study was strongly associated with lower gestational age but not with the severity or age of onset of thrombocytopenia.

Currently, there is not enough evidence to suggest that platelet transfusion or coagulopathy correction by blood products would reduce incidence or severity of IVH. Data based on clinical practices suggest that in preterm sick babies, it may be appropriate to administer **blood products as per current transfusion practice guidelines.**

Administrative Strategies in NICU²⁴

NICUs with high patient volume and **high Neonatologist/staff ratio** had lower rates of severe IVH. Quality improvement collaborative (breath savers) demonstrated **improvement in both clinical care processes** and clinical outcomes (including **decrease in severe IVH**) during the Neonatal Intensive Care Quality Collaborative.

Unproven Therapies

a. Magnesium sulfate¹⁴—The role for antenatal magnesium sulphate therapy **as a neuroprotective agent for the preterm fetus is not yet established.**

In a study, antenatal magnesium sulphate was given to women threatening or likely to give birth at less than 37 weeks' gestational age – there was no significant effect of antenatal magnesium therapy on neurologic outcomes. **There was a significant reduction in the rate of substantial gross motor dysfunction (RR 0.56; 95% CI 0.33 to 0.97; two trials; 2848 infants).**

b. Ethamsylate, vitamin E—There is limited evidence that postnatal vitamin E and ethamsylate reduce IVH.²⁵

SCREENING AND DIAGNOSIS OF PRETERM BRAIN INJURY

Clinical Examination

- a. **Head circumference**—head circumference increasing by more than 1 cm per week can be a pointer to IVH. This may be used for screening when facilities to do frequent neurosonogram are not available.
- b. **Popliteal angle**—tightness and other general tone abnormalities point to IVH.

Neurosonographic Screening for IVH – PVH and WMD

As PVH-IVH can occur **without clinical signs**, serial neurosonogram examinations are necessary for the diagnosis

- Routine screening cranial ultrasound examinations are recommended for all infants born **at 32 weeks' gestation or earlier**. Close to 25% of infants with gestation <30 weeks have significant cranial Ultrasound (US) abnormalities that trigger important changes in acute and long-term care.
- Routine cranial ultrasound examinations are recommended at about the **second week (7-14 days) and the sixth weeks of life (36-40 weeks age)** (at discharge) to predict long-term outcomes. Early USG may help in guiding parents but does not accurately predict outcomes. This recommendation is designed to detect both clinically unsuspected IVH and evidence for PVL and/or ventriculomegaly.
- **Grades 3 and 4 IVH, cystic PVL, and moderate to severe ventriculomegaly** determined by US have all been shown to be significantly associated with CP at 2 to 9 years of age in VLBW PT infants. Grade 4 IVH, and ventriculomegaly have been significantly associated with mental retardation and neuropsychiatric disorders. There is a 10-fold elevation in the risk of adverse outcome for VLBW PT infants with US evidence of grades 3 and 4 IVH, cystic PVL, and moderate to severe ventriculomegaly.
- Infants who have hemorrhagic lesions or any white matter or cystic lesions evident on cranial ultrasound examinations require close, **systematic follow-up after their discharge from NICU** to facilitate the timely initiation of interventions.
- Severe cranial ultrasound abnormalities predict motor disability strongly, but one **third of infants with CP had no ultrasound abnormalities**. Caregivers should be aware that there would be differences in the diagnosis and interpretation of cranial ultrasound examinations according to the available ultrasound technology and expertise. The studies should be performed by a consistent, small number of well-trained radiologists or radiology technicians. The most accurate interpretation is based on

real-time or video evaluation. A standardized set of image cuts based on an agreed on “gold standard” is also important. An agreed-on system of interpretation, consisting of both text and an image set, should be used. Serial studies should be performed to optimize correct diagnosis of choroid plexus and germinal matrix lesions.

- **MRI—role not clearly defined diffusion weighted MRI can diagnose brain injury very early (days).**

May be used in ELBW at 36 – 40 weeks if clinical suspicion on USG Superior to USG and CT in prognosis (diagnosis and classification)

Logistics—availability, repeat testing, sedation, cost limit universal application.

TREATMENT OF IVH

- A. **Treatment of acute IVH - Supportive measures** – Maintain normal blood pressure and perfusion, control seizures, ventilation as needed, correct low platelet and coagulation deficiencies, PRBC in case of resultant anemia. **Avoid drugs like aminophylline for apnoea, sodabi-carbonate for acidosis.**

B. **Treatment of posthemorrhagic hydrocephalus**

- **Repeated lumbar punctures, diuretics to reduce CSF** production (Acetazolamide/CA inhibitors and furosemide) not only fail to prevent shunt dependence, death or disability, but have **significant adverse effects.** (Cochrane review) Intraventricular fibrinolytic therapy (**Streptokinase** - instillation into the Intraventricular space) is also not useful.
- **Surgical interventions^{26,27}** such as subcutaneous reservoir and external drain have not been subjected to controlled trial. **External ventricular drainage (EVD)** was found to be an effective and safe therapy for rapidly progressive PHH and increased intracranial pressure. **Ventriculoperitoneal and ventriculosubgaleal (VSG)** shunting remain the definitive treatments for posthemorrhagic hydrocephalus requiring surgical intervention.

Ventriculoperitoneal shunt is not feasible in the early phase after IVH but, despite the problems with blockages and infections, it remains the only option for infants with excessive head expansion over periods of weeks. New treatment approaches aimed at preventing hydrocephalus are needed.

VSG shunts offer a simple, effective, and relatively safe means of temporizing hydrocephalus, and they avoid the need for external drainage or frequent CSF aspiration in these medically unstable infants until the CSF characteristics and abdomen are acceptable for ventriculoperitoneal shunting.

KEY POINTS – reducing NDD due to preterm brain injury (WMD)

1. Adverse neurodevelopmental outcome in very preterm babies depends primarily on the severity of the intracranial lesion (WMD) rather than on gestational age.
2. In preterm babies with WMD, CP is the commonest NDD. CP is present in about 60% VLBW babies with WMD.
3. But, one third of preterm infants with CP had no ultrasound abnormalities.
4. Conservative management of preterm labor may be preferred and attempts made to prolong pregnancy at gestations lower than 29 weeks. If a tocolytic must be used, calcium channel blockers are preferred.
5. ANS are probably the most important determinants of all complications of prematurity and antecedent brain injury. ANS must be administered whenever preterm delivery is suspected at gestation less than 34 weeks. Betamethasone is the currently recommended steroid (2 doses at 24 hrs interval) although dexamethasone is also tried, and faster regimens, incomplete courses are also considered useful. Repeating courses of ANS in case of prolongation of pregnancy is debated, but evidence currently seems to favor repeating.
6. Antibiotics administered to mother in preterm rupture of membranes reduces preterm brain injury.
7. Outborn, transported babies are at increased risk of IVH and in-utero transport must be encouraged.
8. Vaginal delivery is a risk factor for IVH in VLBW, especially in breech presentation.
9. Optimum resuscitation, delay in cord clamping and stabilization before surfactant administration reduces the risk of IVH.
10. Loss of auto-regulation of cerebral circulation and fluctuations in cerebral blood flow form the central basis of IVH. Prevent perfusion problems especially on 1st day. Dopamine seems to be better than normal saline boluses. Without overt hypovolemia, use maximum of 2 volume boluses. Give bolus infusions over >30 minutes.
11. Indomethacin – decreases incidence of IVH, but not risk of NDD at 18 months. Currently Indomethacin is not routinely indicated; it may be useful in very preterm babies when mother has chorioamnionitis or no ANS given.
12. Low SVC flow is a reliable indicator of cerebral perfusion and is associated with lower gestation, no antenatal steroids, severe RD (higher mean airway pressure), large PDA (>1.6 mm).
13. Optimal respiratory care – prevent hypocarbia, use opioid analgesia only selectively (avoid in extreme preterm and hypotensive babies). Avoid routine suctioning, chest physiotherapy, noxious/painful procedures. Avoid post natal steroids, sodabarbonate.
14. Correct coagulopathy, although the same need not reduce risk of IVH.
15. IVH could be asymptomatic; routine neurosonogram screening is indicated in all babies less than 32 weeks. A late scan at 36 - 40 weeks corrected age correlates best with long term outcomes.
16. The ultrasound should be performed by a consistent, small number of well-trained radiologists or radiology technicians or trained neonatologist.
17. Repeated lumbar punctures, diuretics to reduce CSF production are unproven therapies and not adequately tested.
18. Surgical treatments for posthemorrhagic hydrocephalus are also not tested in systematic/planned trials.

Withdrawal of Care Decision in Severe IVH²⁸

1. The health care team and the parents of a high-risk infant **working together** should make decisions about withdrawal of intensive care.
2. **Compassionate basic care** to ensure comfort must be provided to all infants, including those for whom intensive care is not being provided.
3. The decision to continue intensive care should be based only on the judgment that the **infant will benefit from the intensive care**. It is inappropriate for life-prolonging treatment to be continued when the condition is incompatible with life or when the treatment is judged to be harmful, of no benefit, or futile.

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Preterm/Low Birth Weight

As increasing numbers of smaller babies, preterm and IUGR, graduate from intensive care nurseries, there is concern regarding the future health and long-term “neurodevelopmental outcomes” of these survivors.¹ Because these children are not a homogeneous group, they have a broad spectrum of growth, health, and developmental outcomes including childhood disability, further classified as mild, moderate, and severe.² Definitions of specific learning problems vary across studies and regions.

FACTORS AFFECTING LONG-TERM NEURO-DEVELOPMENTAL OUTCOME

Social and environmental disadvantages clearly affect the long-term developmental outcomes of low birth weight children, whether measured in terms of maternal education, race, or social class. For most **low birth weight children, social risk factors have a far greater effect on long-term cognitive outcomes** than do biological risk factors. However, **biological factors have more important influences on outcome for children with severe neurological insult and in ELBW babies**^{3,4} There is also evidence that the cognitive deficits specifically associated with social or environmental risk become more pronounced over time.^{5,6} Most studies have failed to find evidence supporting long-term effects of social factors on **very low birth weight** infants when compared with normal birth weight children.^{2,4,7} There is little doubt, however, that the combined effects of severe neonatal illness and a deprived environment can be devastating.⁷⁻⁹

Low birth weight is considered as a composite index of biological risk. **(Table 3.1)**. The biological risk factors include male sex, asphyxia, apnea, periventricular hemorrhage, meningitis, seizures, hypoglycemia, polycythemia, severe hyperbilirubinemia, chronic lung disease. These **compli-**

cations of prematurity occur more commonly in infants with birth weights of **less than 1500 grams and 1000 grams** (which explains why this birth weight group is at greatest biological risk). Intrauterine growth failure in preterm very low birth weight children does not seem to contribute to poor developmental outcome over and above that resulting from prematurity and its complications. However, those with **severe growth failure** may have a poorer outcome. **Pathological preterm brain injury** includes periventricular leukomalacia and cerebral atrophy, which can result in CP, nonspecific hypotonia, and cognitive and neuropsychological subnormality. **Lesser degrees of brain damage** are thought to be responsible for fine motor impairments, visuo-perceptual problems, difficulties with mathematics, and hyperactivity.

Table 3.1: Univariate associations between antecedents and cerebral palsy in VLBW infants^{11,12}

<i>Exposure</i>	<i>Summary Odds Ratio</i>
<i>Associated with increased risk</i>	
Intrauterine infection	2.2 (1.6–3.1)
Death of a co-twin	10.5 (5.3–20.9)
Placental abruption	1.4 (1–2.2)
Intrapartum acidosis	2.5 (1.3–4.6)
Neonatal acidosis	—
Hypothyroxinemia	4.4 (1–18.6)
Neonatal sepsis	2.7 (1.9–3.9)
Neonatal hypotension	2.6 (1.7–4.2)
Respiratory distress syndrome	1.8 (1.1–2.9)
Assisted ventilation	5.3 (2.8–10.3)
Hypocarbica	2.7 (1.1–6.4)
Pneumothorax	3.3 (2.1–5.4)
Neonatal chronic lung disease	3 (2–4.6)
Antenatal corticosteroids	0.7 (0.5–1)
Magnesium sulfate	0.5 (0.3–0.7)
Pre-eclampsia	0.4 (0.3–0.6)
Fetal growth restriction	0.5 (0.3–0.8)

NEURODEVELOPMENTAL OUTCOMES OF PRETERM/LBW

A significant proportion of **brain growth, development, and networking occurs during the last weeks of gestation and after birth**. Developing brain tissues are vulnerable to injury during this critical period. Insult may result in direct injury to developing tissues or disruption of critical pathways needed for neuronal and glial development.¹³ For most preterm infants

of **> 32 weeks' gestation**, survival and longer term **neurodevelopment are similar to those of infants born at term**. The period between 20 and 32 weeks after conception is one of rapid brain growth and development. **Greatest impairment occurs in the 0.2% of infants born before 28 weeks' gestation, or with birth weights of < 1000 g (extremely low birth weight)**.¹⁴⁻¹⁶ Illness, under nutrition, and infection during this time may seriously compromise neurodevelopment. Infants who are born after exposure to **infection and asphyxia** have worse outcomes than those who are born after only one or neither of the two processes.

CEREBRAL PALSY (CP)

Incidence of CP increases with decreasing maturity or decreasing birth weight. The slight increase in CP prevalence that is seen reflects the increase in CP in VLBW infants, which is entirely a consequence of their increasing survival. Incidence of CP at all birth weights has been static over the years.¹⁷⁻¹⁹ The recent decline in CP in VLBW **may reflect improvements in perinatal care**. The most common forms of CP in children who have been born preterm are spastic hemiplegia (unilateral) or quadriplegia (bilateral). The functional consequences can vary from abnormalities of muscle tone or power that do not cause serious problems, to severe impairments that result in considerable lifelong disability and handicap, such as being unable to walk or to feed independently. Brain damage '–' periventricular hemorrhage, particularly periventricular cystic leukomalacia and post-hemorrhagic hydrocephalus are strong predictors of future neurodevelopmental problems, especially CP.

VISUAL IMPAIRMENT^{20, 21}

- ROP: Most visual impairment in very preterm infants is secondary to retinopathy of prematurity (ROP), and in developed countries is the commonest cause of childhood blindness, visual field defects, and refractive errors.
 - Strabismus and refractive errors are also very common.
 - Cortical visual impairment
 - Contrast sensitivity, field of vision and color vision.
- Single early visual acuity measures may be misleading, multiple measures are required to aid prognosis.

HEARING IMPAIRMENT²²

The etiology of sensori-neural hearing loss is probably multifactorial, with a variety of interacting factors that are related to illness severity. Hearing

impairment is associated with delayed language development. Even very preterm infants with normal hearing may also develop speech and language problems. Deafness, affects 2 to 3% of low birth weight children. There seems to no added risk in the smallest of babies.

INTELLIGENCE QUOTIENT (IQ)

There is a gestational age-related drop in IQ of infants born before 33 weeks. In the Bavarian Longitudinal Study (BLS) there was no relationship between IQ and GA from 33 to 42 weeks but **below 33 weeks, IQ scores decreased linearly by an average of 2.5 points with each weekly decrease in GA (from 32 to 27 weeks)**. VLBW babies have problems in nonverbal reasoning and simultaneous information processing. IQ is also strongly related to socio economic status for both term and extreme preterm populations. Case-control studies have shown that very preterm children have intelligence quotient (IQ) scores significantly lower than term peers, **even in those who are free of severe disability**. A study comparing VLBW survivors born in the early 1980s to those born in the mid-1990s suggests that despite improved neonatal care and survival intelligence scores have not changed.²³ A recent systematic review found that the IQ of extremely low birth weight children is on average 10 points lower than in children who were born at term.

LEARNING DIFFICULTIES

Non-verbal reasoning, visuo-spatial skills and the ability to perceive, integrate and process stimuli simultaneously are particularly compromised by very preterm birth. Such impaired processing capacity may underlie the behavioral, social and academic difficulties frequently observed in this population. Learning difficulties are often associated with problems such as visual or hearing impairment, but children can have isolated cognitive problems. Learning problems among low birth weight children have been documented by teacher or parent ratings of school performance and direct assessments of academic skills in clinical settings. At school age, **up to 50% of infants born before 28 weeks' gestation need some form of additional educational support**. Other reported problems at school age include poorer vocabulary skills and significant delays in reading, spelling and mathematics. In studies involving very low birth weight children, rates of special education placements are reported to be closer to 50% or higher.^{24,25} There is also a tendency for increasing rates of special education with decreasing birth weight.

A study at 8 years of age documents lower rates of disability for ELBW children born in the 1990s compared to the early 1980s.²⁶ Meta-analysis

of the cognitive and behavioral outcomes of preterm school-age children versus term born controls showed significantly poorer cognitive scores (weighted mean difference 10.9; 95% CI (9.2-12.5) with scores being directly proportional to the degree of immaturity. Longitudinal studies have typically **failed to find evidence of ‘catch-up’** growth over time, with some identifying a trend towards deteriorating performance in comparison to term peers.

ATTENTION DEFICIT HYPERACTIVE DISORDER¹⁶

Increased prevalence of ADHD has been found in 12-year old VLBW children (23%) compared to matched term controls (6%, $p < 0.0001$) and in 10-year-old extreme preterm children (20%) versus controls (8%, $p < 0.05$). In heavier children (LBW, <2000 g) the prevalence of ADHD has been found to be 10% (versus controls 1%, $p = 0.0001$). Neonatal white matter injuries, particularly parenchymal lesions and ventricular enlargements, have been found to be strongly predictive of ADHD in LBW/ELBW children, suggesting a more **biologically determined** form of ADHD.

SOCIAL DEVELOPMENT, BEHAVIOR AND PSYCHOLOGICAL PROBLEMS

There is a higher incidence of behavioral problems in extremely low birth weight children of school age, with attention deficit, social, and thought processing problems being the most commonly detected. Behavioral problems have mainly been described in children with cognitive deficits and neuro-motor dysfunction, suggesting **brain injury** as a cause of these problems. The types of behavioral problems reported in low birth weight children include conduct disorder, hyperactivity, and attention weaknesses. Early social development—for example, responsive smiling and recognizing family members—may be delayed in preterm infants. Interactive and imaginative play may also be delayed. As behavioral problems can adversely affect school performance and development of social relations, these are important long-term effects of preterm birth.

GROWTH^{27,28}

Growth attainment of low birth weight children is less than that of their normal birth weight peers. Birth-weight-related differences in mean weight, height, and head circumference increase with decreasing birth weight. Poor growth attainment is seen in both preterm and term children who are born small for age following intrauterine growth failure, and also in preterm children who have normal intrauterine growth but fail to grow after birth because of severe neonatal complications of prematurity such

as chronic lung disease. Although **very little catch-up of head size occurs after one year of age, catch-up of weight and height can occur later.** The major determinants of catch-up growth include the duration and severity of the initial growth failure, as well as the genetic growth potential of the child as measured by parental height.

HEALTH OUTCOMES

The most common medical conditions found in low birth weight children are **asthma, upper and lower respiratory infections, and ear infections.** Low birth weight children are re-hospitalized for the above medical conditions as well as for surgeries, mainly of the eyes (strabismus), ears, nose, and throat (ear tubes, adenoids, tonsils, tracheal complications); orthopedic surgery is also performed for CP.^{29,30} Although respiratory infections decrease after two years of age, health problems persist and contribute to excessive bed days, restricted activity, school absence, and poor school performance.

QUALITY OF LIFE

It is estimated that the academic achievement of approximately 30% to 50% of VLBW born children is in the subnormal range, fewer graduate from high school, 20% to 30% exhibit the attention deficit hyperactivity disorder, and approximately 25% to 30% are affected by psychiatric disorders at adolescence.^{31, 32} Extremely preterm children have higher rates of **re-hospitalization, special health care needs and functional limitations at school** age. Reported rates of re-hospitalization for ELBW survivors range from 31-82% over the first 2 years of life.³³ Although the rates of re-hospitalization decline after the first 2 years of life, the higher rate of readmission for extremely preterm children continues into later childhood. The most recent long-term study of extremely premature infants' now entering adulthood reports **no significant differences** between the ELBW adults and term-born controls with regard to rates of **high school graduation, college enrollment, permanent employment and independent living** status.^{34,35} A recent study of the children has reported **no difference** in the self-reported **health-related quality of life** between impaired and non-impaired ELBW children at young adulthood.³⁶

PRACTICE POINTERS

- Advances in neonatal care have improved perinatal outcome considerably, but the falling threshold of viability has created a new set of dilemmas for parents and caregivers. The overall prognosis remains poor in neonates who are born before 26 weeks' gestation.

- Although preterm survivors continue to constitute a high-risk population for various kinds of disability, particularly CP, the advances in neonatal intensive care have allowed far more infants to survive without CP than with it. Neonatal intensive care has been successful in improving long-term outcomes for premature infants.
- Most children with CP are not born preterm. However, preterm infants, particularly those born after **very short gestations**, are at increased risk of CP.
- Outcomes improve with increasing gestational age, although for any given length of gestation survival varies **with birth weight**.
- Preterm/LBW are at risk of spectrum of neurological disorders ranging from CP to lesser and more subtle degrees of neuro-motor abnormality.
- Continued research and attempts to decrease the rate of low birth weight and associated perinatal medical sequelae are of primary importance.
- Ongoing documentation of the long-term outcome of low birth weight children needs to be mandated, as does the implementation of environmental enrichment programs to help ameliorate the long-term consequences for infants who are born low birth weight.
- It is important to recognize that there is no moral difference between disabled and able-bodied children and adults born preterm or LBW and we should try not to impose our own values or prejudices.

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Section 3

Neonatal

Encephalopathy

4. Perinatal Asphyxia

5. Neonatal Seizures

Perinatal Asphyxia

It is all too familiar a scenario for neonatologists to see the sequence of events associated with an acute fetal circulatory collapse followed by the birth of a sick and acidotic baby, requiring aggressive resuscitation and then developing an encephalopathy culminating in a neurologically impaired neonate. However, it is difficult to clearly prognosticate very early as to what is the likely outcome of this sick baby, who has suffered from hypoxic-ischemic insult in the intra-partum period, both in terms of immediate survival and long-term neurodevelopmental outcome. Approximately 23% of the 4 million annual global neonatal deaths are attributable to asphyxia. 10-20% of asphyxiated infants die, and **20-45% of survivors have neurodevelopmental disability (NDD)**.

DEFINITION OF PERINATAL ASPHYXIA

There is a general lack of an accepted definition for hypoxic ischemic injury. Asphyxia is defined as **impairment of placental or pulmonary gas exchange** resulting in hypoxemia, hypercapnia and a mixed respiratory and metabolic acidosis. Since there is simultaneous occurrence of hypoxia and ischemia, the term hypoxic-ischemic insult is now preferred.¹ The clinical diagnosis of perinatal asphyxia is based on several criteria, the two main ones being evidence of **cardio-respiratory and neurological depression**, defined as an APGAR score remaining less than 7 at 5 minutes after birth, and evidence of acute hypoxic compromise with acidemia, defined as an arterial blood pH of less than 7 or base excess greater than 12 mmol/L. In many settings however, it may be impossible to assess fetal or neonatal acidemia.^{2,3}

INCIDENCE/PREVALENCE

Approximately 23% of the 4 million annual global neonatal deaths are attributable to asphyxia. Post-asphyxial hypoxic-ischemic encephalopathy

(HIE) occurs in approximately 1 to 2 infants per 1000 live term births. Significant proportions of these infants die or survive with severe long-term morbidity. Among term infants, 6% to 23% of cases of Cerebral Palsy (CP) are attributable to intra-partum asphyxia.⁴⁻⁷

Estimates of the incidence of perinatal asphyxia vary depending on the definitions used. In developed countries, the incidence of severe perinatal asphyxia (causing death or severe neurological impairment) is about 1/1000 live births and overall rate varies from 1.8 to 6.7 per 1000 live births.^{4, 5} In developing countries, perinatal asphyxia is probably much more common. In developing countries, the incidence is much higher varying from 9.4 per 1000 live births to 229 per 1000 live births. As per NNPD report of 2000, perinatal asphyxia was present in 1.4% of all intramural births and it was the primary cause in 20% of all deaths.⁸ However, even this probably represents an underestimate of the true community incidence of perinatal asphyxia in resource poor countries. Of the estimated 1.2 million neonatal deaths in India every year, 300000 –350000 deaths occur due to perinatal asphyxia. Despite advances in neonatal care, deaths due to asphyxia have remained relatively unchanged.

IMPACT OF PERINATAL ASPHYXIA ON NEURODEVELOPMENTAL OUTCOME

Perinatal asphyxia affects dominantly the motor system, but can affect cognitive function without very significant involvement of the motor pathways. The expected long-term neurological abnormalities after perinatal asphyxia include CP (athetoid and spastic tetraplegic in term neonates), learning deficits, seizures /epilepsy; lower IQs, visual and hearing impairments.

CEREBRAL PALSY

Athetoid (dyskinetic) CP

This type of CP is by far the most likely subtype to be caused by acute perinatal hypoxic-ischemia at term and the evidence for a causal link is strong.¹³ There is an acute fetal bradycardia (which may or may not be associated with a 'sentinel event' such as uterine rupture, or cord prolapse), followed by the birth of a baby with low APGAR scores needing resuscitation and who then develops an encephalopathy and on neuro-imaging shows abnormalities in the deep grey matter of the brain. Approximately **80% of all cases of dyskinetic CP are caused by intra-partum hypoxic-ischemia at term.** Specifically, damage which occurs as a result of a short period of profound hypoxic ischemia causes injury to parts of the brain with a high metabolic rate, correspondingly high blood supply, high

glucose metabolism and a large number of excitatory glutaminergic inputs. The brainstem is commonly affected in a very severe abrupt insult. Babies with the basal ganglia/thalamus predominant pattern have the most intensive need for resuscitation and most severe clinical encephalopathy and seizures.

Data suggests that cooling is most likely to be effective in this group especially if started soon after the hypoxic-ischemic insult before the secondary wave of neuronal death. One MRI study demonstrated a decrease in basal ganglia and thalamic lesions in those who had a moderately abnormal recording on the amplitude integrated EEG prior to the onset of cooling.^{15,16}

Spastic Tetraplegic CP¹⁷

This is the **second subtype of CP that can be caused by intrapartum hypoxic ischemia** at term. Spastic tetraplegic CP is almost always associated with a very severe disability in the long-term; hardly any of these children can walk and the vast majority has learning disability, with about half also requiring treatment for epilepsy. MR imaging of the brain of these children usually reveals either parasagittal cerebral injury or damage to the deep grey matter with involvement of the white matter and cerebral atrophy. A prolonged period of mild to moderate hypotension can cause damage to the brain in the parasagittal zones ('watershed areas') that lie between the territories of the circulation of the anterior, middle and posterior cerebral arteries.

Parasagittal cerebral injury usually causes tetraplegic CP, often with learning difficulties. Postnatal head growth is usually poor and the end-stage MR imaging shows atrophy, with ventricular dilatation and widening of the inter-hemispheric fissure and extra-cerebral space.

Hemiplegic CP

In general, **hemiplegic CP is not due to perinatal hypoxic-ischemia and one important cause is focal cerebral infarction, e.g. a 'stroke'** (either arterial or venous).¹⁸ Common risk factors for an arterial stroke in the newborn period, include a 'complicated' delivery with a long, slow primigravid labour in the occipito posterior position, and several inherited thrombophilic tendencies.

Ataxic CP

This disability is very unlikely to be due to perinatal hypoxic-ischemic damage at term.

EPILEPSY

Epilepsy is the most common additional disability (apart from learning difficulty) affecting children with CP who had a potentially damaging encephalopathic illness at term, affecting up to 50% of children with spastic quadriplegia.¹³ It would be very **unusual to see epilepsy without an associated motor disability** as the sole disabling condition as a result of perinatal hypoxic-ischemic damage.

VISUAL IMPAIRMENT

Isolated visual impairment is not likely to be due to perinatal hypoxic-ischemia: Many children with hypoxic-ischemic brain damage have visual impairment as part of their overall disability. Isolated visual impairment or delayed cortical development, without accompanying damage to the motor system, is not seen. Children with moderate basal ganglia lesions have abnormal visual function with poor acuity and weak stereopsis but did develop useful vision.¹³

HEARING IMPAIRMENT

Some view that hypoxia damages the hair cells of the cochlea and hearing impairment is often due to hypoxic-ischemia.²¹

In general, the prevalence of hearing impairment in cohorts of children who had an early neonatal encephalopathy at term **is not significantly increased** compared to those without an encephalopathy.¹³

LEARNING DISABILITY

In addition to functional motor impairment, cognitive impairment is a significant problem in children who have experienced intrapartum hypoxia-ischemia at term.¹⁹ In general, learning difficulties that are caused by hypoxic-ischemia at term **occur in conjunction with CP that causes a severe motor disability**. The presence of abnormal cognitive outcomes, at later time points to postnatal environment, socioeconomic conditions and access to rehabilitation services.

Memory Problems and Problems with Executive Functioning

There are case reports of striking and specific memory problems in individuals with bilateral hippocampal atrophy, some of whom were born at term with birth depression and developed an encephalopathy.²⁰

ATTENTION DEFICIT HYPERACTIVITY DISORDER AND BEHAVIORAL PROBLEMS

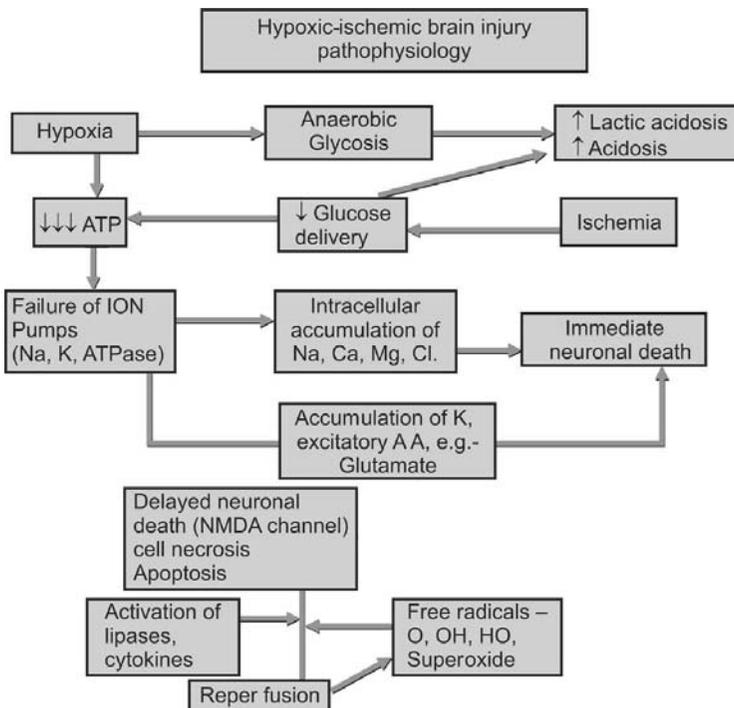
Many children with CP have fidgety behaviour, poor concentration and distractibility, which affect their education and lives, although of course these problems are not confined to such children.

AUTISM AND PERVASIVE DEVELOPMENT DISORDERS

There is currently **no evidence that autism is caused by intrapartum hypoxic ischemia.**

HOW ASPHYXIA CAUSES NEUROLOGICAL BRAIN DEFICITS¹²

In the healthy fetus, there are many adaptive responses to hypoxia-ischemia like redistribution of cardiac output to the vital organs, preferential oxygenation to vital centers to the brain, increased myocardial contractility, accelerated anaerobic glycolysis, etc. **Cerebral auto-regulation** of cerebral blood flow (CBF) initially maintains brain perfusion in spite of an initial drop in the mean BP. The range of blood pressure within which CBF is maintained in newborns is 60–100 mm Hg. With prolonged asphyxia, the early compensatory adjustments fail and CBF may become dependant on systemic blood pressure (pressure-passive). Brain hypoxia occurs when blood pressure



falls, leading to intracellular energy failure. **During the early phases of brain injury, brain temperature drops and local release of the neurotransmitter GABA increases; these changes reduce cerebral oxygen demand, transiently minimizing the impact of asphyxia.**

However, prolonged hypoxic-ischemic damage can cause neuronal death. The **majority of injury leading to neuronal death occurs after recovery from the initial insult and the concept of two stages of neuronal injury** are now formulated.

PRIMARY NEURONAL INJURY

Neuronal cell membranes get affected functionally due to hypoxic-ischemic injury causing **intracellular energy depletion**. Hence there is failure of ionic pump mechanism at the cell membrane level which leads to excess sodium, calcium and water entering the cell causing cytotoxic neuronal injury and death. In addition to this mechanism of neuronal death it is now clear that a majority of cell death occur later even some hours or days after reviving from the insult.

SECONDARY NEURONAL INJURY

Reperfusion of the affected neuronal tissues after a hypoxic-ischemic insult initiates a host of biochemical reactions at the cellular level. The immediate reperfusion which follows resuscitation is possibly due to accumulation of lactic acid causing cerebral vasodilatation.

Free Radical Injury

Reactive oxygen metabolites including oxygen and hydroxyl free radicals further damage the arteriolar endothelium which stimulates xanthine oxidase production leading to further generation of oxygen free radicals which overwhelm endogenous scavenger mechanisms, damage cellular lipids, proteins and nucleic acids and thereby the blood brain barrier.

Excitotoxic Amino Acid Injury

Hypoxic-ischemic insult causes release of excessive amounts of the excitatory neurotransmitter glutamate which acts on the **NMDA receptors** (N methyl D aspartate receptors) which are post synaptic ion channels allowing thereby **sodium and calcium to enter** the neuronal cells causing immediate neuronal death from the osmolar load. Certain regions of the brain appear to be particularly sensitive to NMDA-related injury, especially the basal ganglia and perirolandic cortex, which are particularly vulnerable in neonates following severe hypoxic-ischemic insult. Elevated intra-mitochondrial calcium

interferes with function and may stimulate further reactive oxygen metabolites to be produced. Further, these excitotoxins, because of provoking excessive calcium influx causes delayed neuronal death by activation of undesirable enzyme and secondary messenger systems (e.g. Ca^{2+} dependant lipases and proteases).

Nitric Oxide

Nitric oxide is generated in the cell as the result of stimulation of nitric oxide synthase [NOS]. This generates another reactive metabolite, peroxynitrite, causing lipid peroxidation of intracellular membranes with consequent loss of cell function.

Apoptosis

It is now recognized that neuronal death may occur as a result of necrosis, probably initiated through excessive calcium entry, or apoptosis in which the cell appears to initiate its own demise. Necrosis is initiated by external factors, mitochondrial injury and disruption of the cell. Apoptosis is **regulated by genetic factors with little loss of cellular membrane integrity, leading to contraction of the cells**, which are subsequently consumed by macrophages. Other triggers of apoptosis include cytokines (tumour necrosis factor alpha), reactive oxygen metabolites and NO.

NEUROPATHOLOGY

There is no single distinct or uniform pathological appearance of the brain following hypoxia-ischemia. The pattern of injury depends upon the severity of asphyxial insult (total versus partial), its timing and duration (acute versus chronic), the developmental maturity of the brain and regional variations in vulnerability (due to local vascular factors, distribution of NMDA receptor etc.).

- a. **Cerebral edema:** Within 24-48 hours gross swelling of the cerebral tissue may occur, with marked flattening and widening of the gyri plus obliteration of the sulci, seen on imaging or at post mortem. It arises through two mechanisms: 'cytotoxic', when membrane pump failure leads to intracellular fluid accumulation, and 'vasogenic', when the impaired blood-brain barrier permits capillary leak and interstitial fluid accumulation.
- b. **Selective neuronal necrosis:** This is the most commonly observed pathology following hypoxia-ischemia in term infants, affecting neurons in a scattered fashion and often widely distributed throughout the grey matter. The cerebral cortex layers III and IV and the hippocampus appear

particularly vulnerable. This injury occurs at specific sites to specific cell types (neurons>glia) e.g. CA1 region of the hippocampus, Purkinje cells of the cerebellum (term neonates), intergranule cells of the cerebellum (premature neonates) and brain stem nuclei. This may be due to differing metabolic rates of the various neural structures.

- c. Basal ganglia and brainstem:** In animal models this pattern of injury is seen following 'acute total asphyxia' rather than 'chronic partial asphyxia'. Basal ganglion injury is thought to be responsible for the dyskinetic type of CP seen in survivors of hypoxia-ischemia, and abnormal signal intensity in the basal ganglia is a common finding on magnetic resonance imaging (MRI). If the infant survives for several months, an abnormal myelination pattern is detected on MRI. This is responsible for the marble-like appearance of the basal ganglia seen at post mortem, known as 'status marmoratus'.
- d. Parasagittal injury:** This is an ischemic injury affecting the cerebral cortex and sub-cortical white matter in vascular watersheds between the anterior, middle and posterior arteries, giving rise to a para-sagittal distribution, and is often symmetrical.
- e. White matter injury:** Ischemic insults in preterm infants produce 'periventricular leukomalacia' (PVL) as the periventricular glia is vulnerable to ischemia in preterm infants. When ischemic white matter injury occurs at term, it usually results in sub-cortical leukomalacia. The survivors of the most severe insults usually show a mixed pattern of injury, referred to as multi-cystic leukoencephalopathy.
- f. Focal cerebral infarction:** Infarction of a major cerebral artery, most commonly the left middle cerebral artery, has in the past been reported in association with asphyxia, but it is now realized that this lesion occurs much more commonly in infants with no evidence of intrapartum asphyxia.

ETIOLOGY AND RISK FACTORS FOR PERINATAL ASPHYXIA ..

Perinatal asphyxia may occur *in utero*, during labor and delivery, or in the immediate postnatal period. There are numerous causes, including placental abruption, cord compression, trans-placental anesthetic or narcotic administration, intrauterine pneumonia, severe meconium aspiration, congenital cardiac or pulmonary anomalies, and birth trauma. Postnatal asphyxia can be caused by an obstructed airway, maternal opiates, which can cause respiratory depression, or congenital sepsis. There is considerable debate as to the extent of hypoxia-ischemia at birth contributing to the totality of brain injury and the literature has always suggested that the

brain may have been significantly impaired by events during pregnancy and that birth asphyxia is just the final insult making a relatively small contribution to the burden of damage.

Recent MRI and autopsy studies however, have shown contrarily, that **80% of babies with neonatal encephalopathy showed only evidence of an acute insult without any evident earlier pathology.**⁹ Hence, **evidence for intra-partum asphyxia should always be sought.** In preterm babies in addition to intra-partum hypoxic-ischemic insult many antenatal and postnatal problems like infections, respiratory distress, IVH and leukomalacia can affect neurological morbidity; unlike in term babies where only the hypoxic-ischemic insult plays a role.

MONITORING TOOLS FOR PERINATAL ASPHYXIA AND THEIR CLINICAL VALUE

INTRA-PARTUM FETAL MONITORING

- **Electronic fetal monitoring (EFM) and fetal scalp pH monitoring:** When considering the need to deliver the baby on the basis of an abnormal ECG trace alone, it is recommended that additional fetal blood sampling (FBS) also should be undertaken where possible. A pH of less than 7.20 indicates that delivery should be carried out as rapidly as possible. However, meta-analyses of randomized controlled trials comparing EFM ± FBS versus intermittent auscultation do **not really show any reduction in intra-partum deaths or CP**, despite an increase in cesarean section rates.¹⁴ The prevalence of CP in two randomized controlled trials with follow-up data was not significantly altered by EFM + FBS. The only benefit however, in neonatal outcome seen after electronic fetal monitoring was a **reduction in the incidence of early neonatal seizures.**¹
- **Fetal ECG analysis:** It appears that a **normal heart rate pattern may be reassuring** (negative predictive value of adverse outcome >96% in most studies) but an abnormal fetal heart rate pattern is poorly predictive of fetal compromise.¹ A recent study showed that close CTG monitoring with additional ECG ST-waveform analysis resulted in better intra-partum intervention with a significantly lower rate of acidotic umbilical artery pH values compared with standard CTG monitoring alone.²⁵
- **Others**
 - **Fetal pulse oximetry:** Signal quality derived is limited and the technique has not been tested in large-scale clinical practice, substantiate its usefulness.

- **Near-infrared Spectroscopy:** During labor, an optical probe is inserted through the dilated cervix and on to the fetal head to assess the anterior cerebral artery flows and oxygen saturation. A study of 41 fetuses during labor demonstrated good correlation between the mean cerebral oxygen saturation shortly before delivery and the umbilical arterial acid-base status immediately after birth suggesting it to be a useful clinical tool to screen babies for perinatal hypoxia.²⁶

CLINICAL ASSESSMENT AFTER BIRTH

- **Severity of encephalopathy:** Sarnat and Sarnat introduced a good grading system²² to describe the neurological abnormality, which they referred to as hypoxic-ischemic encephalopathy (HIE) and which has been **modified by Levene et al²³** which is an **excellent and simple clinical tool to assess** and screen these babies.
- **Multi-organ Dysfunction:** During hypoxia-ischemia, blood flow is redistributed in order to preserve circulation to the most vital organs—the brain, heart and adrenals. This is at the expense of the kidneys, liver and gastro intestinal tract, which are therefore vulnerable to hypoxic ischemic damage. Such damage to these and other organs serve as a further marker of hypoxia-ischemia.

POSTNATAL INVESTIGATIONS

Accurate early detection is required in assessing the efficacy of potential neuro-protective therapies. However, some of the newer imaging techniques have not been still fully evaluated because accurate neuro-developmental follow-up data is still awaited.

Cranial Ultrasound

Ultrasound has proved most useful in the detection of IVH and ischemic lesions in preterm infants, and it can also be of use in asphyxiated term infants.^{1,10,13} Initially, cerebral edema can be recognized by a generalized increase in echo-density, a loss of anatomical landmarks, indistinct sulci and compression of the ventricles. ‘Slit –like’ ventricles are seen normally in the first 24 hours in term infants, and are only **abnormal if persisting for more than 36 hours**. The presence of **edema is not a useful prognostic sign**, but later ultrasound scan findings associated with a poor neurodevelopmental outcome include bilateral, uniformly echogenic injury, diffuse parenchymal echodensities (thought to represent neuronal necrosis); multi-focal cystic changes; periventricular echodensities; and ventriculomegaly with cortical atrophy.

CT Scan

CT scan is **most useful as a prognostic help when done about 4-6 weeks¹³ after asphyxia**. During acute stages, CT shows reversal sign-diffuse cerebral hypodensity with loss of gray white differentiation but with relatively increased density of **deep nuclear structures**. In chronic cases CT shows changes in basal ganglia and thalamus (although the MRI is more sensitive). These areas express a **featureless appearance, with loss of distinction of deep nuclear structures** and usually clearly decreased attenuation of these structures, which gradually deteriorates over several months. Rarely the injury can develop **calcification**. Because of the relatively superficial nature of the **parasagittal cerebral injury it is more difficult to appreciate it on CT scan unless it is very severe**. Periventricular leukomalacia in preterm infants can be seen in CT scans as periventricular hypo density with a propensity for involvement of anterior and posterior periventricular areas.

Magnetic Resonance Imaging (MRI)

MRI, particularly when **accompanied by diffusion-weighted images (DWI) becomes the diagnostic modality of choice**, as it is very sensitive for the demonstration of all neonatal hypoxic-ischemic lesions subsequent to the neonatal period.^{10, 13} DWI often can show abnormalities **within the first few hours after the insult** and is pragmatically useful. DWI reveals restricted water diffusion not apparent on conventional MRI by detecting differences in rates of diffusion of water protons. **Atrophy of thalamus, basal ganglia** usually accompanied by increased signal on T2W images is prominent especially in children with extra-pyramidal affection. The sequelae of PVL are distinctive and consist of decreased periventricular white matter, especially in the peri-trigonal area, compensatory ventricular dilation and increased signal in periventricular white matter on T2W images.

Cerebral Blood Flow Velocities

Using pulsed wave duplex Doppler with real-time analysis of the Doppler signal from a **major cerebral artery** (often the anterior), the cerebral blood flow can be determined. The end tidal CO₂ should be kept in the normal range because hypercapnia causes cerebral acidosis and may cause cerebral vasodilation which may cause more flow to uninjured areas with relative ischemia to damaged areas and extension of infarct size. Excessive hypocapnia may decrease CBF. Hyperventilation is not recommended. **The decreasing diastolic blood flow velocity in relation to the peak systolic blood flow velocity (Pourcelot's resistivity index**

<0.55) is associated with a poor outcome in asphyxiated infants.

The cerebral blood flow velocities can take 24 hours to become abnormal following hypoxia-ischemia, and have been found to be of little prognostic value if performed at 6 hours.²⁷

Magnetic Resonance Spectroscopy

Intra-cerebral energy states can be measured *in vivo* by magnetic resonance spectroscopy (MRS) technique. Phosphocreatinine (PCr) and inorganic phosphate (Pi) can be measured from the phosphorus-31 spectra. The PCr/Pi ratio represents the phosphorylated energy status within the brain, and a **low PCr/Pi ratio in asphyxiated neonates is associated with later neurodevelopmental impairment.** Prolonged high levels of lactate peaks predict a bad outcome.²⁸

EEG and Amplitude Integrated EEG (aEEG)— Cerebral Function Monitoring

The severity of EEG abnormalities and the duration are of prognostic importance. **Recovery of normal EEG background by day 7 is associated with a normal outcome. In contrast a burst suppression pattern or isoelectric pattern on any day is invariably associated with a poor outcome.**¹⁰ Amplitude-integrated EEG recordings (Cerebral function monitor) obtained continuously from bipolar electrodes have recently been advocated as an objective tool for early prediction of poor outcome. It was able to predict the neurological outcome **as early as within 12 hours of life** in a recent study.⁴⁰ Their use may lie in the use of newer therapies, which have to be administered within a short window period after birth. The aEEG can be used to predict infants at high risk for HIE. aEEG was predictive of an abnormal outcome with a sensitivity of 78% and specificity of 94%, positive predictive value of 85% and a negative predictive value of 92%. This was much better than either test alone.

BRAIN-ORIENTED MANAGEMENT OF PERINATAL ASPHYXIA

In the immediate postpartum period when resuscitation is being undertaken, it may not be possible to determine whether the neurological and cardio-respiratory depression is secondary to hypoxia-ischemia, or to another condition such as fetomaternal infection or metabolic disease. Consequently, resuscitation and early management will often be of suspected rather than confirmed perinatal asphyxia.

- Resuscitation – as per NRP guidelines
- Correct hypoxia and under-ventilation

- Correct perfusion
- Inotrope support³¹
- Seizure control
- Blood glucose levels between 75 and 100 mg/dl
- Fluid restriction: Systematic review identified no RCTs on the effects of fluid restriction in infants with perinatal asphyxia.
- Osmotic agents: Mannitol has been used in a number of uncontrolled case series. In a heterogeneous group of 225 asphyxiated infants 1g/kg of mannitol was given either early (before 2 hours) or later following hypoxic-ischemia in a non-randomised fashion; the early-treatment group had a better outcome.^{1,10}

RESUSCITATION IN ROOM AIR VERSUS 100% OXYGEN

One systematic review found lower mortality in infants resuscitated in room air when compared with 100% oxygen.³² The review (5 RCTs, 1737 term and preterm infants with low APGAR scores at birth) found that resuscitation in room air was associated with a significantly lower mortality compared with resuscitation using 100% oxygen (AR 69/881 [7.8%] with air *vs* 111/856 [13.0%] with 100% oxygen; OR 0.59, 95% CI 0.48 to 0.74). There is some evidence that using lower concentrations of oxygen limits oxidative stress and secondary neuronal death.³³

SELECTIVE HEAD COOLING

In a study by Gunn et al³⁶ selective head cooling was accomplished by circulating water at 10°C through a coil of tubing wrapped around the head (CoolCap). A servo controlled overhead heater was used to maintain rectal temperature at 34°C to 35°C. Placing a cap forms the other method of inducing hypothermia, from cooled packs around the head at a temperature of 10°C and adjusting this temperature in order to maintain nasopharyngeal temperature at a range between 34°C and 35°C.

SYSTEMIC HYPOTHERMIA

One systematic review and three subsequent RCTs³⁷ found no significant effect of hypothermia on mortality or neurodevelopmental disability in infants with perinatal asphyxia. However, one RCT reported a significantly reduced incidence of the composite outcome “death or moderate/severe disability” in infants treated with systemic hypothermia compared with normothermia. A large randomized study of whole body hypothermia by Shankaran et al³⁸ (demonstrated protection among all infants (irrespective of severity of HIE) studied at 18 to 22 months. Death or moderate or severe disability occurred in 45/102 (44%) in the hypothermia group versus 64/103 (62%)

in the control group (risk ratio 0.72, 95% CI 0.54–0.95, $p=0.01$) and the **number needed to treat (NNT) was 6 infants**. The rate of CP was lower in the hypothermia group, 19% vs 30% (risk ratio 0.68, 95% CI 0.38–1.22, $p=0.20$). Combining the results of the above trials suggests that **mild hypothermia is associated with a significant reduction in death and disability in neonates with HIE**.

At this point in time, one may opine that the results of the brain cooling studies in newborn infants with HIE appear favourable, but they do not provide the necessary evidence of efficacy. The feasibility studies as well as the randomized trials support the safety of mild to moderate hypothermia with minimal adverse events in the infants studied.

MAGNESIUM SULPHATE

The limited evidence from one small RCT found that, when assessing reductions in the composite adverse outcome of survival, abnormal cranial CT and EEG results, and failure to establish oral feeding by 14 days of age, magnesium sulphate /dopamine combination was more effective than no drug treatment.

ANTIOXIDANTS (ALLOPURINOL)

One systematic review provided insufficient evidence from two small RCTs about the effects of antioxidants in infants with perinatal asphyxia. One subsequent small RCT found no significant difference in mortality between infants treated with allopurinol and placebo.³⁵ **No significant difference was found between treatments in the composite outcome of rates of death or developmental delay** (method of assessment not reported).

CALCIUM CHANNEL BLOCKERS

The use of calcium channel blockers has been associated with clinically important **hypotension** in severely asphyxiated newborn infants. We found no systematic review or RCTs on the effects of calcium channel blockers in infants with perinatal asphyxia.

HYPERBARIC OXYGEN TREATMENT

In a study done in China, lower rates of mortality and adverse neurological outcomes were reported in infants treated with hyperbaric oxygen. 7 RCTs, 675 infants. (OR 0.26, 95% CI 0.14 to 0.46). However, the RCTs included in the review used poor methods, and potential publication bias was reported. Therefore, the results should be approached with caution.³⁹

THERAPIES WHERE RISKS EXCEED LIKELY BENEFIT

- **Corticosteroids:** Although corticosteroids may reduce cerebral edema, data from studies in older children or adults with cerebral hypoxia, and from animal studies, suggest that steroids do not improve neurological outcomes. In a small case series of newborn infants with birth asphyxia treated with dexamethasone, there was no evidence of an effect on cerebral perfusion pressure.²⁹ **We found no systematic review or RCTs on the effects of corticosteroids in infants with perinatal asphyxia.**
- **Hyperventilation: No systematic review or RCTs were found though, on the effects of hyperventilation in infants with perinatal asphyxia.**³⁰ Hyperventilation is not recommended.
- **Anticonvulsants (Prophylactic):** One systematic review of three small RCTs, which used flawed methods, found no significant difference in mortality or neurodevelopmental outcomes between barbiturates and no drug treatment in term infants with perinatal asphyxia. One subsequent RCT found no significant difference in mortality prior to hospital discharge in asphyxiated term or near term infants with hypoxic-ischemic encephalopathy treated with phenobarbital versus standard care.³⁴ The systematic review, 3 RCTs, 110 term infants, compared barbiturate versus no drug treatment and found **no significant difference in mortality or in rates of severe neurodevelopmental disability** in the 77 survivors.³⁴

PREDICTORS OF OUTCOME^{1,6,7,10,11,13} (TABLE 4.1)

Data from the national collaborative perinatal project and the British national child development study suggest that **perinatal factors (labor and delivery) contribute little to the incidence of mental retardation and seizure.** Only 3 to 13% of infants with CP had evidence of actual intra-partum asphyxia. Many classically suspected obstetric events do not correlate with CP. Most of the factors, however, reflect preexistent unpreventable sources of neurologic dysfunction that occur independent of asphyxia but that might also predispose to concomitant asphyxia at birth.

- **Fetal distress:** No constant relationship between measures of fetal distress and subsequent long-term neurologic outcome has been demonstrated. Most infants **with only one of the fetal distress predictors do not develop CP.**²⁴ Meconium staining (98% do not develop), pH < 7.1 (no correlation to CP), more than 5 minutes to the first cry (98 % do not develop CP) and 10 minute APGAR score

< 3 (83% do not develop CP). These indices actually reflect clinical status during the perinatal period than they do the ultimate long-term outcome. However, **clustering perinatal events does improve prediction** of CP. For example, seizures, occurring alone, are associated with CP in only 0.13%, but low APGAR score, signs of HIE, and seizures occurring together were identified a small subgroup in whom the risk for CP was 55%.

- **Acidosis:** It is associated with a poor outcome **only when it occurs in combination** with abnormal fetal heart rate patterns, depressed APGAR scores and significant neonatal encephalopathy.
- **Intra-uterine passage of meconium:** This actually occurs in 10-20% of all term deliveries and it is often taken as a marker of fetal distress. However, only 0.4% of term infants with meconium stained liquor develop CP. Richey et al found **no correlation between the passage of meconium and markers of acute asphyxia** (umbilical arterial pH, lactate and hypoxanthine).

Table 4.1: Predictors of long-term neurodevelopmental outcome in perinatal asphyxia

<i>Parameter</i>	<i>Abnormalities and long-term outcome</i>
Fetal acid base measurements	Umbilical artery pH < 7.1, Base deficit > 11: major neurological deficits in 14%
Extended APGAR score	At 20 minutes < 3: CP in 57% survivors
Severity of the encephalopathy	Mild-no neurological sequelae Moderate- 25% have neurological sequelae Severe-100% have neurological sequelae
Seizures	Early onset and refractory seizures
Elevated CPK BB	> 5 IU
Oliguria	Persistently <1 ml/kg/hr for the first 36 hours of life
Background EEG	Burst suppression pattern on any day. Isoelectric tracing on any day
Brainstem auditory, Visual and Somatosensory evoked potentials	Abnormal latencies and amplitude ratios
Neurologic examination at end of 1st week of life	If abnormal, predicts long-term abnormality
head growth	If slow in the first month, is a poor prognosis

Source: Reddy AR, Kumar Praveen. Journal of Neonatology, Year : 2004, Volume: 18, Issue: 2.

- **APGAR score:** A hypoxic-ischemic insult need not always result in a low APGAR score, unless the insult occurs immediately prior to birth. Neonates with **neonatal encephalopathy following a low APGAR score** (<4) followed to 8 to 13 years showed a 3.3 times risk of

problems with mathematics, a 4.6 times risk of problems with reading, a 7 times risk of epilepsy, 13 times risk of minor motor problems, and 14 times risk of attention deficit-hyperactivity disorder compared to controls with normal APGAR scores and no neonatal encephalopathy.

- **Prolonged depression (lower extended APGAR score):** Increases the risk of death or major neurological disability. Term infants with APGAR scores 0 to 3 at 10, 15, 20 minutes have mortality rates of 18, 48 and 59% respectively. In survivors, the CP rates are 5, 9, 57% respectively.
- **Outcome in relation to severity of HIE:** (Table 4.2).

Table 4.2: HIE grade vs Risk of severe handicap in survivors

HIE	Percentage	Likelihood ratio	(95% CI)
Mild (I)	1.6	0.05	0.02-0.15
Moderate (II)	24	0.94	0.71-1.23
Severe (III)	78	10.71	6.71-71.1

- **Neonatal seizures:** Seizures of early onset (<12 hours) that are difficult to control when accompanied by signs of asphyxia in multiple systems. The neonate with seizures was 50 to 70 times more likely to have CP than those without seizures. One half of babies who required resuscitation for 5 minutes after birth and subsequently developed seizures die.
- **Cerebral edema and increased ICP (>10 mm Hg):** Uncommon, when present, denotes extensive cerebral necrosis rather than swelling of intact cells, and has a uniformly bad prognosis. ICP is regarded as an effect rather than a cause of brain damage.
- **MRI findings:** MRI showing abnormality in DWI correlate with poor outcomes in both premature and term neonates.

LATE NEUROLOGICAL DISABILITY ASSOCIATED WITH HYPOXIA-ISCHEMIA

Early assessment of asphyxiated babies allows better correlation between perinatal event and later outcome. Later follow-up, although necessary for assessment of higher-order cognitive functioning, is likely to be confounded by environmental influences. There is little data on long-term outcome of asphyxiated infants. A follow-up of asphyxiated babies to 8 years age showed that there is a graded effect of severity of the asphyxial insult on the IQ. At 3.5 years, the children with moderate HIE had a median (Stanford Binet) IQ of 92.3 compared with 101.5 in babies with mild

HIE. At 8 years there was a difference of 11 points. The difference was that of 17 points when those with moderate HIE were compared to the unasphyxiated group.

KEY POINTS

1. 6% to 23% cases of CP in babies born at term gestation are attributable to intra-partum asphyxia.
2. Although asphyxia is defined differently, the essence is evidence of prenatal events/fetal distress, need for extensive resuscitation at birth, neonatal encephalopathy, metabolic acidosis and multi-organ injury.
3. Athetoid CP (as a result of a short period of profound fetal hypoxic ischemia) and spastic tetraplegic CP (after a prolonged period of mild to moderate fetal hypotension) are the common motor disorders associated with perinatal asphyxia. Ataxic and hemiplegic CP are seldom related to perinatal asphyxia.
4. Epilepsy is the most major co-morbidity of CP in babies with perinatal asphyxia. But, asphyxia is seldom the cause of epilepsy in isolation.
5. Although vision and hearing abnormalities are present in children with CP, perinatal asphyxia per se does not increase risk of these sensory problems. Behavioral problems and autism are again not primary outcomes of perinatal asphyxia. Learning disabilities are seen in some children with serious motor involvement, and may be compounded by postnatal care and environmental factors.
6. During the early phases of brain injury, brain temperature drops and local release of the neurotransmitter GABA increases; these changes reduce cerebral oxygen demand, transiently, minimizing the impact of asphyxia.
7. Prolonged hypoxic-ischemic damage can cause neuronal death; majority of this occurs after recovery from the initial insult and is the result of two stages of neuronal injury.
 - a. Primary neuronal injury is the result of intracellular energy depletion and sodium, calcium and water entering the cell as a result of ionic pump failure.
 - b. Secondary neuronal death
 - i. Reperfusion results in biochemical reactions – release of oxygen free radicals, nitric oxide which cause oxidative injury to cell components and excitotoxic amino acids that cause entry of sodium and calcium and cell death by osmolar load.
 - ii. Besides necrosis of cells by external mediators, apoptosis, i.e. genetically mediated cell death with no loss of cell integrity, is accelerated.
8. MRI and autopsy studies show that 80% of babies with neonatal encephalopathy showed evidence of only an acute insult without any evident earlier pathology, hence, evidence for intra-partum asphyxia should always be sought.
9. Electronic fetal heart monitoring and fetal blood sampling for acidosis have resulted in increased emergency caesarian rates, but, no definite decrease in intra-partum mortality or CP. However, there is a decrease in incidence of early neonatal seizures.
10. Normal heart rate patterns are reassuring, but, abnormal pattern is a poor predictor of fetal distress.

11. Levene's modification of Sarnat staging is excellent simple tool to assess severity of neonatal encephalopathy following perinatal asphyxia.
12. Cerebral edema demonstrated on ultrasound is not a useful prognosticating tool. Only diffuse injury detected later in clinical course correlates with risk of CP.
13. CT scan is most useful prognostic tool when used at 4-6 weeks of life. It shows loss of distinction of deep nuclear structures and a featureless appearance. Para-sagittal injury is difficult to appreciate on CT, unless it is severe.
14. MRI with DWI is the investigation of choice in perinatal asphyxia. It can pick up changes hours after injury.
15. Cerebral blood flow abnormalities are detected by Doppler after 24 hours of asphyxial event. Decreased diastolic flow in relation to systolic flow in major cerebral vessels correlates with poor outcomes.
16. Recovery of normal EEG background by day 7 is associated with a normal outcome. In contrast, a burst suppression pattern or iso-electric pattern on any day is invariably associated with a poor outcome.
17. aEEG predicts poor outcomes more accurately than any other test done singly. This can predict outcomes as early as at 12 hours of birth. It is easily done bed side test.
18. Corner stones of therapy are to prevent post natal injury to brain
 - a. timely and appropriate resuscitation
 - b. optimize respiration
 - c. optimize circulation
 - d. optimize metabolic status—glucose and electrolytes
19. Avoid hyperthermia
20. Control seizures, use anticonvulsants if all metabolic causes excluded. Stop anticonvulsants once seizures controlled and neurological examination is normal. (preferably stop anticonvulsants before discharge from NICU).
21. Fluid restriction and anti-edema (osmotic agents) although common practice, are not supported by evidence.
22. Corticosteroids, hyperventilation, prophylactic anticonvulsants, alkali therapy are therapies associated with more risks than benefit.
23. Resuscitation in room air and selective head cooling are newer therapies that seem to be promising and are areas of current research.

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Neonatal Seizures

NEONATAL SEIZURE—A SERIOUS RISK FACTOR FOR NDD

Seizure is the manifestation of a **serious neurological dysfunction** in a neonate. The mortality of infants developing seizures during the neonatal period has shown a decreasing trend over time (dropped from 40% to 20%), but, long-term neurodevelopmental sequelae in survivors has remained unchanged. The risk of **NDD in a neonate with seizure is very high - around 30%; nearly 20% have recurring seizures in childhood.** Survivors are at risk of abnormal head growth, abnormal motor examinations, cognitive, visual problems (squint, refractory errors) and recurrent seizures during or beyond infancy.

HOW SEIZURES CAUSE THE BRAIN DAMAGE?

Seizures in neonates are most often secondary to a recognizable neuronal insult – hypoxia-ischemia, infection, vascular, metabolic. Primary seizure disorders are rare. The extent of brain damage will depend on the **nature and severity of the underlying insult.**

A seizure by itself can disrupt the development of maturing nervous system. A cascade of biochemical/molecular pathways is normally responsible for brain plasticity or activity-dependent development of the maturing nervous system. Depending on the **degree of brain immaturity,** seizures may **disrupt the processes** of cell division, migration, myelination, sequential expression, receptor formation, and stabilization of synapses, each of which contributes to degrees of neurological sequelae.

WHO IS AT RISK OF SEIZURES AND UNDER WHAT CLINICAL CIRCUMSTANCES?

The list of conditions leading to neonatal seizures is very vast. Common causes are – perinatal asphyxia and birth trauma, prematurity (IVH), serious

neonatal illness with encephalopathy (hypoglycemia, hyponatremia, meningitis), cerebral malformations (abnormal head size and shape), neural tube defects, in born error of metabolism. In term babies *in utero* strokes may cause seizures and encephalopathy in otherwise normal appearing neonate.

Any neonate with encephalopathy – poor feeding, decreased activity must be closely observed for subtle/obvious seizures. **Monitoring with EEG** may be advisable (when feasible) in babies with seriously abnormal sensorium.

OUTCOME PREDICTORS IN NEONATAL SEIZURES

ETIOLOGY

The extent of brain damage and eventual outcomes will depend on the **nature and severity of the underlying insult**. In asphyxia, seizures occur as an epiphenomenon and hence the *severity of asphyxial insult* would determine the long-term morbidity and not the seizure frequency or type. Seizures after IVH are likely in babies with severe brain injury - *parenchymal hemorrhagic infarction or ventricular dilatation*, these are the real determinants of outcome. In focal seizures due to thrombo-occlusive diseases, *infarction with edema* on the diffusion weighted MRI would pinpoint the timing of brain injury and this would have implications on the long-term outcomes.

In arterial strokes, abnormal inter-ictal EEG background, MRI showing involvement of *entire vascular territory or involvement of multiple arteries* is associated with unfavorable outcomes.

Encephalitis and meningitis are examples of postnatal disease processes that can cause brain injury, with coincidental occurrence of neonatal seizures. Brain damage in these infants occurs either directly from central nervous system infection or from inflammatory response to eliminate the source of infection.

Seizures in children with inborn errors of metabolism are associated with brain malformation or damage. *Abnormalities in cortical or white matter development* at variable prenatal time periods may contribute to the later expression of neonatal seizures, as well as other neurological morbidities.

TYPE OF SEIZURE

Seizures should be classified into one of the four categories

- a. Subtle (ocular phenomenon, oral-buccal-lingual movements, apnea, limb movements, and autonomic phenomenon)

<i>Etiology of seizures</i>	<i>Abnormal outcomes (%)</i>
IEM and cerebral dysgenesis	100% (almost)
Hypoxic ischemic encephalopathy (grade-II/III)	50%
Bacterial meningitis	50%
Hypoglycemia	50%
Cerebral venous thrombosis	25 %
SAH	0% (almost)
Late hypocalcemia	0 %

- b. Clonic (focal or multifocal)
- c. Tonic (focal or generalized) and
- d. Myoclonic (focal, multifocal, generalized)

Neonates with **subtle or generalized seizures** are more likely to have CP, epilepsy and mental retardation. Those with **≥ 2 seizure types** are likely to have abnormal outcomes.

DURATION OF SEIZURE

Increasing seizure duration implies a higher risk for seizure-induced brain damage. **Uncoupling of clinical from electrographic seizures** could occur in 25% of neonates with seizures after the use of an antiepileptic medication and in paralyzed neonates. Clinical seizures are often masked. Use of continuous bed-side electroencephalogram is critical in evaluating neonatal seizures. Scher et al identified that nearly one third of term neonates having seizures exhibited electrographic status epilepticus, defined as either 30 minutes of continuous electroencephalographic seizures or 50% of the electroencephalographic recording time, with or without the expression of coincident clinical signs.

ORIGIN OF SEIZURE

Seizures originating within **deep gray matter structures** (i.e., hippocampus or basal ganglia) **and neocortical regions** (arcuate fibers within the depths of cortical sulci, with gyral deformation i.e., ulegyria) are common after an asphyxial insult. Injury to these regions is increasingly associated with neurological morbidities including epilepsy. The model of **“dual-pathology”** which has been applied to pediatric epilepsy patients may also apply to neonatal seizure patients. Mesial temporal sclerosis and cortical dysplasias seen on MRI are also associated with neonatal seizures and with subsequent epilepsy or other neurologic sequelae. Deep white matter necrosis contributes to the formation of acquired focal cortical dysplasia during fetal or preterm life. This results in aberrant gray neuronal aggregate formation in response to gliotic or cystic white matter regions. This type of injury may then leave

the fetus or infant vulnerable to further brain damage because of intra-partum or neonatal diseases.

TIMING OF INSULT

Ante-partum, intra-partum, and neonatal time periods each encompass pathogenic mechanisms which separately or cumulatively can be responsible for brain damage. Chronic placental lesions which occurred during the ante-partum time period may result in a neonate with seizures, either as a result of an ante-partum disease process or from an intra-partum asphyxial event precipitated by uteroplacental insufficiency under conditions of fetal stress. In a study of preterm and term neonates from 23 to 42 weeks corrected age with electrically confirmed seizures, a significant association (odds ratio of 12) was observed between infants with seizures after **intrapartum asphyxia and chronic placental lesions** compared with those having intrapartum asphyxia and only acute placental lesions.

GESTATIONAL AGE

Lower the gestational age worse is the outcome.

NEUROIMAGING

Infants with **abnormal neuroradiologic studies** (CT/MRI) are more likely to have a poor outcome than those with normal studies. Furthermore, infants with **parenchymal brain injury** are more likely to have poor outcome than those with normal studies or those with extra-parenchymal injury. **Multifocal/diffuse cortical lesions or primarily deep gray matter** involvement on MRI are strongly associated with poor outcome. Outcome is favorable in infants with MRI studies that either are normal or show extra-parenchymal or focal cortical lesions.

EEG

EEG is a must in all neonates with seizures and encephalopathy.

Background EEG abnormalities would have bearing on long-term outcomes. Background EEG patterns suggesting poor outcome (80% or more abnormal) are isoelectric, burst suppression, undifferentiated low voltage, diffuse slow activity and gross asynchrony. **Serial EEGs are more predictive** than a one time record.

Seizure management in neonates may be improved with routine monitoring of **amplitude integrated EEG/ video EEG**. Electroclinical uncoupling could occur in nearly 30% of neonates with seizures. Monitoring with aEEG improves detection of electrical seizures and **control of electrographic seizures** with antiepileptic medications, would improve

the long-term outcomes. In an observation by Toet et al, a strikingly lower incidence of post neonatal epilepsy (9.4%) was observed in term infants who received treatment for both clinical and sub-clinical (aEEG seizures) seizures, compared with 20-50% reported in other studies treating only clinical seizures.

The **video EEG** is of particular diagnostic value in infants whose seizures are subtle, or easily confused with **non-epileptic motor behavior**. Video-EEG monitoring studies have shown that these types of movements (eg, generalized tonic posturing, motor automatisms, jitteriness, and some myoclonic jerks) are not associated with ictal EEG patterns. These behaviors may represent “brainstem release” or other non-epileptic phenomena. **Anticonvulsant medications are not indicated for such non-epileptic events** and even may exacerbate some movements.

NEUROLOGICAL EXAMINATION

A **normal neurological examination** during the neonatal period and early infancy predicts a uniformly favorable outcome at 12 and 18 months; an abnormal examination at these times is an unreliable predictor.

BEST PRACTICES FOR THE MANAGEMENT OF NEONATAL SEIZURES

PREVENTION

Prevention/management of primary diseases that can cause CNS insults (discussed under various heads in the chapters that follow)

SCREENING AND DIAGNOSIS

Bed side EEG, aEEG, video EEG

MANAGEMENT OF SEIZURE

Treatment of Neonatal Seizures—Acute Event

Immediate management of seizures includes **stabilization, identification of the cause and specific treatment**, and if needed, administration of an antiepileptic drug (AED) to prevent seizure recurrence. **Before AED are administered, seizures caused by metabolic disorders**, hypoglycemia, hyponatremia, hypocalcemia, hypomagnesemia, or hypophosphatemia require correction of the metabolic abnormality. It is a misconception that metabolic abnormalities do not respond to AED.

AED: Phenobarbitone (Pb) and phenytoin (PHT) are effective as first line AED for control of neonatal seizures. It is **preferable to use monotherapy**

for seizure control. Gal and colleagues studied Pb monotherapy and reported ultimate seizure control in 85%, with effective concentrations between 10.1 and 46.4 mg/L. A total of 60% responded at levels of 20 mg/L or less, 28% responded at levels between 20 and 30 mg/L, and 12% were controlled at a level greater than 30 mg/L. PHT when given as a 15 to 20 mg/kg loading dose results a therapeutic level of 14.5 ± 3 mcg/mL.

PHT should be infused no faster than 1 mg/kg per minute to avoid cardiac arrhythmias or hypotension, and the cardiac rate and blood pressure should be monitored. Fosphenytoin, the prodrug of phenytoin, does not cause the same degree of hypotension or cardiac abnormalities, has high water solubility (therefore can be given IM), and is less likely to lead to soft-tissue injury compared with phenytoin. It is dosed in PHT equivalents at 1.5 mg/kg (1.5 mg/kg of fosphenytoin is equivalent to 1 mg/kg of PHT).

If seizures do not respond to initial treatment with Pb, traditionally PHT is administered, followed by Lorazepam (LZP) or midazolam. With ongoing seizures, **look for a specific cause requiring specific treatment**, such as basic metabolic disorders, the inborn errors of metabolism (IEM), and certain dependency and deficiency states. Of special concern are pyridoxine (B6) and folinic acid-dependent conditions.

If seizures continue despite Pb, PHT, and a benzodiazepine, other AEDs are required (Intravenous: clonazepam, paraldehyde, midazolam, valproic acid, thiopental, lidocaine, and pyridoxine. Oral: clonazepam, vigabatrin, lamotrigine, topiramate, valproic acid and folinic acid).

Investigating a Neonate with Seizures

Electrolytes, CSF analysis (Table 5.1), EEG, and a neuroimaging study should be obtained in nearly all infants who have neonatal seizures.

Blood and CSF cultures should be obtained, and the child should receive appropriate antibiotics until bacterial infections are excluded. If there is a clinical indication of viral encephalitis, specifically HSV, a PCR and culture for HSV may be obtained while the child is treated empirically with antiviral agents such as acyclovir.

The choice **of neuroimaging** is frequently debated. If the infant is critically ill, bedside cranial ultrasonography may be the study of choice until the child is sufficiently stable for CT or MRI. CT is helpful for identifying acute intracranial hemorrhages or calcifications. MRI is the study of choice for patterns of hypoxic-ischemic brain injury and to identify cerebral dysgenesis.

Table 5.1: Baseline Investigations in neonate with seizures apart from EEG and neuroimaging

Blood tests	Random sugar, ionized calcium, sodium, magnesium, Arterial blood gas, lactate and ammonia. Thrombophilic work up if cerebral arterial or venous infarct is suspected.
CSF	Cell count, glucose, protein, bacterial culture Herpes simplex virus (HSV) polymerase chain reaction and culture if HSV encephalitis is suspected Lactate and amino acids if IEM suspected
Urine	Urine culture for CMV if IU infection suspected. Toxicology screen and S-sulphocysteine for sulfite oxidase deficiency.

If seizures continue despite phenobarbitone, phenytoin and or a benzodiazepine, the cause must be specifically investigated and treated. Search for **metabolic abnormalities** and IEMs. Of special concern are pyridoxine (B₆), folinic acid-dependent conditions and glucose transporter defects. These disorders are considered when there is no perinatal or intrapartum insult. IEMs have been associated with neonatal seizures, and the evaluation of these conditions should include investigations that are specific to the case.

Discontinuation of Anticonvulsants after Control of Seizure

When seizures are controlled, Volpe recommends a stepwise approach to discontinuation.

Neurologically normal at discharge: Discontinue AED if the neurological examination is normal at discharge from NICU.

Neurologically abnormal at discharge: Consider the **cause of seizure**, example – cerebral dysgenesis would not recover and AED must continue. Continuation of medication would depend on the **AED used for treatment**. If the patient is receiving PHT, it is best discontinued or another AED considered, depending on the cause of the seizures.

If **neurological examination results remain abnormal**, the clinician should **repeat an EEG** and continue Pb until the EEG results are available and normal. If the neurological status is normal at a **1-month re-evaluation**, Pb can be discontinued over 2 weeks; Even if the neurological status is not normal but the EEG shows no epileptiform abnormalities, Pb can be tapered. If epileptiform features remain, AEDs should be continued, with the sequence **repeated at 3 months**.

Brod and colleagues demonstrated that a normal EEG reading is a reliable predictor of success in tapering AEDs: 18 of 22 term infants and

9 of 10 preterm infants remained seizure-free after a normal EEG reading. **Because AEDs may have detrimental effects on the developing brain, they should be discontinued as soon as possible.** Pb has retarded brain growth in rats. Multiple AEDs have caused toxic effects in cell cultures and have been implicated in apoptosis. AEDs also may interfere with cognitive functioning.

KEY POINTS: reducing NDD due to neonatal seizures			
<ul style="list-style-type: none"> • Neonatal seizure is a manifestation of serious neurological dysfunction • The risk of NDD in a neonate with seizure is very high - around 30%; nearly 20% have recurring seizures. <ul style="list-style-type: none"> • Extent of brain damage will depend on the nature and severity of the underlying insult • Seizure by itself can disrupt the development of maturing nervous system, depending on the degree of brain immaturity (gestation). • Any baby with significant encephalopathy is at risk of seizures, it would be ideal to monitor them with an EEG. • Outcome predictors and modification. 			
<i>Risk factor</i>	<i>Low risk for NDD</i>	<i>High risk of NDD</i>	<i>Poor outcome predictor</i>
Seizure	Late hypocalcemia Subarachnoid hemorrhage	HIE Meningitis Hypoglycemia	Cerebral dysgenesis/IEM Prolonged seizure Abnormal neuro-examination Abnormal imaging Abnormal EEG
<ul style="list-style-type: none"> • Best practice guidelines <ul style="list-style-type: none"> • Screening and diagnosis – Monitoring any neonate with encephalopathy with bed side EEG (or aEEG, video EEG) is recommended. • Management of the risk event <ul style="list-style-type: none"> • Stabilize • Correct metabolic causes • AED may have detrimental effects on the developing brain; they should be discontinued as soon as possible. • AED if necessary – prefer to use mono therapy • Continue AED if neurological exam abnormal at discharge • Reassess at 1month – neurological exam and EEG normal–stop anticonvulsants • Normal EEG reading is a reliable predictor of success in tapering AED • If not reassess at 3 months • Implementation <ul style="list-style-type: none"> • Responsibility – pediatrician, pediatric neurologist, neuro-radiologist • Resource requirements • EEG – neurologist familiar with EEG of newborn including pre-terms • Neuro-imaging – USG portable – pediatrician/radiologist • CT/MRI – neurologist familiar with CT/MRI newborn including pre-terms • Metabolic studies – labs for screening and diagnosis • Drug level monitoring – mandatory for appropriate management of recurring seizures. 			

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Section 4

Metabolic Problems

6. Hypoglycemia

7. Neonatal Jaundice

8. Inborn Errors of Metabolism (IEM)

Hypoglycemia

Hypoglycemia is probably the most common cause of easily preventable NDD in neonates.

PATHOPHYSIOLOGY OF HYPOGLYCEMIA

The basis of neonatal hypoglycemic encephalopathy is that **glucose is the primary metabolic fuel for brain**. The brain utilizes about 20 times more glucose than muscle and fat tissues. Infants have a large brain to body weight ratio (12% in infants versus 2% in an adult), resulting in a higher glucose turnover rate of 6 mg/kg/min in infants compared with 2 mg/kg/min in adults. Further, 90% of total body glucose utilization in infants is by the brain. Hypoglycemic injury has a predilection for the **posterior cerebrum—the occipital cortex** and the lesions involve the **upper cortical neuronal layers**. The caudatoputamen is involved more heavily near the white matter and near the angle of the lateral ventricle; and the hippocampus shows dense neuronal necrosis at the crest of the dentate gyrus. With MRI, a pattern of predominantly **parieto-occipital white matter** abnormalities, often in association with abnormal signal in the **deep grey** matter structures of the thalamus or basal ganglia, has been identified on follow-up of neonates who had experienced symptomatic hypoglycemia, findings-distinct to hypoglycemia.

Immediately after birth, the glucose levels decrease, reach a nadir in the first two hours of life and then gradually increase to normoglycemic levels due to glycogenolysis and later by gluconeogenesis from glycerol and alanine. Lipids are important not only as a source of glycerol for gluconeogenesis but also as a source of free fatty acids, which produce ketone bodies. Ketone bodies, can cross the blood-brain barrier. The neuronal fuel economy depends not only on the circulating blood glucose concentration, but also upon the availability of **alternative fuels** such

as ketone bodies, lactate and possibly amino acids. The local **adaptation of the microcirculation**, the interaction with other brain cells, and the **concurrent neonatal conditions** such as hypoxia and sepsis also determine the neuronal response to hypoglycemia.

The newborn brain is relatively resistant to the deleterious effects of hypoglycemia compared to the adult brain. The major reasons for this relative resistance are:

- Diminished cerebral energy utilization
- Increased cerebral blood flow with even moderate hypoglycemia
- Increased cerebral uptake and utilization of lactate
- Resistance of the heart to hypoglycemia.

Hypoglycemia however potentiates the deleterious effects of hypoxemia, asphyxia, ischemia and seizures. These suggest that degrees of hypoxemia or asphyxia or moderate hypotension which alone would not cause brain injury might do so when hypoglycemia is present concurrently. These observations emphasize the importance of controlling ventilation, circulatory function and seizures in hypoglycemic infants.

IMPACT ON NEURODEVELOPMENT

Neurodevelopment sequelae include disturbances of neurological and intellectual function-motor deficits, especially spasticity and ataxia, seizure disorders, autistic features, learning and behavioral problems and a smaller head circumference.

Neurological outcome depends on the **rapidity of appropriate therapy** and control of the **associated disorders**.^{1,2,3}

- Hypoglycemia, if **severe or prolonged**, results in injury primarily to neurons but to glia as well.
- Severity of hypoglycemia < 25 mg/dl.^{4,5}
- Recurrence of hypoglycemia (6,7) – When hypoglycemia was present on 5 or more days, the incidence of cerebral palsy or developmental delay is increased by a factor of 3.5.
- Duration of hypoglycemia.^{4,8}
- When **associated with other insults to brain**, e.g. hypoxia-ischemia, hypoglycemia of a degree not sufficient to cause brain injury alone can cause neuronal injury.

In a study of 90 infants with hyperinsulinemic hypoglycemia, Menni et al documented psychomotor retardation in 26% of the patients, 8% with major retardation and 18% with an intermediate disability.⁹ Transient mild hypoglycemia in healthy, term LGA newborns does not appear to be harmful to psychomotor development at the age of 4 years.¹⁰

EPIDEMIOLOGY

As per the National Neonatal Perinatal database 2002-2003, the incidence of hypoglycemia in all neonates is 0.9%.¹¹ Hypoglycemia is **commoner in sick neonates unable to feed normally and dominantly on intravenous fluids**. Preterm babies, growth restricted neonates, and infant's delivered to mothers with diabetes are at increased risk of hypoglycemia. The incidence depends upon the population screened, the time of screening, the time and type of feeding and above all, the definition of hypoglycemia.

DEFINITION OF HYPOGLYCEMIA

Unfortunately, the actual level or duration of hypoglycemia that is harmful to an infant's developing brain is not known. Although symptomatic babies are at greater risk there is **not good correlation between plasma glucose values, clinical symptoms and long-term sequelae**.¹² Attempts have been made to identify a threshold blood glucose concentration below which there is a substantial likelihood of functional impairment, particularly of the brain.

The clinical, epidemiological and metabolic approaches have little relevance to outcomes.

Neurophysiological approach: Koh et al in a study of 17 neonates demonstrated alteration of brain stem auditory and somatosensory evoked potentials at blood glucose concentrations < 47 mg %.¹³ Cerebral blood flow changes have been described at blood glucose concentrations of 30 mg%.

Neurodevelopmental approach: A deleterious effect on subsequent cognitive development has been described in infants whose plasma glucose was less than approximately 47 mg% at least on one occasion on three or more separate days. In another study of 661 infants weighing less than 1750 g at birth, a strong association was described between hypoglycemia < 47 mg% on > 5 days and lower Bayley developmental scores at 18 months of age.⁶

Concept of 'Operational threshold': The concept of a rigid threshold blood glucose concentration as a definition of hypoglycemia applicable to all neonates at all times has been challenged. Instead, practical 'operational thresholds' are proposed — **blood glucose concentrations at which clinical interventions**, e.g. increased feed should be initiated. Such thresholds do not define "normal or abnormal" blood glucose concentrations but provide a margin of safety and thus enable the clinician to target the nutritional management of a baby towards 'normoglycemia'.¹⁴

CORNBLATH'S 'OPERATIONAL THRESHOLD'

- Baby with abnormal clinical signs—operational threshold is 45 mg%.
- At risk infants with no clinical signs—operational threshold is 36 mg%.
- Infants with hyperinsulinism—operational threshold is 63 mg%.

BEST PRACTICES***Who should be screened?***

Unwell infants and 'at risk' infants should be screened for hypoglycemia

- Unwell infants: As the symptoms of hypoglycemia are non-specific, all unwell infants should be routinely screened for hypoglycemia at regular intervals.¹⁴
- 'At-risk' infants who require monitoring of blood glucose concentrations are:

A. Maternal conditions

- Diabetes (pregestational and gestational)¹⁵
- Drug treatment (b-blockers, oral hypoglycemic agents)
- Intrapartum glucose administration.

B. Neonatal problems

- Preterm
- Intrauterine growth restriction¹⁶
- Perinatal hypoxia-ischemia
- Hypothermia
- Infection
- Polycythemia
- Infants on parenteral nutrition
- Following exchange transfusion
- Obvious syndromes (e.g. midline defects, Beckwith-Wiedemann syndrome).

WHO SHOULD NOT BE SCREENED?

Normal healthy term AGA infants on breastfeeding should not be screened as a routine.³ This may have an adverse effect on breastfeeding.^{15,16} Moreover, asymptomatic neonates should not be screened in the first 3 hours of life as this would detect only the physiological nadir and the blood glucose rises significantly by 3 hours of age.¹⁷

WHO SHOULD DO THE SCREENING?

The nursing personnel should monitor the 'at risk' newborn for hypoglycemia. At various teaching institutions, with poor nurse: infant ratio, the monitoring for hypoglycemia may be assigned to junior doctors/resident doctors.

WHAT ARE THE BEST SCREENING TOOLS?

The ideal method of blood sugar estimation should be rapid, accurate, inexpensive, require a small sample volume, preferably based on whole blood and available for point-of-care testing.

Reagent strips and glucose reflectance meters are used extensively for screening for hypoglycemia owing mainly to their convenience, cost and rapidity, these devices lack reproducibility and quality-control assurance, are subject to error from skin-cleansing agents and hematocrit variation, and are thus notoriously inaccurate and unreliable for estimation of blood glucose in babies. **Any abnormal value should be confirmed by a laboratory test. However, considering the risk of brain injury, the intervention for hypoglycemia should be instituted.** Care should be taken to ensure the heel prick is at the recommended lateral aspect of the heel, the cleansing agent is dry before the prick and an adequate sized drop of blood is obtained without squeezing the heel.

The laboratory sample should be processed immediately as the glucose value falls by 18 mg % per hour. This can be avoided by collecting the sample in fluoridated tube. Plasma or serum is the preferred sample for measurement of glucose by the analytical procedures in the laboratory, whilst whole blood samples are often used for point-of-care testing due to their ease. Whole-blood-based methods are affected by varying hematocrit in the neonates. Plasma blood glucose values tend to be about 10-18% higher. Recently, an accurate and precise isotope dilution mass spectroscopy (ID GC-MS) method has been proposed as a reference method for determining glucose in whole blood.

RECENT ADVANCES IN MEASURING BLOOD GLUCOSE

The glucose measuring devices are based on glucose oxidase, glucose dehydrogenase, or hexokinase/glucose-6-phosphate dehydrogenase reactions. In recent years, the incorporation of direct measuring electrochemical glucose biosensors into the blood gas and electrolyte analysers has added a further dimension to the measurement and reporting of blood glucose concentrations. Typically, the biosensors report blood glucose 'concentrations' 6-10% higher than those reported by the traditional methods involving sample dilution.¹⁷

CLINICAL DIAGNOSIS

Hypoglycemia is asymptomatic on more than half the occasions. The signs and symptoms of hypoglycemia, when present, are often non-specific. Irritability, jitteriness, feeding difficulties, lethargy, cyanosis, tachypnea, and hypothermia can all be manifestations of hypoglycemia, but these are

also early signs of a number of other disorders, including septicemia, congenital heart disease, ventricular hemorrhage and respiratory distress syndrome. It is important **to have a high index of suspicion** for hypoglycemia when evaluating an infant with any of the above symptoms, since prolonged hypoglycemia causes severe neuroglycopenia with resultant seizures, coma, neurological damage and even death.

PREVENTION OF HYPOGLYCEMIA

Prevention of neonatal hypoglycemia begins in pregnancy, labor, delivery and continues into early neonatal period. The control of maternal diabetes, toxemia, nutrition and factors that cause prematurity must be optimal. Postnatally, the emphasis is on:

- Identification of the high risk neonate
- Minimization of energy expenditure by maintenance of temperature
- Implementation of early oral feedings
- Blood glucose level determinations in the high risk newborn
- Delay discharge of preterm babies till firm establishment of oral feedings to prevent post-discharge hypoglycemia
- Careful monitoring for clinical symptoms.

BEST MANAGEMENT PRACTICES

When to treat?

Based on the neurophysiological, epidemiological and clinical observations, **blood glucose values < 45 to 50 mg% requires intervention. This value is higher than the previously recommended 40 mg%** considering the lack of precise information regarding the level of blood glucose below which neuronal injury is likely to occur and also considering the ample evidence that blood glucose levels are not accurate predictors of brain glucose. In case of hyperinsulinism the target blood glucose levels should be 63 mg%.

Therapy for hypoglycemia includes:

- Encourage and assist oral feeding and frequent monitoring for hypoglycemia in the asymptomatic low risk neonates.
- If hypoglycemia is severe (<25), recurrent, symptomatic or noted in high risk neonates give minibolus of 2 ml/kg 10% dextrose. Lilien et al demonstrated the effectiveness and apparent safety of the 'minibolus' instead of bolus of 0.5 to 1.0 g/kg (2-4 ml/kg of 25% glucose).¹⁸ The minibolus avoids hyperglycemia, osmotic diuresis, dehydration, and rebound hypoglycemia.

- Minibolus should be followed by an uninterrupted.
- IV infusion of glucose to provide a GIR of 6-8 mg/kg/min.
- If the blood sugar levels are not “normal” in spite of above said infusion rate, higher concentrations of glucose infusion must be used to achieve greater infusion rates, conventionally targeting an increase of 2 mg/kg/min.

WHEN SHOULD FURTHER INVESTIGATIONS BE DONE?

An underlying metabolic-hormonal etiology should be suspected when the hypoglycemia is of unusual severity or occurs in an otherwise low-risk infant such as:

- Symptomatic hypoglycemia in a healthy, well grown term infant
- Hypoglycemia with seizures or abnormalities of consciousness
- Persistent or recurrent hypoglycemia

KEY POINTS: Reducing NDD due to hypoglycemia

- Hypoglycemia is probably the most common cause of easily preventable NDD in neonates.
- The basis of neonatal hypoglycemic encephalopathy is that glucose is the primary metabolic fuel for brain and the basal requirements are higher in neonates. The injury has a predilection for the parietooccipital whitematter (MRI)
- Outcome predictors—alternative fuels such as ketone bodies, lactate and possibly amino acids. The local adaptation of the microcirculation, concurrent neonatal conditions.

<i>Risk factor</i>	<i>Low risk for NDD</i>	<i>High risk of NDD</i>	<i>Poor outcome predictors</i>
Hypoglycemia	Transient mild hypoglycemia in infants not at risk	Delay in correction of hypoglycemia recurrent severe < 25	Symptomatic (neuro) hypoglycemia-seizures, coma Associated CNS insults

- Hypoglycemia is commoner in sick neonates unable to feed normally and dominantly on intravenous fluids.
- Preterm babies, growth restricted neonates, and infant’s delivered to mothers with diabetes are at increased risk of hypoglycemia.
- Prevention
 - Identification of the high risk neonate
 - Minimization of energy expenditure by maintenance of temperature
 - Implementation of early oral (breast) feedings
 - Blood glucose level determinations in the high risk newborn
 - Delay discharge of at risk babies till firm establishment of oral feedings to prevent post-discharge hypoglycemia
 - Blood glucose values < 45 to 50 mg% require intervention. In case of hyperinsulinism the target blood glucose levels should be 63 mg%.
- Treatment may be initiated based on reagent strip value, but diagnosis must be confirmed by lab sugars.

- Hypoglycemia requiring >10 mg/kg per min of glucose
- Hypoglycemia in association with other abnormalities (midline defects, micropenis, exomphalos, erratic temperature control)
- Family history of sudden infant deaths, Reye's syndrome, or developmental delay.

FURTHER READING

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UNANSWERED QUERIES/FURTHER RESEARCH^{17,19}

Future research should concentrate on:

- Development of a bedside glucose analyser comparable to the laboratory-standard.
- Mechanisms of hypoglycemic neural injury and refinement of thresholds of safe blood glucose concentrations based on their relationship with both acute and long-term neurological outcomes.

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Neonatal Jaundice

Jaundice is a common physiological event. It can lead to bilirubin encephalopathy and chronic sequelae in a minority. In neonates with bilirubin encephalopathy, 80% either die in the neonatal period or end up having sequelae such as **as athetoid CP, tone abnormalities, lower IQs and or sensorineural hearing deficit**. Term and near term healthy neonates with serum bilirubin ≥ 20 mg/dl, even in the absence of any clinical signs of encephalopathy could have acute effect on the auditory brainstem, minor motor disturbances, dysconjugate gaze and suspicious neurological examinations. But no chronic sequelae such as CP or sensorineural hearing deafness are reported (Table 7.1). However in the presence of co-morbid factors, low birth weight or hemolysis, rarely, permanent ill effects could be seen on the auditory and cognitive functions.

HOW BILIRUBIN CAUSES BRAIN DAMAGE?

Bilirubin is the metabolic product of Hemoglobin (commonly, ineffective erythropoiesis). In blood it is bound to albumin and is excreted from the liver after conjugation. However, is when the capacity of albumin to bind bilirubin is exceeded, free bilirubin exists in the blood. It is the free bilirubin which crosses the blood brain barrier (BBB) and causes neurotoxicity. The factors which **increase the level of free bilirubin or those which damage the BBB** increase the risk of **bilirubin induced brain damage (BIND)**.

- Endogenous substances such as free fatty acids, organic anions
- exogenous substances such as sulphonamides, salicylates, ceftriaxone, moxalactam and benzoates displace bilirubin from albumin and increase the free bilirubin
- Acidosis, hyperosmolar solutions, asphyxia, intracranial hemorrhage, abrupt increase in blood pressure, abrupt increase in venous back pressure and meningitis damage the BBB and precipitate BIND.

In the brain bilirubin affects every aspect of cellular function. It damages the neurons by **membrane injury and excitotoxic mechanisms similar to hypoxic ischemia and hypoglycemia**. The typical areas affected in BIND are globus pallidus, subthalamic nuclei, hypothalamic sectors CA 2, 3 (only in term), hippocampus, substantia nigra, cochlear nuclei, oculomotor nuclei, reticular formation, dentate nuclei, Purkinje cells and anterior horn cells. This pattern of distribution is ascribed to - differential blood flow patterns, local susceptibility of blood brain barrier and differential abundance of gangliosides. Concomitant **intrauterine growth restriction (IUGR), prematurity, asphyxia, hypoglycemia, intracranial hemorrhage, infections, trauma, TNF α and endotoxins increase neuronal susceptibility to BIND**.

EXPECTED LONG-TERM SEQUELAE OF SEVERE JAUNDICE ...

Chronic kernicteric sequelae include sensori-neural hearing deafness, tone abnormalities (hypotonia or dystonia), minor neurological abnormalities, abnormal DDST and lower intelligence quotients. The **earliest changes** of bilirubin encephalopathy (non clinical) are seen on the **MRI, auditory brainstem evoked responses**, somato-sensory evoked responses and cry analysis.

MRI

In severe jaundice bilateral symmetrical hyperintense signals are seen in the globus pallidus on both T₁ and T₂ weighted images (Fig. 7.1). High signal intensity also has been seen in hippocampus and the thalamus. **These MRI changes could disappear with treatment of jaundice but persistent abnormal signals on the MRI could predict long-term neurological deficits.**

BERA

Waves I, III, and IV/V complex are normally present in full-term neonates. Wave I represents the auditory nerve, wave III the superior olive, and wave IV-V complex the lateral meniscus and inferior colliculi, respectively. The latter three sites are classically involved in kernicterus. Severe jaundice leads to loss of waves IV and V, and prolonged latency of the brainstem response (wave I-III, I-V, and Wave III-V: Fig. 7.2). These changes represent aberrant brainstem function, at both upper and lower brainstem levels. The auditory brainstem response reflects auditory neural function; aberrant auditory brainstem response recordings may represent only a part of a more widespread neural malfunction. **Persistent abnormalities on the**



Figure 7.1: Classical MRI changes: Hyperintense signals in the globus pallidus

Hyperbilirubinemia–Neonate

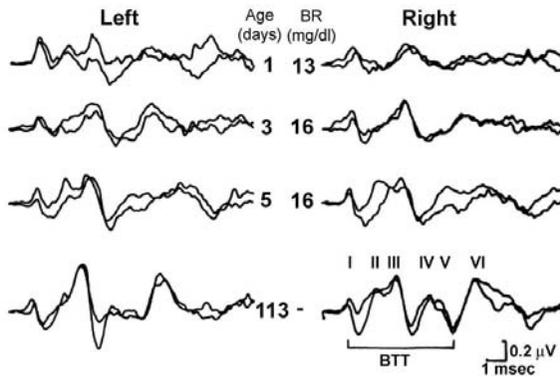


Figure 7.2: BERA in hyperbilirubinemia showing relation of bilirubin (BR) to BERA changes. Increasing levels of jaundice decreases amplitude of Wave IV/V and increased brainstem latencies. However, these changes are transient and disappear by 3 to 4 months in most neonates

BERA at 3 and 9 months of age could predict long-term hearing deficits and sometimes neurological handicaps.

The classic **Perlstein's** tetrad of kernicterus includes extrapyramidal abnormalities, sensori-neural hearing loss, gaze abnormality, and dental dysplasia. **In the first year, infants typically feed poorly, develop high-pitched cry; examination may show persistent and often-**

obligatory atonic neck reflex and righting reflexes. Babies are hypotonic but have exaggerated deep tendon reflexes.

Athetosis (involuntary, sinuous, writhing movements) may develop as early as 18 months but may be delayed as late as 8 to 9 years. Chorea and dystonia are the other abnormal movements, which can occur in these children. Affected children may also have dysarthria, facial grimacing, drooling and difficulty in chewing or swallowing.

Hearing loss is generally most severe in high frequencies and is usually bilateral. **The hearing deficit even when severe, very often escapes clinical detection** for months or even longer and this may be reflected in delayed acquisition of language. The pathological substrate for hearing deficit resides in the neurons in the brainstem particularly the cochlear nuclei and in the auditory nerve. Thus hearing disturbance is both peripheral and central. Auditory system is the most sensitive neural system in bilirubin injury and hence hearing impairment is always present in any form of bilirubin encephalopathy. Extrapyrmidal symptoms in children without hearing impairment rules out bilirubin brain injury.

Gaze abnormality, in particular, limitation of upward gaze is typical of bilirubin brain injury. Occasionally both horizontal and vertical movements are affected. In most cases vertical eye movements can be elicited by Doll's eye maneuver, thus indicating the lesion is above the level of oculomotor nuclei.

About 75% of children with kernicterus have some degree of dental enamel hypoplasia. A smaller percentage has green discoloration of teeth.

Marked intellectual deficits occur only in a minority of patients with kernicterus. Most of these patients are mistaken to be mentally retarded because of their contorted countenance and writhing limbs, as well as undetected hearing deficits.

BEST PRACTICES: REDUCING NDD DUE TO NEONATAL JAUNDICE

1. Follow the AAP guidelines for the screening and management of severe hyperbilirubinemia. It allows a lower threshold for near term babies, infants of diabetic mothers, those with hemolysis, and G6PD deficient neonates.
2. Early and aggressive therapy (one line below the indicated line on AAP chart) is indicated in babies with IUGR, asphyxia, sepsis, acidosis, symptomatic hypoglycemia and certain East Asian races.
3. MRI, BERA and periodic neurological assessment should/may be done in all babies with acute bilirubin encephalopathy and in all those with TSB > 20 mg/dl. **An initial normal BERA and or MRI is reassuring.** If the initial BERA is abnormal repeat may be requested at ages of

Table 7.1: Outcomes of babies with severe jaundice but no clinical encephalopathy

Study	No. of neonates	Bilirubin levels (TSB)	Outcomes	Remarks
Vohr et al (1990)	50	10-20mg/dl (14.3mg/dl)	On day 1 to 2: BNBAS. Jaundiced infants had significantly lower BNBAS scores in every behavioral item except autonomic stability. Significant correlations were found in increased levels of TSB with decreased scores on the individual BNBAS items.	Most babies included had ABO incompatibility
Wolf et al (1997)	45	28.5 + 6.3	4 months of age: infant motor screening (IMS). Linear correlation showed an association between maximum TSB and test rating at 4 months ($r = .32, P < .05$) and test scores at 4 months ($r = .44, P < .03$).	Included premature infants
Agarwal et al (1998)	55	22.4 + 2.7 mg/dl	At 1 year of age: DDST. Neurological development was normal in all infants with TSB levels of 15–20 mg/dL, in 89% of infants with TSB levels of 21–25 mg/dL, and in 67% infants with TSB >25 mg/dL.	
Wolf et al (1999)	35	25-35 mg/dl	At 1 year of age: Bayley (BSID-PDI). Eight (23%) term infants, with a mean TSB level of 33.4 mg/dL, had abnormal and suspect BSID. Twenty-seven (77%) term infants, with a mean TSB level of 26.5 mg/dL, scored normal on the BSID.	
Chen et al (1995)	72	10- >20 mg/dl	DDST at 1 year. None of infants with TSB <20 mg/dl had abnormal findings. 22% with TSB > 20 mg/dl had abnormal findings in gross and fine motor sectors.	
Yilmetz (2001)	87	10-30 mg/dl	At 10 – 72 months: TSB < 20 mg/dL did not show any neurological abnormalities, whereas 9.3% of the subjects with TSB 20–23.9 mg/dL had only disconjugate gaze and 17.6% of the subjects with TSB > 24 mg/dL had neurological manifestations.	
Valaes (1980)	45	16-20 mg/dl	At 61 – 81 months of age: visual-motor integration test. Degree of jaundice was found not to be associated with neurological scores.	Included premature infants
Newman (2006)	659	25-29 and > 30 mg/dl	At 2 years: severe jaundice did not affect the cognition or behavior or neurological examinations. However, those with positive DCT had lower cognitive scores but had no effect on the behavior or neurological examination	Term and near term infants included

- 3 and 9 months and if the initial MRI is abnormal, a repeat scan may be done at an age of 9 months.
4. In high risk neonates with severe hyperbilirubinemia, periodic neurological assessment of tone and neurodevelopment should be done at 3 monthly intervals in the first one year of life and at 6 monthly intervals till 5 years of life.
 5. Appropriate physiotherapy, medications for choreoathetosis, early hearing aids for sensorineural deafness improve the long-term outcomes of neonates with BIND.

Inborn Errors of Metabolism (IEM)

Inborn errors of metabolism (IEM) are rare disorders characterized by a block at some point in the normal metabolic pathway caused by a genetic defect of a specific enzyme. The number of diseases in humans attributable to inherited point defects in metabolism now exceeds 500.¹ While the individual diseases are rare, they collectively account for a significant proportion of neonatal and childhood morbidity and mortality. Metabolic diseases have a varied clinical presentation involving virtually all the organ-systems. Some of them are amenable to treatment and in many others it is possible to make an antenatal diagnosis thereby preventing recurrence. Therefore, an accurate diagnosis is important.

The estimated burden of IEM is 3-4/1000 live births. As high as 20% of acute illnesses in newborns in developed countries are due to IEM. There is a paucity of data on the epidemiology of IEM in Indian population. **In a hospital-based study in India, biochemical screening of 4,400 cases of mental retardation revealed that 5.8% were due to a metabolic disorder.**² In a study at AIIMS, out of over 2000 cases referred with diagnosis of suspected IEM, 1.9% were found to have amino acid disorders.³ The common disorders reported were homocystinuria, alkaptonuria, maple syrup urine disease, and non-ketotic hyperglycinemia.

CURRENT UNDERSTANDING OF PATHOPHYSIOLOGY

The clinical features of IEM are a result of metabolic disturbances caused by deficiency of some catalytic or transport protein. This could have any of the following consequences.⁴

ACCUMULATION OF A SUBSTRATE

Substrate accumulation is the major pathogenetic factor in many IEM, e.g. Tay-Sachs disease (accumulation of GM₂ ganglioside leading to cerebral

neurodegeneration), urea cycle disorders (accumulation of ammonia resulting in encephalopathy), phenylketonuria (accumulation of phenylalanine leading to mental retardation).

ACCUMULATION OF A NORMALLY MINOR METABOLITE

In some IEM, the primary cause of disease is accumulation of a normally minor metabolite produced in excess, because of block in the major degradative pathway, e.g. in untreated galactosemia, cataracts result because of accumulation of galactitol, a normally minor metabolite of galactose.

DEFICIENCY OF A PRODUCT

This is another important primary consequence of many inherited metabolic diseases. The extent to which it contributes to disease depends on the importance of the product, e.g. Hartnup disease (deficiency of product niacinamide leading to pellagra), lysinuric protein intolerance (deficiency of product ornithine leading to hyperammonemia).

SECONDARY METABOLIC PHENOMENA

Because of the close relationship between the various processes comprising intermediary metabolism, enzyme deficiencies invariably have secondary metabolic effects, e.g. glycogen storage disorder type 1 (secondary metabolic effects include lactic acidosis, hyperuricemia, and hypertriglyceridemia), and methylmalonic acidemia (secondary metabolic effects include hyperammonemia and hyperglycinemia).

IMPACT ON NEURODEVELOPMENT

As mentioned above, IEM are responsible for about five percent cases of mental retardation and global developmental delay. They **rare cause isolated developmental delay, mostly present with other clinical clues.**⁵ However, they remain an important cause to be looked for as specific therapy may be available, acute metabolic decompensation may be avoided, and accurate prognosis and genetic counseling can be offered to the families.

COMMON NEUROLOGICAL PRESENTATIONS ASSOCIATED WITH IEM INCLUDE⁴

Many of the disorders may not have neonatal signs or symptoms but their screening is possible in perinatal period and therapy may start in the asymptomatic newborn (e.g. PKU).

CHRONIC ENCEPHALOPATHY WITHOUT NON-NEURONAL INVOLVEMENT

Patients often have predominant features of grey or white matter involvement. Disorders with predominant grey matter involvement present with developmental delay or regression of attained milestones, cognitive earlier than motor, seizures, vision problems, e.g neuronal ceroid lipofuscinosis. Disorders with predominant white matter involvement present with motor regression, spasticity and ataxia, e.g. metachromatic leukodystrophy.

CHRONIC ENCEPHALOPATHY WITH NON-NEURAL INVOLVEMENT

Include disorders like mucopolysaccharidoses (hepatosplenomegaly, dysostosis multiplex, coarse facies in addition to psychomotor retardation), Menke's disease (kinky hair, seizures, and severe regression).

ACUTE ENCEPHALOPATHY

Urea cycle defects, organic acidemias, fatty acid oxidation defects (More likely to present in neonatal period).

SEIZURES

Seizures without other manifestations may be seen in some IEM e.g. pyridoxine dependency, folinic acid responsive seizures, glucose transporter defect.

STROKE

IEM are important causes of stroke and stroke like episodes in children. Examples of such IEM include homocystinuria, Fabry disease, organic acidemias and mitochondrial disorders.

MOVEMENT DISORDERS

Extrapyramidal features like dystonias and choreoathetoid movements are predominant features in some IEM, e.g. glutaric aciduria type 1, Lesch-Nyhan disease.

ATAXIA

Intermittent ataxias are seen in urea cycle defects, organic acidemias, pyruvate dehydrogenase deficiency. Progressive ataxias are seen in abetalipoproteinemia, mitochondrial defects etc.

MYOPATHY

Glycogen storage diseases, fatty acid oxidation defects, mitochondrial disorders.

MANAGEMENT AND PREVENTION

IEM clinically manifesting in the neonatal period are usually severe and are often lethal if proper therapy is not promptly initiated. Clinical findings are usually non-specific such as **poor feeding, lethargy, drowsiness and failure to thrive; and may mimic sepsis**. A high index of suspicion needs to be maintained in all acutely sick newborns, **especially if the illness occurred after a period of apparent normalcy**. The following circumstances increase the likelihood of the presence of an underlying IEM:

- Parental consanguinity
- Previous history of neonatal death
- Rapidly progressive encephalopathy of unknown etiology
- Severe metabolic acidosis
- Hyperammonemia
- Peculiar odor.

INVESTIGATIONS

Metabolic investigations should be initiated as soon as the possibility is considered. The outcome of treatment of many IEM, especially those associated with hyperammonemia, is **directly related to the rapidity with which appropriate management is instituted**.

First line investigations include:

- Blood counts (neutropenia and thrombocytopenia seen in organic acidemias)
- Blood urea and electrolytes (low blood urea in urea cycle defects)
- Blood gases and lactate
- Blood ammonia
- Liver function tests (hepatic derangements in fatty acid oxidation defects)
- Urine reducing substances and ketones.

Second line investigations:

- Urine amino acids and organic acids
- Plasma amino acids
- Lactate/pyruvate ratio
- Urinary orotic acid
- Biotinidase levels.

Neuroimaging:

Neuroimaging especially MRI may provide helpful pointers towards etiology while results of definitive investigations are pending. Some IEM may be associated with structural malformations, e.g. Zellweger syndrome

has diffuse cortical migration and sulcation abnormalities. Agenesis of corpus callosum has been reported in Menke's disease, pyruvate decarboxylase deficiency and nonketotic hyperglycinemia.⁶ Examples of other neuroimaging findings in IEM include:

- Maple syrup urine disease: brainstem and cerebellar edema
- Propionic and methylmalonic acidemia: Basal ganglia signal change
- Glutaric aciduria: frontotemporal atrophy, subdural hematomas.

TREATMENT

In most cases, treatment needs to be instituted empirically before definitive diagnosis. The aims of treatment are to:⁷

- Reduce the formation of toxic metabolites by decreasing substrate availability (by stopping feeds and preventing endogenous catabolism)
- Provide adequate calories
- Enhance the excretion of toxic metabolites.
- Institute co-factor therapy for specific disease and also empirically until diagnosis is established.

IMMEDIATE THERAPY

- Stop oral feeds, process/ store blood and urine samples before stopping feeds
- Start parenteral fluids
- Correct dehydration, acidosis and dyselectrolytemias
- Start specific therapy if any: e.g. sodium benzoate for hyperammonemia
- Monitor and maintain vitals, blood sugar, electrolytes, and blood gases
- Severe hyperammonemia: peritoneal or hemodialysis may be needed.

LONG-TERM TREATMENT

The following modalities are available:

Dietary Treatment

This is the mainstay of treatment in phenylketonuria, maple syrup urine disease, homocystinuria, galactosemia, and glycogen storage disease type I and III. Some disorders like urea cycle disorders and organic acidurias require dietary modification (protein restriction) in addition to other modalities.

Acceleration of Removal of Substrate

Toxic metabolites which are produced due to the block, are removed by various mechanisms. Examples include peritoneal dialysis, hemodialysis, continuous venous-venous hemofiltration for treatment of urea cycle disorders with sodium benzoate and sodium phenylbutyrate.

Reaction Product Replacement

Examples include creatine monohydrate in guanidinoacetate methyltransferase deficiency, arginine in argininosuccinicaciduria, L-Serine in 3-phosphoglycerate dehydrogenase deficiency.

Enzyme Replacement Therapy (ERT)

The principle behind ERT is that the missing enzyme is supplied exogenously, through repeated intravenous infusion. ERT is now commercially available for three lysosomal storage disorders: Gaucher disease (recombinant human macrophage-targeted glucocerebrosidase), Fabry disease (human alpha-galactosidase) and Hurler disease (human alpha L-iduronidase). Phase I and II trials in Pompe's disease have also shown promise. Clinical trials are also underway for MPS II (Hunter disease) and MPS VI (Maroteaux-Lamy disease). Responses to ERT in these disorders have generally been encouraging although the degree and extent of benefit vary considerably.⁸

Cofactor Replacement Therapy

The catalytic properties of many enzymes depend on the participation of non-protein prosthetic groups, such as vitamins and minerals, as obligatory co-factors. The following co-factors may be beneficial in certain IEM:⁹

- Thiamine: Mitochondrial disorders, thiamine responsive variants of MSUD, PDH deficiency and complex I deficiency)
- Riboflavin: Glutaric aciduria Type I, Type II, mild variants of ETF, ETF-DH, complex I deficiency
- Pyridoxine: 50% of cases of homocystinuria due to cystathionine β -synthetase deficiency, pyridoxine dependency with seizures, xanthurenic aciduria, primary hyperoxaluria type I, hyperornithemia with gyrate atrophy
- Cobalamin: Methylmalonic acidemia (*cbIA*, *cbIB*), homocystinuria and methylmalonic acidemia (*cbIC*, *cbID*, *cbIF*)
- Folic acid: Hereditary orotic aciduria, Methionine synthase deficiency, Cerebral folate transporter deficiency, hereditary folate malabsorption, Kearns-Sayre syndrome
- Biotin: Biotinidase deficiency, holocarboxylase synthetase deficiency.

PREVENTION**GENETIC COUNSELLING AND PRENATAL DIAGNOSIS**

Most of the IEM are single gene defects, inherited in an autosomal recessive manner, with a 25% recurrence risk. Therefore, when the diagnosis is known

and confirmed in the index case, prenatal diagnosis can be offered, wherever available for the subsequent pregnancies. The samples required are chorionic villus tissue or amniotic fluid. Modalities available are¹⁰:

- **Substrate or metabolite detection:** useful in phenylketonuria, peroxisomal defects.
- **Enzyme assay:** useful in lysosomal storage disorders like Niemann-Pick disease, Gaucher disease.
- **DNA based (molecular) diagnosis:** Detection of mutation in proband/ carrier parents is a prerequisite.

NEONATAL SCREENING

Newborn screening is a public health initiative to ensure a healthy start for the newborn. Although it is well established in developed countries, India does not as yet have a program at a national level. Goals of screening include: medical intervention in pre-symptomatic stage (e.g. phenylketonuria and congenital hypothyroidism), screening for reproductive planning (e.g. in carriers for Tay-Sach disease) and to determine the epidemiology of various IEM. There is a limited experience from India on neonatal screening. A pilot program carried out in Hyderabad on 20,000 babies revealed a high prevalence of congenital hypothyroidism (1: 1985), followed by congenital adrenal hyperplasia (1: 2600) and aminoacidopathies (1: 3771).¹¹

Techniques of screening include bacterial inhibition assay or "Guthrie's" test for phenylketonuria (now seldom used), tandem mass spectrometry (used for organic acidemias and aminoacidopathies), radioimmunoassay (for hormonal analysis), enzyme assay (galactosemia, biotinidase deficiency), and specific mutation testing (useful when small number of mutations are responsible and disorder is relatively common).

Disorders which can be detected by tandem mass spectrometry (TMS) include aminoacidopathies (phenylketonuria, MSUD, homocystinuria, citrullinemia, argininosuccinic aciduria, hepatorenal tyrosinemia), fatty acid oxidation defects, organic acidemias (glutaric aciduria, propionic acidemia, methylmalonic acidemia, isovaleric acidemia). The cost of this procedure is high, a limiting factor in resource poor countries. The predictive value of a positive screening test is less than 10%; i.e. 90% of positive results are not indicative of an IEM.¹² Being a costly investigation, adequate discretion should be exercised in ordering a TMS test. Based on estimates of the incidence of various IEM, it has been predicted that one out of 4000 newborns would be identified presymptomatically with a treatable IEM.⁴

Problems associated with TMS include confusing reports which can result in a dilemma both in the healthy newborn and newborn with suspected

IEM. For example, TMS has resulted in the identification of apparently healthy individuals with acylcarnitine abnormalities. Another frequently encountered abnormality is elevated C₅OH (3-hydroxyisovalerylcarnitine). The significance of these abnormalities is unclear; some causes may be maternal enzyme deficiency, enzyme polymorphisms or lab error. Close follow-up with clinical and biochemical monitoring are needed to determine the significance of the abnormality in any individual infant.

FREQUENTLY ASKED QUESTIONS

WHAT SAMPLES SHOULD BE OBTAINED IN AN INFANT WITH SUSPECTED IEM WHEN DIAGNOSIS IS UNCERTAIN AND DEATH SEEMS INEVITABLE?

Some patients with IEM will not survive, despite intensive treatment. In such cases, establishing a diagnosis is very important for genetic counselling and later prenatal diagnosis. Parents should be explained the prognosis and permission for samples/ biopsies obtained. The following samples should be taken as part of a 'metabolic autopsy':

- Blood: 5-10 mL; frozen at -20°C; both heparinized and EDTA samples to be taken.
- Urine: freeze at -20°C
- CSF
- Skin biopsy: including dermis in culture medium or saline with glucose
- Liver, muscle, kidney and heart biopsy (in cases of cardiac involvement)
- Clinical photograph (in cases with dysmorphism)
- Infantogram (in cases with skeletal abnormalities).

HOW SHOULD A NEWBORN WITH A HISTORY OF SIBLING DEATH WITH SUSPECTED IEM BE MANAGED?

In such cases feeds should be started under monitoring. A suggested protocol is to start with oral dextrose feeds and after 24 hours add medium chain triglycerides. Monitor sugar, blood gases, ketones, ammonia. If all tests are within normal limits, add low protein milk. Repeat tests after 48 hours; if negative; start breast feeds. After 48 hours, tandem MS and urine organic acid tests should be obtained.

SHOULD ALL CHILDREN WITH GLOBAL DEVELOPMENTAL DELAY OR MENTAL RETARDATION BE TESTED FOR IEM?

IEM's are responsible for only 5% of cases of global developmental delay. However, diagnosis is i e likelihood for an underlying IEM and testing in such cases can be considered:

- Parental consanguinity

- Unexplained neonatal or infantile deaths
- Encephalopathy
- Protein aversion
- Self-injurious behavior
- Seizures
- Regression of attained milestones
- Hypotonia
- Extrapyramidal features
- Hepatosplenomegaly
- Cardiomyopathy
- Failure to thrive
- Recurrent vomitings.

WHAT IS TANDEM MASS SPECTROMETRY (TMS)?

TMS is a technically advanced method in which compounds are separated by molecular weight by means of a mass spectrometer. The analysis of acylcarnitines, amino acids, and other metabolic intermediates is performed on dried blood spots. TMS has revolutionized newborn screening for IEM in developed countries. As mentioned earlier problems with TMS include prohibitively high cost and low positive predictive value. Cost effectiveness studies available from a few developed countries suggest screening for a few presymptomatically treatable IEM's e.g. **Phenylketonuria and Medium-chain acyl CoA dehydrogenase deficiency.**

UNANSWERED QUERIES/ FURTHER RESEARCH

There is a paucity of data regarding the epidemiology of IEM in India. Large-scale studies are needed to understand the prevalence and clinical profile of various IEM so that newborn screening programs can be planned.

The treatment of IEM in developing countries remains a frustrating experience despite timely diagnosis. Special diets and enzyme replacement therapy are prohibitively expensive, most patients can not afford even co-factor therapy. Research is needed on indigenous diets in IEM.

Newer treatments for IEM include: solid organ transplant, bone marrow transplant, and single gene transfer therapy. The goal of therapy is to achieve the incorporation and expression of sufficient amounts of normal genetic material in appropriate tissues to achieve long-term correction of genetic defect. Liver transplant is beneficial in tyrosinemia, glycogen storage disorders, urea cycle disorders.

The rationale behind bone marrow transplantation (BMT) is that a reconstituted hematopoietic system from a healthy matched donor will contain

stem cells that can produce the missing enzyme. BMT has been at least partially successful in severe MPS I, MPS II, MPS VI, mannosidosis, Wolman's disease, metachromatic leukodystrophy, and Krabbe's disease.¹³

Single gene transfer therapy is still in the experimental stage. For lysosomal storage disorders, two different approaches to gene therapy are being pursued. The first involves the direct delivery of genes to specific organs, such as the central nervous system, using viral vectors. A second approach involves genetically altering hematopoietic stem cells from patients to produce the missing enzyme and returning the altered cells to the patient through BMT. Both approaches have shown promise in animal models.¹⁴

KEY POINTS – reducing NDD due to IEM

1. IEM are responsible for about five percent cases of mental retardation and global developmental delay. They rarely cause isolated developmental delay; mostly they present with other clinical clues.
2. Presentations include acute/chronic encephalopathy with/without non-neuronal involvement, seizures, movement disorders, muscle weakness etc.
3. The basis of disease is accumulation of a normal/abnormal metabolite/or deficiency resulting from enzyme defect. Some of these are treatable and some form basis of prenatal testing and counseling
4. In many IEM, e.g. hyperammonemia, outcomes depend directly on early diagnosis and treatment.
5. Most IEM are single gene defects with AR inheritance and allow opportunity for prenatal diagnosis.
6. Neonatal screening for IEM although expensive, offers an opportunity for pre-symptomatic diagnosis. The current concerns are the large number of false positives and difficult availability of definitive therapies (drugs and special diets).

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INTERNET RESOURCES

1. www.ncbi.nlm.nih.gov/entrez/query.fcgi: Excellent search engine for articles and abstracts in vast array of journals dating over 50 years.

2. www.genetests.org: resource for information on clinics and laboratories providing genetic diagnostic services.
3. www.slh.wisc.edu/newborn/guide: guide to newborn screening.
4. archive.uwcm.ac.uk/uwcm/mg/docs/oth_mut.html: Index of locus specific mutation databases with many links.
5. www.rarediseases.org: information and links related to several inherited diseases.

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Section 5

Respiratory Problems

- 9. Apnea
- 10. Meconium Aspiration Syndrome (MAS)
- 11. Persistent Pulmonary Hypertension
of Newborn (PPHN)

Apnea

Apnea or cessation of breathing is common in preterm babies born before 34 weeks gestation and almost universal in babies born before 26 weeks. Despite being such a common problem, we are **neither sure of the impact, apnea has on the neurodevelopmental outcome of neonates nor are we sure that treatment of apnea by different modalities improves neurodevelopment.**

DEFINITION

Most of the available literature defines apnea in infants as breathing pauses, which last more than 20 seconds, or a shorter duration if associated with bradycardia or oxygen desaturation.¹ However, there is no consensus about the duration of apnea, the degree of change in oxygen desaturation, or severity of bradycardia that should be considered pathologic, i.e. we don't have an answer as of now, whether an apnea which last 20 seconds will have the same connotation as a pause for 40 seconds and whether apnea which leads to desaturation to a value of 30% will differ in neurodevelopmental outcome from an apnea which results in a oxygen saturation levels of 80%. Apnea events exceeding 30 seconds are occasionally seen in both healthy term and preterm infants.² This suggests that apnea duration per se may not be the critical feature of altered breathing and its relation to circulatory consequences. Lack of standardization of this data is the most important reason for ambiguity in outcome measure in neonatal apnea.

PATHOPHYSIOLOGY OF APNEA

Although pathogenesis of apnea of prematurity has not been fully elucidated, it is probably related to both the overall neurological and cardio-respiratory

immaturity of preterm babies. Apnea of prematurity results from immaturity of brain stem respiratory control centers. As immaturity is more pronounced with decreasing gestational age, there are more chances of apneas at lesser gestational age. In normal individuals, the respiratory centre (situated in the medullary region of brain stem) responds to the various signals like increase in carbon dioxide, decrease in oxygen, and decrease in pH by increasing the firing of respiratory neurons. This increased firing results in increased impulses to respiratory muscles and hence results in increased ventilation. These responses are impaired in newborns and this result in apneas.³

- Respiratory responses to increased carbon dioxide are decreased in preterm babies and slope of response continues to increase from 26 weeks onwards till 33 weeks and hence in face of hypoventilation due to any reason, babies are not able to increase their respiratory drive and land in apnea.
- Responses to hypoxia are also altered in preterm babies. In contrast to events in older infants where hypoxia results in sustained hyperventilation, preterm babies are characterized by a very brief period of hyperventilation followed by depressed ventilation despite continued hypoxia. Initial hyperventilation may be completely blunted in preterm babies.
- Negative pressure in the upper airways in preterm babies can result in inhibition of diaphragmatic contraction. In cases of mixed apneas, the lack of airflow due to obstruction, e.g due to passive neck flexion, results in generation of a negative pressure in airways and as a result cause decrease in central respiratory drive. One of the mechanism by which CPAP helps in apnea is by splinting the upper airways and hence obviating this reflex inhibition. Also neonates are obligate nose breather and cannot make an immediate switch to oral breathing when nose is obstructed.
- Active or REM sleep is marked by irregularity of tidal volume and REM sleep predominates in preterm infants. Coupled to this fact is that chest wall compliance of premature infants is poor and hence they have more episodes of hypoventilation.

APNEA AND NEURODEVELOPMENT

Since apnea is associated with desaturation and bradycardia, it is plausible to think that significant episodes of apneas may have a significant impact on neurodevelopment. However, this information at present is not clear. Earlier reports found little evidence of any neurodevelopmental risk directly attributed

to a history of apnea of prematurity or acute life threatening episode (ALTE).^{4,5} Studies are few due to non standardized criteria for diagnosis and for quantifying severity of apnea related events in NICU and also due to variable treatment strategies. Also separating the consequences of conditions associated with premature births like sepsis, intraventricular hemorrhage from effects of apnea of prematurity has proven difficult.

Cheung et al⁶ followed 124 very low birth weight babies upto 24 months of age, to evaluate the relationship between precisely measured pre-discharge apnea that persisted beyond 35 weeks and the neurodevelopmental outcome. They found that **duration of artificial ventilation and the grade of IVH** were independent predictors of neurodevelopmental outcome and the **mean oximetry desaturation and frequency of pre-discharge apnea** correlated with mental and motor developmental scores. Mean oximetry desaturation during apnea was an independent predictor for both mental and motor scores in infants with grade 3 or 4 intraventricular hemorrhage. Authors suggested that pre-discharge respiratory recordings may be useful in predicting subsequent neurodevelopment of high-risk preterm infants, especially those with severe intraventricular hemorrhage. Increasing **number of days** on which at least one apnea occurred also has been associated with impaired neurodevelopmental outcome.⁷ In the same study, number of days ventilation was required for apnea was also associated with poor neurodevelopmental outcome. Even delay in resolution of apnea beyond the 36 weeks post conceptional age has been associated with impaired neurodevelopmental outcome.⁸ Apnea of prematurity has been shown to be an independent predictor of poor early school age outcome like cognitive functions and other neuropsychological rating.⁹ These events are probably related to **hypoxemia/blood flow** during the episodes of apnea. CHIME study¹⁰ also provides some insights regarding risk of neurodevelopmental sequelae in infants with events documented using home memory monitoring. Of the infants included in the study there was an inverse relation between number of conventional events detected by home monitoring and neurodevelopmental outcome. This association was seen both in term and preterm babies. The adjusted difference in mean MDI scores with at least five events compared to no events was 5.6 points lower in full term babies and 4.9 points lower in preterm babies. A dose effect was also suggested by tendency for mean BSID – II values with 1 to 4 events to be intermediate between 0 and at least 5 events. Changes in cerebral blood flow velocity have been documented to decrease to the level of no or minimal diastolic blood flow during prolonged apnea.¹¹

Although no authoritative statements can be made based on sparse data, it may be worthwhile keeping a close check on neurodevelopment in newborn **with recurrent apneas** and in whom the **apneas persist beyond term gestation**. Validity of pre-discharge apnea event recording still has to be confirmed in larger trials before it can be used as a predictive tool for neurodevelopment in newborns.

MONITORING AND EVALUATION OF APNEA.....

WHO ALL TO MONITOR?

All infants less than 35 weeks of gestation should be monitored for apneic spells for at least the first week of life, because of high risk of apneas in this group of babies. Apneic spells generally begin after 24 hours although it can begin on the first postnatal day of life also. Progesterone (which is a known respiratory stimulant) transferred from the mother before delivery has been suggested as the reason for the delayed presentation of apnea. In addition **term babies who have any central nervous system disorder, systemic illness or has received drugs, which depress respiration like narcotics etc should be monitored for apnea**.

Routine monitoring for apnea includes monitoring of heart and respiratory rates as well as oxygen saturations, since impedance monitors cannot detect obstructive apneas. Polysomnogram which measures cardio-respiratory patterns, muscular activity, ETCO_2 , TcO_2 , oral and nasal flow and chest and abdominal movements is ideal but is not routinely used in clinical practice.

HOW LONG TO MONITOR?

Both term and preterm babies show a progressive decline in apneic episodes over time. In an old citation involving 249 term and preterm infants, 92% had no further apnea beyond 37 weeks and by 40 weeks 98% of the babies were apnea free.¹² That study involved larger preterm babies. In a recent study involving preterm babies between 24-28 weeks, apnea frequently persisted beyond 36 weeks and continued beyond 40 weeks post-conceptual age in some.¹³ CHIME study data showed that cardio-respiratory events in preterm babies return to baseline normal level at 43-44 weeks post-conceptual age. Only one study till date has attempted to answer the question of what constitutes a safe period and it concluded 8 days as a safe period but again there is paucity of data in extremely premature babies.¹⁴

Hence based on available literature, one should monitor for apnea **till at least 37 weeks gestation**, but in extremely premature babies one may have to monitor for a longer time. An **apnea free period of 8 days** seems to be a reasonable period.

ROLE OF HOME MONITORING

Home monitoring has not shown to decrease the incidence of sudden infant death syndromes (SIDS). Home monitor could be used as an alternative to prolonged hospital stay in babies who are otherwise well but continue to have non-life threatening apneas at the time of discharge. Such monitoring should continue for a maximum of 44 weeks post conceptional age as suggested by the CHIME study. Infants with frequent events at home should be re-hospitalized and have further studies associated illnesses have been diagnosed after admission in such babies.¹⁵

MANAGEMENT OF APNEA

Once apnea is diagnosed, the clinician must investigate for a number of causes while continuing to monitor and provide supportive care. In term babies, most cases are likely to have secondary causes of apnea, whereas in extremely premature babies, although investigations for secondary causes must be completed, 80% of the infants would have no identifiable cause and diagnosis is of apnea of prematurity.

Physical examination should include observation of the infants breathing pattern and careful neurological and respiratory examination. One should look for presence of secretions in the oropharynx which may have resulted in occlusion of the airway. It is particularly important to **rule out systemic conditions like seizures, gastroesophageal reflux** as pharmacotherapy with **methylxanthines is known to decrease the threshold for seizures and reflux**. Among the first tests to be done is blood sugar, as symptomatic hypoglycemia is independently associated with poor neuro-developmental outcome. Infants should be evaluated for stability of thermal environment. Other blood tests include complete blood counts for sepsis, electrolytes including calcium. Other test like ECG, chest radiograph, spinal fluid analysis also may be carried out based on circumstances.

BEST PRACTICE GUIDELINES FOR THE PREVENTION AND TREATMENT OF APNEA

Prevention of Prematurity

Since the incidence of apneas is directly related to the gestational age at birth, decrease in incidence of premature births may offer the simplest

solution to decrease the incidence of apneas. However, this is most difficult to achieve.

Tocolysis

Tocolysis has not been able to prolong a preterm birth for long time in preterm labor. In fact, magnesium sulphate used for preeclampsia and tocolysis in mother has been associated with increased risk of apneas in neonates.¹⁶ Hypermagnesemia during parenteral nutrition has also been a cause of apnea.¹⁷

Antenatal Steroids

Although antenatal steroids do not directly affect the maturation of respiratory centers, it does decrease the incidence of respiratory distress syndrome which can present as apnea in extremely premature babies.

Noxious Stimuli

Like deep suctioning, painful procedure should be avoided or done gently as these promote a vagal inhibition of respiration.

Kangaroo Mother Care

Skin-to-skin contact, or kangaroo care, for preterm infants has been associated with an increased occurrence of apnea, bradycardia, and desaturation and irregular breathing;¹⁸ this appears to be unrelated to hyperthermia.¹⁹ The observation suggests that obstructive events may occur during skin-to-skin contact. Recent investigators however found no adverse events during kangaroo care.²⁰ The disparity among the reported studies may be related to the specific practice of skin-to-skin care in a particular NICU or the validity of monitoring during skin-to-skin contact. Till further data is available, given the benefits of KMC in reducing serious infections and preventing hypothermia in preterm babies (which independently increase the risk of apneas), KMC does hold promise in care of premature babies.

Blood Transfusions

Classical teaching recommends red blood cell transfusions if apnea coexisted with anemia. However, data available at present in preterm babies with both mild (Hb 8-12 mg/dl)²¹ and moderate anemia (< 8 mg/dl)²² have shown that giving transfusion to such babies does not decrease the episodes of hypoxia/bradycardia. Given all the hazards associated with blood transfusions in neonates, ***apnea of prematurity alone should not be an indication*** for transfusions.

Sensory Stimulation

Introduction of pleasant odour in the incubator in preterm babies who continued to have apneas despite pharmacological therapy has been shown to decrease the incidence of apneas by almost 30%.²³ Presence of a pleasant odor in the environment may help the infant to regulate his physiological state, however, it is possible that vanillin used in the study possesses pharmacological properties and therefore, has direct or indirect effects on the respiratory centers. Since some of the odors can have negative influence on the respiration use of this modality **should wait further trials**.

CO₂ Inhalation

Although one of the pathophysiological mechanisms of apnea is decreased respiratory drive to increased CO₂ in the blood, inhalation of low concentration of CO₂ has also been proposed as an effective treatment. In one study involving 10 preterm babies with gestational age between 31-33 weeks exposure to one hour of CO₂ concentration ranging from 0.5 to 1.5 percent was associated with significant decrease in the episodes of apnea and improved oxygenation. This data **however, is too limited to recommend this therapy at this time**.²⁴

Oxygen Supplementation

Oxygen may decrease the frequency of apneas. Oxygen replaces other gases in the functional residual space of lung ensuring that during brief episodes of apnea there is enough oxygen in the lungs to diffuse into the blood and avert hypoxemia. However, oxygen therapy in the neonates is fraught with dangers of oxygen mediated free radical injury like BPD, ROP, etc. **Hence, oxygen should be used to keep the pulse oximeter values in the 88-93% range**. If a newborn requires oxygen supplementation to keep oxygen saturation in that range, then one must search for secondary causes of apnea like sepsis, PDA, etc. and not label as apnea of prematurity.

Temperature

Hypothermia is a known risk factor for apnea and should be avoided or corrected before considering any further therapy. Increase in ambient temperature to 30°C has been shown to increase the incidence of apneas in preterm babies reaching term as compared to keeping the babies at 24°C.²⁵ Even a slight increase in body temperature of 0.8°C increased the indices of periodic breathing with apneic oscillations.²⁶ Air temperature in an **incubator should be kept near the lower end of the thermo-neutral zone to lessen the episodes of apnea**.

Position

Extremes of flexion and extension should be avoided to decrease the likelihood of airway obstruction. Although physiologically ventilation is better in prone position, central apneas tend to be more in prone position²⁷ with less arousals emphasizing the importance of recommending supine sleeping, after neonatal unit discharge for prematurely born infants.

Kinesthetic Stimulation

Physical stimulation by nursing staff is commonly used to arouse the apneic infant and stimulate breathing. This led people to speculate whether frequent physical stimulation by means of oscillating mattress to provide kinesthetic stimulation might reduce the number of apneic events. Kinesthetic stimulation has not been shown to prevent occurrence of apnea.²⁸ Cochrane review²⁹ on kinesthetic stimulation to treat established apneas has shown decreased frequency of apnea of short duration but had no impact on the clinically significant apneas (those more than 20 seconds) in duration or those with hypoxia and bradycardia. All the studies included in the review used a different method of providing stimulation and because of the cross over design, later outcomes on neurodevelopment could not be studied.

Further research with larger trials is needed with focus on neurodevelopment before recommending this modality.

Carnitine Supplementation

Preterm infants have lower muscle carnitine reserves compared to term infants. This is probably related to poor tissue uptake due to immaturity of the carnitine biosynthetic pathways, reduced placental transfer and reduced intakes from breast milk. Treatment with carnitine has shown benefit in the respiratory status of ventilator dependent adults, as well as stabilization of respiratory parameters and increased physical performance in adult patients with chronic respiratory insufficiency. Cochrane review³⁰ on carnitine for apnea in neonates has shown no benefit and **hence its use at present is not recommended.**

Immunization

There is an increase in adverse cardio-respiratory events following the first dose of DTP-IPV-Hib in preterm infants. The increase in apnea has been attributed to the whole-cell pertussis component.³¹ Investigators have observed reduced morbidity with newer vaccines that contain acellular pertussis.³² However, one recent study showed no difference between those who received whole cell as compared to the acellular variant.³³ Chronic diseases in preterm babies at the time of immunization greatly

increased the risk of apneas.³⁴ If the neonate is in the NICU for chronic diseases at 2 months post-birth, **monitoring for apnea, bradycardia and desaturation is recommended after vaccination**. Healthy preterm infants without chronic disease and therapy seem to be less vulnerable to such adverse effects **but still should be vaccinated in hospital settings**. **Acellular pertussis** should be used for immunization in preterm babies if cost is not a factor.

Pharmacological Treatment

There are no definite guidelines, when to start pharmacological therapy, but most would start treatment when apneic spells continue despite supportive measures or if one apneic episode was severe enough require bag and mask ventilation.

Methylxanthines

Most commonly prescribed drug therapy for AOP.

- Caffeine citrate (not available in India at present),
- Aminophylline and its oral substitute theophylline.

Mechanisms of action of methylxanthines

- Increased response to CO₂ and decreased hypoxic depression of central respiratory drive
- Increased diaphragmatic activity
- Increased minute ventilation.

Pharmacokinetics

Theophylline: Mean half life of theophylline is approximately 30 hours in infants. Oral theophylline is given with a loading dose of 5 mg/kg followed by a maintenance dose of 1-2 mg/kg every 8 hours. A therapeutic effect is seen at a plasma concentration of at least 5 mg/L, although a target plasma concentration is around 10. Plasma concentration of theophylline may vary widely at the same dosage levels, which necessitates **frequent monitoring and dose adjustments**.³⁵ Toxicity usually starts after 20 mg/L but can be seen at plasma concentration of more than 13 mg/L. Side effects include tachycardia, abdominal distension, feed intolerance, seizures, hyperglycemia and electrolyte imbalances.

Caffeine citrate can be administered either orally or intravenously. The recommended loading dose of 10 mg/kg of caffeine (equivalent to 20 mg/kg of caffeine citrate) followed 24 to 48 hours later by a single daily maintenance dose of 2.5 mg/kg (5 mg/kg of caffeine citrate). Caffeine toxicity is rarely observed at plasma concentration below 50 mg/L, which is markedly higher than the therapeutic concentration of 5-20 mg/L. Side

effects commonly seen with caffeine are jitteriness, tachycardia, and occasionally GI intolerance.

Choice of methylxanthine therapy: Evidence suggests that caffeine is equal in efficacy with fewer drawbacks.³⁵ Dosing regimens of caffeine are simpler and produce more predictable results. Moreover, caffeine has a wider therapeutic window and required very infrequent monitoring of plasma levels. Although caffeine at present is not available in India, given the better profile **caffeine is likely to replace theophylline** once it is available.

Reasons for concern with methylxanthines

Xanthines inhibit two (A1 and A2a) of the four known (A1, A2a, A2b and A3) adenosine receptors and experimental evidence suggests that **non-specific adenosine receptor blockade in very preterm infants may have detrimental effects on growth, neurological and cognitive development and childhood behavior.**

Effect on growth: Methylxanthines increase oxygen consumption³⁶ in preterm babies by 20-25% and it has been shown that even a single loading dose of theophylline 5 mg/kg can increase the energy expenditure by 15 KJ/kg/day. This data although not conclusive suggests that use of methylxanthines may increase energy consumption and hence affect growth of premature babies.

Effect on neurological development and behavior: Adenosine is neuro-protective in many experimental models of hypoxia/ischemia.³⁷ However, the results are not consistent and Bona et al³⁸ found that theophylline reduced rather than increased brain injury after hypoxia-ischaemia in 7-day old rats. Efforts to manipulate adenosine receptors in neonatal and adult animal models of hypoxic-ischemic brain injury with specific agonists and antagonists for the adenosine A₁ and A_{2a} receptors have yielded complex and occasionally contradictory results. Furthermore, there is evidence that chronic administration of adenosine receptor ligands has different effects on hypoxic-ischemic brain injury than acute ligand administration.³⁹ Mice with experimental deficiency of A1 and A2 receptors are more anxious and aggressive.⁴⁰

In summary, experimental evidence of physiological and pathophysiological roles of the adenosine receptor system in the immature brain are complex and, as yet, incompletely understood and one cannot at present make predictions based on experimental data. There is at present no significant data available from randomized controlled trials in newborn on long-term safety of methylxanthines because most of the trials have focused on short-term benefits. Since adenosine receptors are found in

all tissues, methylxanthines may have beneficial or harmful effects on many clinically important outcomes. These include neonatal morbidities such as necrotizing enterocolitis, retinopathy of prematurity, chronic lung disease and ultrasonographic evidence of brain injury (which are independent predictors of poor neurodevelopmental outcome) as well as growth, neurological development and childhood behavior.

A large multicentric trial, caffeine for apnea of prematurity trial,⁴¹ involving more than 2000 neonates has shown that caffeine therapy decreased incidence of bronchopulmonary dysplasia and mean duration of mechanical ventilation by a week. Besides, caffeine did not increase the incidence of ultrasonic evidence of brain injury and necrotizing enterocolitis.

DOXAPRAM

Doxapram is a respiratory stimulant that acts on both peripheral chemoreceptors and the central nervous system. Dose: 3 mg/kg bolus followed by 1.5 mg/kg/hr as infusion. Cochrane review on doxapram (only one study) showed decreased apnea in first 48 hours after starting the drug, but the benefit was not sustained. No major side effects were reported. But, number of subjects in the study was too small to make useful conclusions. Doxapram has been shown to decrease the cerebral blood flow in preterm babies⁴² and even mental developmental delay has also been associated with prolonged days of doxapram therapy for apnea.⁴³ Other short term side effects like hypertension, central nervous system stimulation, gastrointestinal disturbances and even heart block has been reported in some of the observational studies. Given that there are no substantial data available on the benefit/side effects, doxapram use **should be restricted** to scenarios where recurrent apneas are continuing despite use of methylxanthines and **facilities for ventilator support are not available**. Doxapram infusion could be used to transfer the baby to a NICU with such facilities.

VENTILATION

CONTINUOUS POSITIVE AIRWAY PRESSURE

CPAP delivered by a nasal interface is an effective treatment of apnea of prematurity.⁴⁴ Mechanisms proposed - patency of upper airways, stabilizing chest wall, maintaining functional residual capacity. Cochrane review⁴⁵ comparing CPAP with methylxanthines suggested higher failure rates with CPAP. The only trial included in the review, used mask CPAP – a modality which is no longer being used. Masks require a complete seal and improper use might have resulted in a higher failure rates. Recent studies on VLBW babies show that early application of nCPAP and

avoidance of mechanical ventilation resulted in no adverse neurodevelopment/growth.⁴⁶ A significantly higher developmental quotient was found in the nCPAP group at 18 months' corrected age. Several trends were also noted in the nCPAP group with a decrease of intraventricular hemorrhage and "abnormal neurodevelopment" at 6 months corrected age. However, these studies were not in babies having apnea. **Prophylactic CPAP has no role in prevention of apnea.**

NASAL INTERMITTENT POSITIVE PRESSURE VENTILATION

If apneas continue despite CPAP and methylxanthines, intubation and ventilation become necessary. Owing to the risks of invasive ventilation, nasal intermittent positive pressure ventilation is an alternative worth considering. NIPPV reduces asynchronus thoracoabdominal motion as a result of better stabilization of chest wall.⁴⁷ Two trials^{48,49} comparing the NCPAP to NIPPV have shown different results – one showing no difference whereas the more recent one⁴⁹ has shown NIPPV to be more effective in reducing apneas. Gastrointestinal perforation has also been reported by some authors.⁵⁰ Newer machines can synchronize ventilator breaths (SNIPP) with the infant's respiratory cycle. For practical purposes NIPPV may be used ***if apneas continue despite NCPAP.***

INTUBATION AND ASSISTED VENTILATION

If the infant continues to have clinically significant episodes of apnea despite maximum pharmacological and non-invasive positive airway pressure ventilation, intubation and assisted ventilation become necessary.

HIGH-FLOW NASAL CANNULAE

Recently it has been shown that NC can deliver positive distending pressure (PDP) to premature neonates if the flow is increased to 1 to 2 L/min (high-flow nasal cannulae [HFNC]). Only one study has compared nasal cannulae (with air oxygen blender) to nasal CPAP. NC was as effective as NCPAP in the management of apnea of prematurity with no difference in the number of apneas, bradycardias, or desaturation during a 6-hour period.⁵¹ This was a small study with period of observation limited to 6 hours. The nasal cannulae being inexpensive and easier to use, **need to be studied in larger trials.**

FURTHER RESEARCH

- Understanding of the relationship of apneic episodes to oxygenation of vital organs, particularly the brain. Defining a method for quantifying apnea in the newborn.

- Determining whether apnea has any long-term outcome consequences independent of preterm birth.
- Determining the long-term consequences of treating apnea with methylxanthines. Hopefully this should be answered in the CAP trial.
- Role of GABA antagonist biculline (Adenosine acts through GABA receptors).

KEY POINTS – reducing NDD due to apnea

- There is not enough systematic information of impact of apnea on NDD or that of various treatments. Many of very preterm babies have co – morbidities (like IVH, hypoglycemia) that may be equally or more important.
- Hypoxemia or decreased cerebral blood flow in event of apnea is considered as possible mechanism of brain injury.
- Outcome predictors
 - Persisting apnea beyond term gestation
 - Recurrent severe apnea
 - Co-morbidities like IVH
 - Degree of hypoxemia, number of days apnea persists, days on ventilator
 - Who to monitor for apnea
 - All preterm babies < 35 weeks gestation till 37 weeks corrected age or till 8 days apnea free period.
 - All term babies with encephalopathy
- How to monitor – pulse oximetry (saturation and heart rate) and respiratory rate monitoring (impedance)
- Management of apnea
 - Check air way
 - Breathing pattern
 - Screen for hypoglycemia, hypocalcemia
 - Neurological assessment
- Caffeine is safer than aminophylline, and is equally effective
 - Rule out GERD/seizure before using methylxanthine
- nCPAP with appropriate interface is as effective.
- Ventilation (or NIPPV) is resorted to, when above mentioned modalities fail
- Doxapram may be used in an emergency, if ventilation facility is not available
- Noxious stimuli, hyper/hypothermia, vaccination of chronically ill preterms out of hospital setting must be avoided

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Meconium Aspiration Syndrome (MAS)

Meconium aspiration syndrome is defined as respiratory distress associated with the passage of meconium around the time of birth with characteristic radiological changes and without an obvious alternate etiology for respiratory distress.¹ Meconium stained amniotic fluid (MSAF) may be a **sign of fetal distress**, also, meconium aspiration syndrome in its severest form is associated with **severe hypoxia**, both of which may result in brain injury.

CURRENT UNDERSTANDING OF PATHOPHYSIOLOGY AND IMPACT ON NEURODEVELOPMENT

Meconium aspiration syndrome results from aspiration of meconium during intrauterine gasping or at the first breath. **Chronic fetal hypoxia and acidosis may cause fetal gasping and the subsequent in utero aspiration of meconium.**

The pathophysiology of MAS is complex^{2,3}

- Acute airway obstruction
- Chemical pneumonitis with release of vasoconstrictive and inflammatory mediators
- Surfactant dysfunction or inactivation and
- Persistent pulmonary hypertension of newborns who have right-to-left extrapulmonary shunting

The common disturbances of lung function in MAS are hypoxemia and decreased lung compliance. **Poor oxygenation** is attributable to a combination of ventilation perfusion mismatching, intrapulmonary shunting related to regional atelectasis and extrapulmonary shunting related to pulmonary hypertension. The severe form of MAS is often associated with **pulmonary hypertension and refractory hypoxemia**. Hypoxic

changes in the brain are similar to what is seen in perinatal asphyxia. But, meconium staining of amniotic fluid by itself does not predict cerebral palsy (CP). Of the infants born through MSAF, and those who had **a low 5 minute APGAR scores (0 to 3), 94 in 1000 (9.4%), subsequently developed CP.**⁴ The rate of severe mental retardation and are significantly higher among infants born through MSAF.^{5,6} An increased risk for persistent pulmonary hypertension (acute respiratory failure) of the newborn⁷ is associated with **cesarean delivery; late preterm or postterm birth; being large for gestational age;** and maternal black or Asian race, **overweight, diabetes,** and asthma. It remains unclear whether some of these factors are direct causes of persistent pulmonary hypertension of the newborn or simply share common causes with it. Survivors of MAS are at relatively **high risk for CP, neonatal seizures and adverse neurological outcome.**^{6,8} The babies with severest of acute respiratory failure are referred for ECMO. In a prospective follow-up study on 82 of the 93 ECMO survivors were classed as normal, 7 as having “impairment”, and 4 as having “severe disability”.⁹

EPIDEMIOLOGY OF MAS: WHO IS AT RISK AND UNDER WHAT CONDITIONS?

MSAF is present in 10 to 15% of all deliveries,¹ increasing to between 23-52% of births at > 42 weeks.^{10, 11} Because meconium is rarely found in the amniotic fluid prior to 34 weeks' gestation, meconium aspiration chiefly affects infants at term and post-term. **Intrauterine distress** can cause passage of meconium into the amniotic fluid. Factors that promote the passage of meconium in utero include placental insufficiency, maternal hypertension, pre-eclampsia, oligohydramnios and maternal drug abuse, especially of tobacco and cocaine. Interestingly, MAS does not occur in all infants born through MSAF. About 2% to 9% of infants born through MSAF developed MAS.¹² At least one third of infants with MAS require intubation and mechanical ventilation. Factors associated with development of MAS among MSAF include thicker consistency of meconium, non-reassuring fetal heart tracing, fetal acidosis, cesarean delivery, meconium below the vocal cords, infants who needed intubation at birth and low Apgar score.^{12, 13} Presence of **perinatal fetal compromise** increases the risk for pulmonary dysfunction 2.8 to 4.8 fold in infants born through MSAF.¹⁴

BEST PRACTICE GUIDELINES FOR THE PREVENTION OF MAS

PREVENTION OF POST TERM PREGNANCY

Since meconium staining of amniotic fluid occurs more commonly with post term pregnancies, obstetricians should **avoid post term pregnancy by induction of labor**. Gelisen et al¹⁵ reported that the frequency of meconium-stained amniotic fluid and meconium aspiration syndrome were significantly less with induction of labor at 41 weeks (9.3 and 1.3%) as compare to follow up until 42 weeks.

INTRAPARTUM MONITORING

Fetal heart rate monitoring, fetal scalp pH determination and fetal pulse oximetry¹⁶ have all been used to help decision making in timing of delivery with the hope of improving outcome. In fetuses with IUGR, Doppler showing absent or reversal of diastolic flow in umbilical circulation are now generally accepted as major predictors of death and neurodevelopmental disability.

AMNIOINFUSION

Amnioinfusion has been proposed to reduce the risk of MAS by diluting the meconium, thus reducing its mechanical and inflammatory effects. Amnioinfusion also helps by cushioning of umbilical cord, thus correcting the recurrent umbilical compressions that lead to fetal academia.

A meta-analysis of 12 good quality studies involving 4030 pregnant women reported that amnioinfusion was associated with an overall borderline reduction of MAS (RR 0.47, 95% CI 0.22-0.99).¹⁷ However, in **clinical settings with standard peripartum surveillance**, (10 studies, 3178 participants), amnioinfusion did not reduce the incidence of MAS (RR 0.59, 95% CI 0.28 -1.25) and did not reduce perinatal death either. In **clinical setting with limited peripartum surveillance** (2 studies, 852 participants), amnioinfusion was associated with reduction in the risk of MAS (RR 0.25, 95% CI 0.13-0.47). Amnioinfusion has been associated with adverse events such as uterine overdistension, uterine hypertonia, uterine rupture in association with previous scar, fetal heart rate abnormality, umbilical cord prolapse and chorioamnionitis. Based on the current literature, American College of Obstetrics and Gynecology (ACOG) stated that **routine prophylactic amnioinfusion** for dilution of MSAF is **not recommended for prevention of MAS**.¹⁸

INTRAPARTUM SUCTIONING

The goal of intrapartum suctioning before the delivery of shoulder is to clear as much meconium as possible from airway, before infant is able

to take a breath. These practices were performed without much evidence in the past. Vain et al¹⁹ have reported a large multicenter randomized controlled trial comparing routine suctioning of oropharyngeal and nasopharynx before delivery of shoulder (n=1263) or no suctioning (n=1251). There were no difference in the incidence of MAS (4% versus 4%, RR 0.9 95%CI 0.6-1.3), need for mechanical ventilation and mortality between suction and no suction groups. Intrapartum suctioning has potential risks such as apnea, cardiac arrhythmias triggered by pharyngeal stimulation, worsening hypoxia, delay in resuscitation and damage to upper airway.^{2,20} Currently, **routine intrapartum** oropharyngeal and nasopharyngeal **suctioning is not recommended for prevention of MAS** in infants born through MSAF.²¹

POST DELIVERY INTUBATION AND ENDOTRACHEAL SUCTIONING

Neonatal resuscitation Program (NRP) recommends intubation and direct endotracheal suction soon after delivery for infant born with MSAF, who has **depressed respiration, depressed muscle tone or heart rate less than 100/minute.**²² Vigorous infants born through thick or thin MSAF does not alter the incidence of MAS or mortality if they are not intubated and suctioned at birth. Cochrane meta-analysis of four randomized studies did not show a difference in the incidence of MAS between intubated and non-intubated vigorous infants.²³ Hence, if the baby born with meconium-stained fluid has a normal respiratory effort, normal muscle tone, and a heart rate greater than 100 beats per minute, direct endotracheal suction is not recommended. Only suctioning of mouth and nose using a bulb syringe or large bore suction catheter is indicated.

BEST PRACTICE GUIDELINES FOR MANAGEMENT OF MAS...

VENTILATION

Approximately 40% of babies with MAS required mechanical ventilation and additional 10% required continuous positive airway pressure.²⁴ Conventional therapy is aimed at increasing oxygenation while minimizing the barotrauma that lead to air leak syndromes. Pre nitric oxide era showed great variation in management of therapies for acute respiratory failure (PPHN) a severe complication of MAS and a major determinant of outcomes.²⁵ Theoretically high frequency ventilation minimizes the barotrauma and may reduce air leak syndromes in MAS. No prospective randomized trials have compared the conventional ventilation versus high frequency ventilation in MAS. High frequency oscillatory ventilation augments the response to inhaled nitric oxide therapy in PPHN associated

with MAS or diffuses parenchymal lung disease (pneumonia).²⁶ In animal models of MAS, partial liquid ventilation resulted in improved oxygenation and lung mechanics.^{27, 28} There is no randomized clinical trial about the use of partial liquid ventilation in human neonates.

SURFACTANT THERAPY

Evidence of surfactant inactivation by meconium led to use of surfactant therapy in the management of MAS. Bolus surfactant therapy for MAS has been associated with reduction in the severity of respiratory distress and decreases the number of infants with progressive respiratory failure requiring extracorporeal membrane oxygenation (ECMO).²⁹ Meta-analysis of 4 randomised trials enrolling 326 infants showed **reduction in the severity of respiratory illness and decrease in the number of infants with progressive respiratory failure requiring extracorporeal membrane oxygenation** (RR 0.64, 95% CI 0.46-0.91).²⁹ However, there was no significant difference in mortality, hospital stay, length of ventilation, duration of oxygen use, pneumothorax, pulmonary interstitial emphysema or chronic lung disease. In animal models, therapeutic lung lavage with surfactant has been found to be effective in clearing meconium from the lungs and thereby improving oxygenation, lung mechanics and degree of lung injury.³⁰ However, clinical trials of surfactant lavage in conventionally ventilated infants with MAS found no difference between lavage infants and controls in terms of ECMO requirements, air leak or duration of ventilation.³¹

STEROIDS

Role of steroid therapy for MAS remains to be proven. Corticosteroids possess a potent anti-inflammatory activity by modulating the action of inflammatory mediators and reducing the activation and recruitment of leucocytes in the lung. Four clinical trials of steroid in MAS in neonates have been reported with conflicting results.³²⁻³⁵ Two trials showed decrease in the duration of oxygen therapy and hospital stay in steroid treated groups.^{32, 33} But one study showed prolonged oxygen requirement and respiratory distress score in infants treated with steroid.³⁴ Wu et al³⁵ reported that steroid treatment in infants with MAS showed decrease in the duration of ventilation, but no difference in chronic lung disease or duration of oxygen therapy. There is **not enough evidence to recommend use of steroid for treatment of meconium aspiration syndrome.**

ANTIBIOTICS

Routine antibiotic therapy does not affect the clinical course and outcome related to infection in meconium aspiration syndrome in those without any perinatal risk factors for infection.³⁶⁻³⁸ Unless there is definite risk for infection, prophylactic use of antibiotics in MAS did not reduce infection. If antibiotics are started for suspected infection due to perinatal risk factors, consider to discontinue antibiotics once the blood culture results showed negative.

NITRIC OXIDE

Severe MAS is often associated with persistent pulmonary hypertension, resulting in severe hypoxemia. Inhaled nitric oxide (iNO) causes selective pulmonary vasodilatation by acting directly on smooth muscle. Nitric oxide is proven helpful in the treatment of PPHN associated with MAS. For hypoxic respiratory failure due to MAS, infants responded well with combined inhaled nitric oxide and high frequency ventilation (HFV) as compared to either treatment alone.²⁶ The response to combined treatment with HFV and inhaled nitric oxide reflects both decreased intrapulmonary shunt and augmented nitric oxide delivery to its site of action.

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

Approximately 40% of infants with MAS treated with nitric oxide or high frequency oscillation ventilation failed to respond and required ECMO.²⁶ Infants with MAS form approximately 35% of the infant population who required ECMO.³⁹ The survival rate has gone up to 95% with ECMO.⁴⁰

SILDENAFIL

Nitric oxide is costly and may not be easily available in resource-poor settings. Approximately 30% of patients fail to respond to iNO. High concentrations of phosphodiesterases in the pulmonary vasculature has led to the use of phosphodiesterase inhibitors such as sildenafil. Two studies enrolling 37 babies were included in the Cochrane review;⁴¹ both from centers in resource-limited settings (no HFV or iNO) and reported significant improvement in oxygenation in Sildenafil group. No clinically significant side effects were reported. Long term outcomes are still not available.

KEY POINTS – reducing NDD due to MAS

1. Some babies born through MSAF are at increased risk of CP, mental retardation and neonatal seizures. Mere MSAF is not a predictor of NDD.
2. Perinatal asphyxia (fetal and immediately after birth may be reasons for poor outcomes)
 - a. Meconium staining of amniotic fluid may be a sign of fetal distress. Chronic fetal hypoxia and acidosis are common reasons for MSAF.
 - b. Of the infants born through MSAF with a low 5 minute APGAR, 9.4% developed CP.
3. MAS is associated with severe hypoxia (acute respiratory failure/PPHN) in its severest form. Among the babies with severest of hypoxia (acute respiratory failure/PPHN, referred for ECMO) a good proportion had normal outcomes.
4. Prevention of PPHN - Babies born through cesarean delivery, born late preterm or postterm, large for gestational age and born to overweight, diabetic, asthmatic mothers were more likely to develop PPHN.
5. Effective fetal monitoring reduces fetal mortality and likely to reduce poor outcomes.
6. Amnioinfusion has shown benefit only in centers where intrapartum monitoring is not easily available (resource limited) and cannot be recommended as a routine.
7. Routine intra-partum suctioning of baby's mouth after delivery of head is now not recommended.
8. Resuscitation at birth includes intubation of only depressed (poor tone, respiratory efforts or bradycardia) babies delivered through MSAF.
9. A large number of babies born through MSAF may require ventilator support.
10. High Frequency Ventilation may reduce barotraumas in babies requiring high ventilator supports.
11. Wide variations are noted in practices (Alkali, hyperventilation, sedation and paralysis) for management of acute respiratory failure (PPHN) indicating that neither of them is proven superior.
12. Surfactant therapy improves respiratory outcomes of babies with MAS and oxygen requirement >50 % on optimal ventilation.
13. There are no scientific data to endorse routine use of antibiotics or steroids in management of MAS.
14. Newer therapies – iNO and ECMO have improved survival of babies with severe respiratory failure and have not increased burden of handicapped survivors.
15. Newer untested therapies like Sildenafil must be used with caution and as a part of systematic trials recording complications and long term outcomes.

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Persistent Pulmonary Hypertension of Newborn (PPHN)

Persistent pulmonary hypertension of newborn (PPHN) is not a disease, rather a state with complex physiologic common end point arising from a variety of disease processes resulting in **severe hypoxemia in neonates** with a mortality of 10-20%.¹ In neonates with PPHN, the severity of illness and likely outcomes are related to the nature of the underlying disease or abnormality and resultant pathological changes in the pulmonary vasculature. Survivors of infants with PPHN remain at a **significant risk for neurodevelopmental impairment, cognitive delays, hearing loss** and a high rate of rehospitalization.²

CURRENT UNDERSTANDING OF PATHOPHYSIOLOGY OF PPHN

PPHN is a state of **persistent hypoxemia** and cyanosis in the neonate resulting from failure of the postnatal decline of pulmonary artery pressure and a persistence of right to left shunting across the ductus arteriosus and foramen ovale. PPHN is characterized by (a) severe hypoxemia shortly after birth, (b) marked pulmonary arterial hypertension, (c) absence of congenital heart disease and (d) vasoreactivity with extrapulmonary right to left shunting across ductus arteriosus or foramen ovale.

To understand the pathophysiology of PPHN, one needs to know the normal fetal and neonatal physiology. In normal fetus, pulmonary and systemic pressures are nearly equal. The pulmonary vessels are constricted in utero and allows only 5-10% of cardiac output to go to pulmonary circulation, and remaining bypass the lung. The low arterial oxygen tension in the fetus facilitates this vasoconstriction. Once the umbilical cord is clamped and with the removal of low resistance placental circuit, systemic vascular resistance increase. After the baby is born, pulmonary artery pressure should

decrease rapidly to 50% of systemic pressure and pulmonary blood flow increases nearly tenfold to match lung perfusion with the onset of ventilation.

PPHN occurs when pulmonary vasculature resistance **fails to** decrease at or shortly after birth. A **high pulmonary vascular resistance (PVR)**, resulting in **right to left shunting of deoxygenated** blood across the patent ductus arteriosus and patent foramen ovale, is the **hallmark** of pulmonary hypertension. The regulation of pulmonary vascular tone represents a balance between the vasoconstrictor and vasodilator mechanisms. The increased PVR is secondary to endothelial dysfunction, leading to imbalance between the endogenous vasoconstrictors and vasodilators. Conditions that lead to chronic hypoxia in utero or abnormal muscularisation of pulmonary vessels can lead to persistent pulmonary vasoconstriction and pulmonary hypertension after birth. Perinatal stressors including hypoxia, hypoglycemia, cold stress, sepsis and direct lung injury alter the course of normal transition. Vascular biology of pulmonary vasodilatation at birth and pathophysiology of PPHN has been well described in the review articles (3,4). Apart from the effects of physical and chemical (oxygen) stimuli, the important mediators involved in the vasodilatation of pulmonary vessels at birth are prostaglandins and nitric oxide (NO) release by pulmonary endothelium. The influence of this dilator effect is opposed by several vasoconstrictors such as endothelin, thromboxane and product of cytochrome p450 pathways. Hypoxia, acidosis and alveolar atelectasis promote pulmonary vasoconstriction and are significant contributors in the pathophysiology of PPHN.

PPHN AND NEURODEVELOPMENTAL OUTCOME

Severe hypoxia associated with PPHN can lead to brain injury. The type of neurodevelopmental problem depends on the **severity of hypoxemia** and **underlying disease** or abnormality. PPHN infants with severe perinatal asphyxia have very poor prognosis for survival and long term neurodevelopmental problem. Similarly, infants with congenital diaphragmatic hernia and PPHN often require ECMO and have increased risk of neurodevelopmental delay.

Apart from the hypoxia per se, various **treatment modalities** which are use in the treatment of PPHN itself could be associated with neurodevelopmental disability. High incidence of seizure and **cerebral infarction** has been documented in infants with PPHN.^{5,6} Klesh et al⁶ reported 9 out of 19 (47%) infants with PPHN had cerebral infarction whereas Oelberg et al⁷ documented a 40% incidence of intracranial hemorrhage. These can be associated with cerebral palsy (CP), mental

retardation and seizures. Follow up studies on PPHN published before 1990s reported higher rates of neurodevelopmental impairment ranging from 5% to 53%. **Hyperventilation and hypocarbia** for the treatment of PPHN can cause cerebrovascular vasoconstriction with a subsequent reduction in cerebral blood flow. One of the areas in the brain with highest blood flow is auditory nucleus, and the high metabolic rate in this region makes it more susceptible to a decrease in blood flow. **Sensorineural hearing loss** is more common in infants with **PPHN treated with alkalosis and extracorporeal membrane oxygenation (ECMO)**. More than half (53%) of surviving infants with PPHN treated with hyperventilation and respiratory paralysis had hearing impairment.⁸ Bifano and Pfannensteil in 1988 evaluated a series of 21 infants with PPHN who were treated with hyperventilation.⁹ Four infants (19%) had severe neurologic impairment; seven babies had mild to moderate delay, and 11 babies were found to have no abnormality. The only **perinatal or treatment variable** associated with **abnormal outcome is duration of PaCO₂ < 25 mm Hg** after hyperventilation strategy.⁹ Neurodevelopmental and audiologic impairment were seen in 46%, followed by cognitive delays (30%) and hearing loss in 19% of surviving infants.² Following the introduction of inhaled nitric oxide and availability of ECMO, the neurodevelopmental impairment were lower (15-18%).^{10,11}

Severity of hypoxemia may be a prognostic factor. Highest alveolar-arterial oxygen gradient (AaDO₂) was a good early predictor of mortality. AaDO₂ exceeding 610 for 8 hours once maximal therapy had been offered was associated with a 78% mortality risk, with a specificity of 71% and a sensitivity of 94%.¹² AaDO₂ values of 600 mm Hg or greater were more frequent in the nonsurvivors compared with the survivors (92% vs 37%). Air leak also proved to be a good predictor of nonsurvival.¹³ The drawback of the use of AaDO₂ is that it does not account for the degree of ventilator support required to obtain any given oxygenation value. Oxygenation index accounts for both oxygen toxicity and barotrauma in the assessment of severity. Oxygenation index greater than 40 on three to five arterial blood gases taken 30 minutes apart correlated with 80% mortality.¹⁴ Survivors of neonatal hypoxic respiratory failure remain at a significant risk for neurodevelopmental and hearing deficit and need close monitoring and follow-up.

EPIDEMIOLOGY OF PPHN

The incidence of PPHN is estimated to be 1.9 per 1,000 live births with a wide variation observed among centers (0.43-6.82 per 1,000 live births).¹¹ The incidence is higher in pregnancies with no prenatal care and with the use of

tobacco and illicit drugs. The factors associated with **increased risk for PPHN** include **cesarean section deliveries, maternal black or Asian race, male gender, high prepregnancy body mass index (BMI > 27), diabetes** and asthma.¹⁵ The risk of PPHN was 7 times higher after cesarean section deliveries than after vaginal deliveries.¹⁵ PPHN can occur in both term and preterm infants depending on the associated illnesses.

PPHN can occur without any associated parenchymal lung disease and are called **idiopathic PPHN**. Causes of PPHN are listed in Table 11.1. Neonatal illnesses associated with increased risk for developing PPHN include meconium aspiration syndrome (MAS), perinatal asphyxia, pneumonia, respiratory distress syndrome, pulmonary hypoplasia, congenital diaphragmatic hernia (CDH). Infants born to mothers who are exposed to certain medications such as NSAID, tricyclic antidepressants during pregnancy are also at increased risk for PPHN. In terms of frequency, PPHN occurs most commonly in association with MAS (41%), followed by idiopathic PPHN (17%), pneumonia/sepsis (14%), respiratory distress syndrome (13%), congenital diaphragmatic hernia (10%) and other causes (asphyxia, maternal diabetes, polycythemia, etc.).¹¹

Table 11.1: Causes of persistent pulmonary hypertension of newborn

1. Idiopathic.
2. Persistent pulmonary vasoconstriction
 - Asphyxia
 - Meconium aspiration syndrome
 - Neonatal respiratory distress syndrome
 - Sepsis/pneumonia (e.g. group B streptococcal disease)
 - Maternal Drugs—
 - a. NSAID drugs (like Indomethacin after 31 weeks, Naproxen)
 - b. SSRI drugs (e.g. Paroxetine, Fluoxetine)
 - c. Octreotide causes pulmonary vasospasm.
 - d. Diazoxide
 - Others (e.g. pulmonary alveolar dysplasia)
3. Functional obstruction of pulmonary vascular bed
 - Hyper viscosity secondary to polycythemia
4. Decreased pulmonary vascular bed
 - Congenital diaphragmatic hernia (CDH)
 - Pulmonary hypoplasia – oligohydramnios, pleural effusion, vascular anomalies, asphyxiating thoracic dystrophy, phrenic nerve agenesis.
5. Pulmonary venous hypertension
 - Total anomalous pulmonary venous return
 - Left atrial or mitral obstruction
 - Hypoplastic left heart syndrome
 - Myopathic left ventricular disease (e.g. endocardial fibroelastosis and Pompe disease)
 - Obstruction to left ventricular outflow (e.g. aortic arch, interrupted arch, and coarctation).

BEST PRACTICE GUIDELINES: PREVENTION OF THE RISK FACTOR, SCREENING AND DIAGNOSIS, MANAGEMENT OF THE PPHN ..

PREVENTION OF RISK FACTOR

- Routine prenatal care and identification of high risk pregnancy
- Avoidance of using NSAID's and SSRIs during pregnancy, if possible
- Prevention of associated illnesses (mentioned in various chapters in this book).

DIAGNOSIS OF PPHN

PPHN should be suspected in high risk neonates with progressive cyanosis or lability in oxygen saturation within the first few hours of life. Diagnosis of PPHN is made from the history, physical examination, preductal and postductal blood gases and echocardiogram.

Preductal and Postductal Oxygenation

In PPHN, the right to left shunt can occur either at patent ductus arteriosus or at foramen ovale or both. A simultaneous preductal (right radial artery) and postductal (umbilical artery) **arterial oxygen gradient of > 20 mmHg** suggest right to left shunt at the level of patent ductus arteriosus.¹⁶ Negative test does not exclude PPHN because shunting at atrial level does not produce ductal gradient. Simple bedside monitoring of preductal (right upper limb) and postductal (preferably lower limb) oxygen saturation difference of 5-10% by pulse oximetry in a high risk infant should suspect PPHN.

Hyperoxia/Hyperventilation Test

This diagnostic test with hyperventilation to a critical $\text{PaCO}_2 < 25$ mm Hg test is **not recommended** any more due to deleterious effects of hypocarbia, barotrauma and long term neurodevelopment impairment, hence of historical interest only.

Echocardiographic

Diagnosis of PPHN is based on presence of high pulmonary artery pressures (more than systemic pressures) with right to left shunting through patent ductus arteriosus and/or patent foramen ovale. Deviation of interatrial septum into the left atrium is seen in severe PPHN. Echocardiogram also excludes the presence of serious congenital cyanotic heart disease.

Direct Measurement of Pulmonary Pressure by Cardiac Catheterization

Direct measurement of pulmonary artery pressure seems to be the most optimal method to diagnose PPHN. However, it is difficult and invasive procedure and **not routinely used for** diagnosis.

TREATMENT OF PPHN

The goal of medical treatment of PPHN is to lower pulmonary vascular resistance to systemic vascular resistance (PVR:SVR) ratio, reduce intracardiac shunting and right ventricular afterload, improve postductal oxygen saturation without systemic hypotension as well as correction of underlying cause of PPHN.

Ten commandments of PPHN therapy are as follows:¹⁷

1. Minimal handling and maintenance of euthermia.
2. Correction of acidosis (metabolic and respiratory) and metabolic imbalances (fluid and electrolytes).
3. Support blood pressure (e.g. plasma expanders/Inotropes).
4. Treat associated conditions (e.g. antibiotics, partial exchange transfusion).
5. Sedation/paralysis (morphine, fentanyl, pancuronium).
6. Ventilation support.
7. Surfactant therapy.
8. Inhaled nitric oxide.
9. Extracorporeal membrane oxygenation (ECMO).
10. Other vasodilators (prostacyclin, magnesium sulfate, etc.).

Minimal Handling

Minimal handling, nursing in a quiet environment and maintenance in thermoneutral environment is recommended. Infant should be monitored using noninvasive monitors (transcutaneous O₂/CO₂ methods) and blood gas sampling should preferably be done with indwelling arterial line.

Correction of Acidosis

Acidosis correction to achieve acceptable pH (7.35-7.45) is recommended because acidosis is a potent pulmonary vasoconstrictor. Forced alkalosis with sodium bicarbonate and hyperventilation were popular therapies before nitric oxide. Extreme alkalosis and hypocarbia are not recommended as it is associated with later neurodevelopmental deficit, including CP and sensorineural hearing loss. Metabolic equilibrium is desired especially with normal values of ionized calcium, lactate and glucose.

Correction of Hypovolemia/Hypotension

The goal is to correct systemic arterial hypotension and maintain adequate systolic blood pressure (BP) to minimize right to left shunting. Aggressive support of cardiac function involves judicious use of volumes along with inotropic agents (dopamine, dobutamine, epinephrine and/or milrinone) to enhance cardiac output and systemic oxygen transport. Dopamine is used frequently as the first line but dose should be given at 2-10 mcg/kg/min to avoid alpha adrenergic effects on pulmonary vasoconstriction and an increase in afterload. Dobutamine is indicated in cases of poor ventricular function. Milrinone has been used to improve inotropy and reduce afterload. Milrinone has also shown improvement in oxygenation in severe PPHN.¹⁸

Treatment of Associated Conditions

Correction of the underlying causes of PPHN is important, if known. Broad spectrum antibiotics are used to treat sepsis and pneumonia. Partial exchange transfusion for polycythemia and surgery for congenital diaphragmatic hernia are indicated.

Sedation and Paralysis

To optimize gas exchange, sedation with fentanyl or morphine is advocated to avoid asynchrony, reflex catecholamine release and aggravation of pulmonary vascular resistance. The use of neuromuscular blockade remains controversial and is reserved for the infant that cannot be treated with sedatives alone. Neuromuscular blockage can promote atelectasis of dependent lung regions and ventilation perfusion mismatch. Neuromuscular paralysis may be associated with increased risk of death and that exceeded the mortality risk associated with either high frequency oscillatory ventilation (HFOV) or ECMO.¹¹

Mechanical Ventilation

The maintenance of adequate oxygenation is the primary goal in the management of PPHN and mechanical ventilation is one of the treatment modalities to achieve this goal. In the past, hyperventilation is used as main therapy to increase blood pH, reverse ductal shunting and induce pulmonary vasodilatation. However, it was associated with adverse neurological sequelae. The use of gentler ventilation along with therapies that reduce oxygen demand while maximizing oxygen delivery has been advocated but it has been slow in becoming standard management.¹¹

Recent management strategies usually aimed at accepting pH: 7.4-7.5, PaCO₂ at 40-60 mm Hg, PaO₂ at 60-90 mm Hg to avoid barotraumas.¹⁷

Permissive hypercapnia promises to maintain gas exchanges with lower tidal volume and thus decrease lung injury.¹⁹ High frequency ventilation (HFV) is the alternative mode of ventilation in infants who are non-responsive to conventional ventilator therapy.²⁰ High frequency oscillatory ventilation (HFOV) is the preferred mode when there is coexisting parenchyma disease in PPHN.¹⁷ HFV is shown to improve lung inflation while decreasing the lung injury due to volutrauma and barotrauma. HFOV has become the mainstay of ventilating difficult PPHN with inhaled nitric oxide (iNO). HFOV has been shown to augment an inhaled nitric oxide response by improving lung inflation and allowing better alveolar recruitment.^{21,22}

Surfactant Therapy

Certain causes of PPHN such as meconium aspiration syndrome, pneumonia, respiratory distress syndrome and diaphragmatic hernia are associated with surfactant deficiency or dysfunction. Surfactant therapy should be given in patients with meconium aspiration syndrome and pneumonia associated with PPHN. Surfactant therapy is found to improve oxygenation and decrease the need for ECMO, particularly when given early in the disease in infants with severe hypoxemic respiratory failure.^{23,24}

Inhaled Nitric Oxide (iNO)

Inhaled nitric oxide (iNO) is the mainstay of treatment and the recommended pulmonary vasodilator for PPHN. It selectively causes pulmonary vasodilatation by relaxing the smooth muscle cells by increasing cyclic guanosine monophosphate (cGMP) levels through the guanylate cyclase pathway.²⁵ iNO cause selective pulmonary vasodilatation and does not cause systemic hypotension. Nitric oxide also causes a better ventilation perfusion match with redistribution of pulmonary blood flow to better ventilated alveoli. Cochrane meta-analysis of 14 randomized controlled studies reported that inhaled nitric oxide appears to improve outcome in hypoxemic term and near term infants by reducing the incidence of the combined endpoint of death or need for ECMO.²⁶ The reduction seems to be entirely a reduction in need for ECMO; mortality is not reduced. It is recommended to use inhaled nitric oxide in an initial concentration of 20 ppm for term and near term infants with hypoxic respiratory failure who do not have a diaphragmatic hernia.²⁷ In preterm infants with PPHN; it is suggested to start at a lower dose (usually 5-10 ppm). Low dose inhaled nitric oxide at 5 ppm improve the oxygenation but did not affect the rate of severity of intracranial hemorrhage or survival.²⁸ Standard iNO therapy is initiated when the oxygenation index (OI) is more than 25. However, a randomized control trial of iNO given early in the respiratory

failure at an OI of 15 to 25, demonstrated that early iNO improves oxygenation and decreases the progression to severe respiratory failure (OI > 40) compared to standard iNO therapy initiated at an OI of 25.²⁹ Oxygenation improves in approximately 50% of infants receiving nitric oxide. However, strategies to optimize lung recruitment and cardiac performance are necessary to increase the response to iNO. Nitric oxide therapy does not consistently improve oxygenation and does not decrease the use of ECMO/mortality in infants with congenital diaphragmatic hernia.³⁰ Indeed there is a suggestion that outcome may be slightly worse.

Weaning of iNO is indicated after improvement in oxygenation and when the oxygen requirement (50-60%) is stable for at least 12 hours. Weaning of iNO from 20 ppm is done in steps of 5 ppm if patient maintains stable good oxygenation for about 12 hours.³¹ When it reaches to 5 ppm; further weaning is slower at 1 ppm each time in a frequency of 6-12 hours. Mostly iNO can be weaned off successfully in 4-5 days. Some infants may develop rebound hypoxemia and pulmonary hypertension when weaning iNO. Prolonged iNO therapy may be associated with decrease endogenous NO synthase activity³² and increased endothelin levels.³³ Prolonged high dose of iNO can cause toxicity such as methemoglobinemia, increased bleeding time, immune suppression and formation of nitrogen dioxide or peroxynitrites.³⁴ It is important to monitor these levels closely; severe methemoglobinemia is an indication to stop iNO. Inhaled NO therapy for hypoxic respiratory failure in term and near-term infants is not associated with an increase in neurodevelopmental impairment or hearing loss at 18 to 24 months postnatal age.^{35,36}

Extracorporeal Membrane Oxygenation (ECMO)

ECMO is the final rescue therapy in infants with refractory hypoxemia due to reversible pulmonary or cardiac disease when all other non invasive measures fail.¹⁸ Since ECMO is an invasive procedure; it is reserved for infants receiving maximum ventilatory support and those that meet Barlett criteria, (i.e. Oxygenation index > 40), which is indicative of = 80% risk of dying.^{37, 38} Cochrane meta-analysis of four trials showed a strong benefit of ECMO on mortality (relative risk 0.44, 95% CI 0.31, 0.61), especially for babies without congenital diaphragmatic hernia (RR 0.33, 95% CI 0.21, 0.53).³⁹ Fortunately, following the introduction of HFV, surfactant, and iNO therapy in the early 1990s, the number of infants requiring ECMO has decreased by more than 40% from 1992 to 2001.⁴⁰ All of the decrease has been in babies with respiratory failure due to parenchymal lung disease and idiopathic PPHN. In a prospective follow up study of newborn infants with acute respiratory failure treated with ECMO, 82 of 93 (88%) were

classed as normal, seven (8%) as having “impairment”, and four (4%) as having “severe disability” at 11-19 months of postnatal age.⁴¹

Alternative Vasodilator Therapy

Nearly 30-50% of infants with PPHN do not respond to iNO therapy. Infants who do not show initial response to iNO and those that deteriorate subsequently while on iNO therapy continue to have significant pulmonary hypertension and need the alternative therapy (2). Alternatives available include: (a) Phosphodiesterase-5 inhibitors like sildenafil, (b) Prostaglandins like prostacyclin or PGE1, (c) Tolazoline, magnesium sulfate, (d) NO precursor L-arginine, (e) Free radical scavengers like Superoxide Dismutase, (f) experimental agents like Bosentan (endothelin antagonist)

a. Sildenafil is a phosphodiesterase inhibitor type 5(PDE5) that has been shown to selectively reduce pulmonary vascular resistance. Sildenafil produces vasodilatation by increasing cyclic guanosine monophosphate involve in the degradation of cGMP to guanosine monophosphate.⁴² Cochrane review included two small trials enrolling 37 infants in resource-limited settings where iNO and high frequency ventilation are not available.⁴³ Both studies reported statistically significant improvement in oxygenation (reduction in oxygenation index) in the Sildenafil group. One study reported a strongly protective effect on mortality, (RR 0.17, 95% CI 0.03, 1.09) favoring the Sildenafil group. However, this result needs to be replicated in larger studies. No clinically important side effects were reported. The major concern about the use of Sildenafil is that it can cause systemic hypotension, which can worsen the right to left shunting and hypoxemia in PPHN.⁴⁴ Although the potential adverse effects may limit the use of Sildenafil as the drug of choice in babies with PPHN, its use is still holds immense promise for resource limited countries and need further randomized trials.

b. Prostacyclin (PGI2) is a potent vasodilator and its effect on vascular tone is complementary to that of nitric oxide. Studies have shown a potential synergistic action with combined usage with iNO due to interaction between NO and PGI2 pathways.⁴⁵ Intravenous prostacycline infusion has been shown to decrease pulmonary artery pressure and improved oxygenation in neonates with PPHN in uncontrolled studies.^{46,47} Prostacycline infusion is shown to cause significant hypotension. Bindl et al⁴⁸ reported aerosol PGI2 improved oxygenation and decreased pulmonary artery pressure without affecting systemic blood pressure. Similarly Kelly et al⁴⁹ has shown improvement in oxygenation by using aerosol PGI2 along with iNO when oxygenation failed to improve with iNO or deteriorated while on iNO. There is potential role for PGI2

in babies with hypoxic respiratory failure that failed to respond adequately iNO or in centers where iNO is not available as a rescue therapy. Randomized controlled trials are needed to establish safety and efficacy of this therapy.

- c. **Magnesium Sulfate:** Magnesium is a nonspecific vasodilator. It causes smooth muscle relaxation by antagonizing calcium ion entry to smooth muscle. Intravenous magnesium sulphate in a dose of 200 mg/kg given as bolus followed by infusion of 20-150 mg/kg/hr has been found to improve oxygenation and decreased oxygenation index in uncontrolled trials.⁵⁰⁻⁵⁴ There are no randomized controlled trials on this agent in the neonates. Despite low cost and easy availability, it can cause a hypotension and central nervous system depression. Cochrane review found no eligible randomized trials. Based on the lack of evidence, the authors conclude the use of magnesium sulphate cannot be recommended in the treatment of PPHN.⁵⁵
- d. **Tolazoline:** Tolazoline is a potent nonspecific vasodilator used in the treatment of PPHN in the pre nitric oxide era.²¹ No randomized controlled trials are available. Systemic infusion of tolazoline was associated with serious adverse effects including profound hypotension, pulmonary and gastrointestinal hemorrhage.⁵⁶ Administration of tolazoline via endotracheal route was effective in treatment of PPHN in small uncontrolled trials without systemic hypotension.^{57,58}
- e. Arginine, adenosine and Superoxide dismutase and Bonestan (anti endothelin I) are currently in early experimental stage.⁴

CONCLUSION

Management of PPHN is in New Era of “HFOV and iNO, rescued by ECMO”, with remarkable success. PPHN may be a Neonatologist’s nightmare! A Challenge. However, there can be no better satisfaction than when a sick PPHN baby recovers and is ready for discharge!

KEY POINTS – reducing NDD due to PPHN (severe respiratory failure)

1. PPHN is associated with severe hypoxemia and survivors of infants with PPHN remain a significant risk for neurodevelopmental impairment, cognitive delays, hearing loss and a high rate of rehospitalization.
2. PPHN is a complex physiologic common end point arising from a variety of disease processes resulting in severe hypoxemia in neonates with a mortality of 10-20%.
3. Prevention of three major illnesses (MAS, RDS and pneumonia) will decrease the frequency of PPHN by 2/3rd.
4. Cesarean section delivery increases the risk of PPHN.
5. The type of neurodevelopmental problem depends on the severity of hypoxemia and underlying disease or abnormality.

6. Hyperventilation strategy and hypocarbia are associated with sensorineural hearing loss, hence, avoid hyperventilation.
7. Supportive management of PPHN includes minimal handling, correction of temperature instability, hypoglycemia, hypocalcemia, anemia and metabolic acidosis and hypotension.
8. Sedation is necessary but paralysis may increase the risk of death.
9. High frequency ventilation may reduce barotrauma and has become the mainstay of ventilating difficult PPHN with inhaled nitric oxide (iNO).
10. Surfactant therapy is indicated in the management of hypoxic respiratory failure associated with MAS, pneumonia and RDS.
11. Inhaled nitric oxide is the main stay of therapy.
12. ECMO is the rescue therapy and early transfer to ECMO centre should be considered.
13. Other vasodilators such as Sildenafil have a promising role in resource limited areas (HFV and NO unavailable) but larger trials are required for safety and efficacy.
 - a. Magnesium sulphate therapy is used as a vasodilator, with improvement in oxygenation, but can caused profound hypotension and CNS depression.
 - b. Tolazoline and prostacyclines are non specific vasodilators and are associated with adverse side effects and not recommended.

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Section 6

Perfusion Problems

- 12. Neonatal Shock**
- 13. Neonatal Sepsis**

Neonatal Shock

Shock is a clinical syndrome characterized by **inadequate tissue and organ perfusion**. When this occurs, inadequate amounts of oxygen and nutrient substrate are delivered to body tissues, and removal of metabolic waste products is inadequate. This results in cellular dysfunction, which may eventually lead to cell death. Failure of perfusion may involve isolated organs or the entire organism. **Hypotension** (i.e. lower than expected blood pressure) frequently, **but not always, accompanies shock**.

NORMAL BLOOD PRESSURE

WHAT IS NORMAL BLOOD PRESSURE?

Epidemiology: The 'normal' blood pressure limits have been defined as the gestational and postnatal-age dependent blood pressure values between the 10th and 90th percentiles (Fig. 12.1).¹ A linear **relationship exists between blood pressure and both gestational age or birth weight and postnatal age**. The statistically defined lower limits of mean BP during the first day of life are approximately numerically similar to the gestational age of the infant. However, by the third day of life, most preterm infants, even with 24-26 weeks' gestation, have a mean BP of 30 mm Hg or greater. The increase in blood pressure with advancing gestational and postnatal age is clearly developmentally regulated. In the absence of a PDA and past the immediate newborn period, cardiac output is similar in both term and preterm infants. Therefore, the increase in BP is primarily the result of **increase in SVR**. Maturation of vascular smooth muscle, changes in the expression of vascular angiotensin II receptor subtypes and maturation of the central autonomic and peripheral nervous system play a significant role in increasing vascular tone and therefore, SVR with increasing gestational age.²

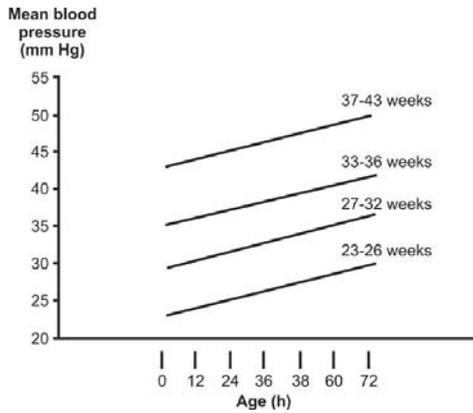


Fig. 12.1: Gestational and postnatal-age-dependent normogram for mean BP values in neonates during the first wks of life. Each line represents the lower limit of 80% CI of mean BP for each gest. age gp (Nuntnarumit et al¹)

PHYSIOLOGY

In terms of physiology, the normal range for blood pressure is best defined by the presence of intact organ/issue perfusion. However, the lower and upper limits of this **physiologic blood pressure range** have not been determined in the newborn. In clinical situations, decision to treat a hypotensive newborn on the basis of “numbers” is without proven physiologic relevance.

PHASES OF NEONATAL SHOCK

Shock presents in distinct phases of advancing severity characterized by specific pathological alterations in cardiovascular and renal function.³ In the initial *compensated phase of shock*, vital organ function and blood pressure are maintained by neurohormonal compensatory mechanisms. However, especially in the immediate postnatal period in the preterm infant, the associated changes in **cardiovascular and renal function are difficult to assess** and the compensated phase of shock frequently goes undetected. With progression of the condition, shock enters its *uncompensated phase*. In this phase, failure of the neurohormonal compensatory mechanisms results in the clinically recognizable symptoms of systemic hypotension and, with further progression of the process, the development of metabolic acidosis. Thus, **in the preterm infant, shock is most frequently recognized in its uncompensated phase.**

ETIOLOGY OF SHOCK IN NEONATE

Adequate tissue perfusion depends on

- Cardiac output
- Integrity and maintenance of peripheral vascular tone
- Blood volume
- Oxygen carrying capacity.

In neonates, **abnormal peripheral vasoregulation with or without myocardial dysfunction** is the most frequently encountered primary etiological factor of shock.⁴⁻⁶ In most of the cases of shock in neonates like sepsis, asphyxia, NEC, etc. the culprit is abnormal peripheral vasoregulation with or without myocardial dysfunction.

Studies showing lack of relationship between blood volume and BP in neonates^{7,8} and the finding that dopamine is at least twice as effective in normalizing blood pressure as compared to volume administration⁹ strongly support the view that **absolute hypovolemia is a less frequent primary cause of neonatal hypotension**. However, if evidence of acute blood loss, excessive transepidermal water loss or excessive urine output is there, absolute hypovolemia should be considered as the primary cause.

CEREBRAL BLOOD FLOW (CBF)

CBF is obviously the most physiological and reliable indicator of cerebral perfusion. A major problem in exploring the relation between early changes in the CBF and brain injury in newborns is how to measure it. BP gives only a loose indication of systemic blood flow and the effect of shunting at PDA on left ventricular output and of atrial shunts on right ventricular output can cause either of these measures to overestimate the real systemic (cerebral) blood flow. The **flow returning to the heart via the superior vena cava (SVC)** offers a solution to this problem in that it represents flow to the upper body, approximately **80% of which goes to the brain**.¹⁰

Kluckow M et al¹¹ assessed SVC flow together with right ventricular output and atrial or ductal shunting. Normal range was established in 14 infants born after 36 weeks gestation and 25 uncomplicated infants born before 30 weeks. It was found that in term babies median SVC flow rose from 76 ml/kg/min on day 1 to 93 ml/kg/min on day 2 and in preterm infants, it rose from 62 ml/kg/min at 5 hours to 86 ml/kg/min at 48 hours.

RELIABILITY OF CLINICAL PARAMETERS IN ASSESSMENT OF CEREBRAL BLOOD FLOW IN PRETERM BABIES

SVC flow measurement or near infrared spectroscopy (NIRS) may not be possible in all settings, thus it is important to know whether clinical parameters like BP, capillary refilling time (CRT) or central-peripheral

temperature difference (CPdT) can detect low systemic/cerebral blood flow states. In clinical practice during the first postnatal day, lower limit of normal mean arterial pressure (MAP) is considered to be equal to baby's gestational age. However, physiology studies of CBF have found that the **lower limit of the auto-regulatory BP range is around 30 mm Hg even in the 1-day-old extremely low birth weight (ELBW) neonate**. Loss of autoregulation does not necessarily result in cerebral injury unless significant swings in systemic blood pressure occur and/or hypotension reaches the ischemic threshold¹⁴ (Fig. 12.2).

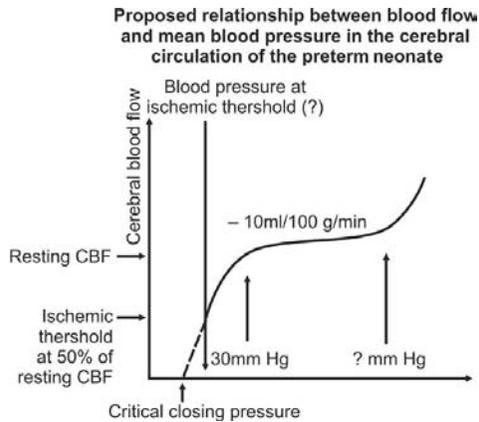


Fig. 12.2: The flat portion represents the autoregulatory plateau. The upper threshold is not known. Below the lower threshold (30 mm Hg), blood flow falls more in proportion to BP. The critical closing pressure (CrCP) depends on arterial elasticity and intracranial pressure. The ischemic threshold is assumed to be around 50% of resting CBF but the BP at that point is not known¹⁴

In the **ELBW infant** in the immediate postnatal period^{11,15} (**on the first day of life**), **blood pressure in the normal range may not always guarantee normal vital organ (brain) blood flow**. The reason for this finding is not known. However, by the second postnatal day, normal blood pressure is highly likely to be associated with normal brain and systemic blood flow¹⁵. In another study of premature babies, cerebral blood flow assessed by NIRS was not significantly different¹⁶ in the groups with MAP <30 mm Hg and MAP >30 mm Hg.

In a prospective, study of infants born at < 30 weeks gestation, Invasive BP, CRT and CPTd (center peripheral temperature difference) and SVC flow were measured at three, 5–10, and 24 hours after birth. **CPTd did not detect infants with low flows, CRT > 3 seconds had 55% sensitivity and 81% specificity, mean BP < 30 mm Hg had 59% sensitivity and 77% specificity for detecting low SVC flow**. Combining

a mean BP < 30 mm Hg and/or central CRT > 3 seconds increases the sensitivity to 78%. Thus the conclusion was that these **clinical parameters are likely to miss unacceptably high number of preterm babies with low cerebral blood flow on first day of life.**¹⁷

HYPOTENSION AND CNS MORBIDITY/NEURODEVELOPMENTAL OUTCOME

Several studies have found an association between hypotension and central nervous system morbidity (IVH, PVL) and neurodevelopmental outcome.¹⁸⁻²⁶ However, it is important to note that very little data are available demonstrating a causative relationship among these factors.

MAP and IVH/PVL: In a study recording hourly blood pressures in 131 very low birth weight infants in intensive care during the first 4 days of life, cranial ultrasound **evidence of intraventricular hemorrhage correlated well with periods of hypotension** however, ischemic lesions did not correlate with hypotension.¹⁹ Another similar study using computerized continuous measurement of MAP and serial cranial ultrasonography in 33 infants of less than 31 weeks gestation showed that a **MAP of < 30 mm Hg for over an hour was significantly associated with severe hemorrhage, ischemic cerebral lesions, or death within 48 hours.** No severe lesions developed with a MAP = 30 mm Hg.²⁰ Bada et al²¹ noted microcomputer-derived, minute-to-minute MAP values during the first 48 hours of life in 100 preterm VLBW babies. In 72 babies with no IVH or grade 1 IVH, the MAP values increased during the study period, but in infants with grades 2 to 4 IVH (n = 28) consistently lower MAP values were recorded. In a 5 year retrospective study on 232 VLBW babies assessing association between intra-arterial MAP in first 7 days of life and morbidity, it was found that **IVH was predominantly associated with a low and variable MAP** on the day IVH was noted or the day before. PVL and ROP were not associated with blood pressure.²²

MAP and cerebral fractional oxygen extraction (CFOE): CFOE is also used as a surrogate for CBF because these two are inversely related. Two recent studies evaluating relationship between CFOE and MAP had apparently contrasting results. Tsuji et al¹⁸ used NIRS to determine quantitative changes in cerebral concentrations of oxygenated hemoglobin (HbO₂) and deoxygenated hemoglobin (Hb) in VLBW infants. Impaired cerebrovascular autoregulation was observed in 17 (53%). Eight of the 17 infants (47%) developed severe IVH or PVL or both. Of the 15 infants with apparently intact autoregulation, only 2 (13%) developed severe ultrasonographic lesions. Thus, 8 of the 10 with severe lesions exhibited high correlation between MAP and HbD.

Another study showed no relationship between MAP and CFOE.^{23,24} *MAP and Long term outcome:* Long term outcome is considered to be the best yardstick against which all neonatal problems, their treatments and interventions are weighed. In a study examining influence of acidosis, hypoxia and hypotension on neurodevelopmental outcome, 191 VLBW babies were enrolled and parameters like the type of acidosis (metabolic or respiratory) present, duration of single and cumulative episodes of acidosis, hypoxia and hypotension were measured. At 6 months, both respiratory and metabolic acidosis as well as the total duration and longest single episode of acidosis were significantly correlated with cognitive, motor, and neurologic outcome ($P < .0001$). By 24 months, only the metabolic component of acidosis had any significant association with all three outcome measures. Duration of hypotension independently correlated with outcome at both testing periods ($P < .002$) but isolated hypoxemia did not. **the metabolic component of acidosis and isolated hypotension contributed significantly to adverse outcomes – abnormal neurological examination and Bayley scores at 6 and 24 months** ($P < .05$).²⁵

Another study enrolled, 98 newborns, less than 34 weeks at birth to examine the relationship between newborn hypotension and hypoxemia and brain damage. Heart rate, blood pressure and oxygen saturation were recorded continuously during the 96 hours following delivery. Outcome measures included neuropathology in children who died, and motor and cognitive development at one year corrected age in children who survived. There were 22 children with a minor and 27 with a major abnormal outcome. There was a relationship between newborn hypotension, newborn hypoxemia and low birth weight, and a major abnormal outcome. The probability of a **major abnormal outcome increased from 8% in newborns with no hypotension or hypoxemia, to 53% in children with both hypotension and hypoxemia.**²⁶

LOW CEREBRAL BLOOD FLOW AND CNS MORBIDITY/ NEURODEVELOPMENTAL OUTCOME

Low CBF and IVH: Low or fluctuating cerebral blood flow is considered to be one of the most important pathophysiological basis of IVH.²⁷ The relation between CBF on the first day of life and the severity of any subsequent IVH was investigated by Meek et al.²⁸ CBF was measured in 24 babies during the first 24 hours of life using NIRS. Infants were classified as: normal scan, minor IVH or severe IVH. **CBF was significantly lower in the infants with IVH** than those without hemorrhage, **despite no difference in carbon dioxide tension and a higher MAP.** On subgroup analysis, those **infants with severe IVH had the lowest cerebral blood flow.**

In another study¹⁵, SVC flow was used as a surrogate for CBF¹¹ in babies born before 30 weeks gestation. SVC flow below the range recorded in well preterm babies¹¹ was common in the first 24 hours (38%) babies, becoming significantly less common by 48 hours (5%) babies. 13 of 14 babies with grade 2 to 4 IVH had SVC flow below the normal range before development of an IVH. Two of 4 babies with grade 1 IVH also had SVC flow below the normal range before developing IVH. In all, IVH was first seen after the SVC flow had improved, and the **grade of IVH related significantly to the severity and duration of low SVC flow**.

Another study by same authors on risk factors of IVH in premature infants prospectively followed 2 cohorts of 126 (1995-1996) and 128 (1998-1999) infants born <30 weeks gestation. It was found that **early IVH was associated with vaginal delivery and possibly low APGAR** scores and low SVC flow was the only independent risk factor for late IVH in both cohorts (1995-1996 adjusted OR: 20.39; 1998-1999 adjusted OR: 5.16).²⁹ On comparing the SVC flow disturbances and middle cerebral artery (MCA) indices for strength of association with IVH³⁰, it was found that after controlling for gestation, there was a **highly significant association between lowest SVC flow and subsequent IVH** but no association between IVH and lowest MCA mean velocity, estimated diameter, pulsatility, or MAP.

LOW CBF AND LONG TERM OUTCOME³¹⁻³³

A prospective observational study was performed on a cohort of 126 babies (<30 weeks) who had serial measurement of SVC flow, during the first 48 hours after birth. Neurodevelopmental follow-up data was available for 93% of this cohort at 3 years of age. After controlling for confounding variables, average SVC flow over the first 24 hours of life was significantly associated with the primary outcome of death or survival with any disability ($P = .004$) and with the secondary outcome of abnormal developmental quotient ($P = .006$). A **greater number of low SVC flow readings** during the first 24 hours were significantly **related to death and adverse developmental outcome**, but the individual lowest SVC flow was not, **suggesting the importance of duration of low SVC flow**. After adjustment, there was no significant association between average mean blood pressure over the first 24 hours and abnormal developmental outcome, whereas, the **proportion of mean blood pressure readings less than the gestational age** showed a trend toward an association with death and any disability.³²

TREATMENT OF SHOCK AND NEURODEVELOPMENTAL OUTCOME

Hypotension may cause brain injury and other serious problems and treatment aims to maintain blood flow to brain and other vital organs by using fluids or drugs.

VOLUME EXPANSION

Products used—albumin, blood or blood substitute or salt solutions. Osborn et al³⁴ reviewed the evidence from various trials on the subject and performed a meta-analysis to study whether volume expansion is effective and what type of fluid is most effective. Seven studies were included.³⁵⁻⁴² Five studies, four with data for mortality, compared volume to no treatment. Two studies, comparing different types of volume expansion enrolled very preterm infants with hypotension.

One study examined the effect of volume expansion on blood flow but in normotensive very preterm infants. Comparing volume and no treatment, 4 studies with a total of 940 very preterm infants reported no significant difference in mortality (RR 1.11, 95% CI 0.88, 1.40). The large NNNI 1996⁴¹ study reported no significant difference in severe disability (RR 0.80, 95% CI 0.52, 1.23), cerebral palsy (RR 0.76, 95% CI 0.48, 1.20) and combined death or severe disability (RR 1.00, 95% CI 0.80, 1.24). No significant difference was reported in grade 3-4 P/IVH and combined death or grade 3-4 P/IVH. One study (NNNI 1996⁴¹) reported no significant difference in the incidence of hypotension.

Comparing albumin and saline in hypotensive infants, one study (Lynch 2002⁴⁰) reported a significant increase in mean BP and reduced incidence of treatment failure (persistent hypotension). The other study (So 1997⁴²) and the meta-analysis of the two studies found no significant difference in treatment failure (RR 0.75, 95% CI 0.53, 1.06) or in any other clinical outcome. They concluded that there **is no evidence to support the routine use of early volume expansion in very preterm infants without cardiovascular compromise. There is insufficient evidence to determine whether infants with cardiovascular compromise benefit from volume expansion.** There is insufficient evidence to determine what type of volume expansion should be used in preterm infants (*if at all*) or for the use of early red cell transfusions.

VOLUME EXPANSION VERSUS INOTROPES

A meta-analysis of trials comparing volume expansion and inotropes was done.⁴³ Two small studies^{39,44} comparing volume expansion, using albumin, with dopamine were included. Both studies were adequately randomised,

unblinded studies of albumin versus dopamine with no losses to follow up and analysed by intention to treat. Data for clinical outcomes were available from one study in hypotensive preterm infants on the first day of life.⁴⁴ In this study, albumin had a higher failure rate for correcting hypotension than dopamine (RR 5.23; 95% CI 1.33 to 20.55). As 49% of these infants had already been given volume, the question of which treatment should be given first was not answered. A second study³⁹ compared albumin with dopamine in preterm infants with a normal mean blood pressure at a mean age of 32 hours. Dopamine produced a significant increase in mean blood pressure when compared to infants who received albumin or no treatment, although the difference between the dopamine and albumin groups did not reach significance. No difference was found in mortality (RR 1.45; 95% CI 0.53 to 3.95) or morbidity including any P/IVH, chronic lung disease or retinopathy. There was a higher rate of grade 2-4 P/IVH of borderline statistical significance in infants who received albumin in one study (RR 1.47; 95% CI 0.96 to 2.25; RD 0.27, 95% CI 0.00 to 0.54). No data were available for neurodevelopmental outcomes. The conclusion was that **dopamine was more successful than albumin in correcting low blood pressure in hypotensive preterm infants**, many of whom had already received volume. Neither intervention has been shown to be superior at improving blood flow, or in improving mortality and morbidity in preterm infants.

INOTROPES (DOPAMINE VERSUS DOBUTAMINE)

Inotropes, including dopamine and dobutamine, are commonly used to increase blood pressure. However, the safest and most effective drug for treating hypotension in preterm babies has been unclear. There are multiple trials on this subject but only five satisfied the inclusion criteria of Cochrane meta-analysis.⁴⁵ There was **no evidence of a significant difference between dopamine and dobutamine** in terms of neonatal mortality (RD 0.02 95% CI -0.12 to 0.16), incidence of periventricular leukomalacia (RD -0.08, 95% CI -0.19 to 0.04), or severe periventricular hemorrhage (RD -0.02, 95% CI -0.13 to 0.09). Dopamine was more successful than dobutamine in treating systemic hypotension, with fewer infants having treatment failure (RD -0.23, 95% CI -0.34 to -0.13; NNT = 4.4, 95% CI 2.9 to 7.7). Treatment with dobutamine was associated with a significantly greater increase in left ventricular output in the single study reporting that outcome. There was no evidence of a significant difference between the two agents with respect to the incidence of tachycardia (RD -0.06, 95% CI -0.25 to 0.14). None of the studies reported the incidence of adverse long term neurodevelopmental outcome. **Dopamine is more effective**

than dobutamine in the short term treatment of systemic hypotension in preterm infants. However, in the absence of data confirming long term benefit and safety of dopamine compared to dobutamine, no firm recommendations can be made regarding the choice of drug to treat hypotension.

CORTICOSTEROIDS

In most hypotensive preterm infants, cautious and limited volume administration and the early use of dopamine are effective in improving the cardiovascular status and renal function. However, a subgroup of hypotensive preterm infants do not respond even when treatment is escalated and aggressive volume resuscitation and dopamine doses well beyond the conventional (2–20 $\mu\text{g}/\text{kg}/\text{min}$) dose range are used. In these patients with **volume- and pressor-resistant hypotension**, several therapeutic approaches have been attempted including additional escalation of dopamine treatment, addition of epinephrine or nor epinephrine and more recently, initiation of steroid administration.^{51–55} Cochrane meta-analysis on this topic identified two small studies and it was not considered appropriate to perform a meta-analysis.⁵⁶

Thus, there is no evidence linking various treatment modalities of shock to the neurodevelopmental outcome.

TREATMENT OF LOW SVC FLOW AND NEURODEVELOPMENTAL OUTCOME

Osborn et al⁵⁷ performed a two-center, randomized, double-blind study. Infants ($n = 42$) with low SVC flow ($<41 \text{ ml}/\text{kg}/\text{min}$) in the first 12 hours were randomly assigned to receive 10 ml/kg normal saline solution, followed by 10 $\mu\text{g}/\text{kg}/\text{min}$ of dobutamine or dopamine. If low flow persisted or recurred, the inotrope was increased to 20 $\mu\text{g}/\text{kg}/\text{min}$, with crossover to the other inotrope if treatment failed to maintain flow. It was found that volume produced a more significant increase in SVC flow than dopamine (+43%). At the highest dose, **dobutamine resulted in a significantly greater increase in SVC flow** than dopamine (mean, +9.9 vs -3.2 ml/kg/min, $P = .02$). **Dopamine resulted in a significantly greater increase in blood pressure. Forty percent failed to increase or maintain SVC flow in response to either inotrope.** No significant differences in mortality or morbidity were found.

The surviving babies of the above study were followed up by blinded neurodevelopmental assessments at corrected ages of 1 and 3 years.⁵⁸ No significant differences were found in clinical outcomes, except for reduced

rates of late severe periventricular/intraventricular hemorrhage in the dobutamine group. At 3 years, infants in the dopamine group had significantly more disability and a lower Griffiths General Quotient. At the latest time measured, however, **combined rates of death or disability were similar.**

KEY POINTS – reducing NDD due to neonatal shock

1. Neonatal shock is a major outcome determinant in sick neonates – in preterm babies major NDD increased from 8% in newborns with no hypotension or hypoxemia, to 53% in children with both hypotension and hypoxemia.
2. A MAP of < 30 mm Hg for over an hour was significantly associated with severe IVH and ischemic cerebral lesions.
3. IVH was predominantly associated with a low and variable mean arterial pressure on the day IVH was noted or the day before.
4. In VLBW, metabolic acidosis and isolated hypotension contributed significantly to adverse outcomes – abnormal neurological examination and Bayley scores at 6 and 24 months.
5. On the first day of life, in VLBW babies, clinical tools used to measure systemic perfusion like invasive BP, CRT and CPTd (center peripheral temperature difference) are highly likely to miss cerebral hypoperfusion.
6. SVC flow is probably the best available tool to assess cerebral perfusion. Highly significant association is observed between lowest SVC flow and subsequent IVH.
7. Hypovolemia is not a common mechanism of shock in VLBW babies. Fluid boluses have not shown to be useful in management of shock in VLBW.
8. There is no demonstrable difference between dopamine and dobutamine in clinically relevant long-term outcomes.
9. Dopamine is more effective than fluid boluses and dobutamine in treatment of hypotensive (low blood pressure) preterm babies. Dobutamine is associated with greater increase in tissue perfusion.
10. There are not good studies to comment on use of steroids in volume and inotropes resistant shock.
11. Best evidence is still not available on what is the end point (measurement parameter) to assess therapies. Even babies in whom SVC flows (currently considered best measure of physiology) were compared as outcome of therapy, no differences could be demonstrated in long term outcomes.

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Neonatal Sepsis

Neonatal sepsis can cause **devastating damage to developing brain**. While the **term neonate** is affected only when there is direct brain involvement particularly with **meningitis**, the scenario in **preterm VLBW/ELBW babies is more complex** and sinister.

PATHOPHYSIOLOGY AND IMPACT ON NEURODEVELOPMENT ..

Inflammatory cytokines released in sepsis can cause increased **permeability of blood brain barrier, disturb cerebral auto-regulation** mediate release of free oxygen radicals and many other **cytotoxic** products.¹⁻⁹

In intrauterine infection, clinical and/or histologic **chorioamnionitis, is associated with cerebral white matter injury** and subsequent neurodevelopmental impairment.¹⁰⁻¹⁴ A key role for an inflammatory response by the fetus as well as the mother in the pathogenesis of brain injury has been postulated.¹⁵⁻¹⁷ **Proinflammatory cytokines in amniotic fluid and in fetal or neonatal blood** appear to increase the risk for neonatal brain injury and adverse long-term outcome.

In neonates, inflammatory cytokines may be neurotoxic *in vitro* and *in vivo* and may increase the permeability of the preterm **blood-brain barrier**.¹⁸⁻²² Although it appears that the inflammatory cytokine response precedes and contributes to brain injury, a cytokine response may also be the result and/or marker of damaged white matter. Efforts to reduce the inflammatory responses of the neonate with infection might reduce the risk of brain injury associated with infection.^{23,24}

Neonates with infection are at risk for **circulatory and/or respiratory insufficiency** with decreased systemic blood pressure, hypoxemia, and pathologic alterations in cerebral blood flow. A maturation-dependent **impairment in regulation of cerebral blood flow** in preterm infants

increases the risk of ischemic injury.²⁵ The long-term impact of cerebral ischemia–reperfusion precipitated by sepsis-related cardiovascular instability is unclear. Volpe and others have shown that **oligodendroglial precursor cells**, the major cellular target in the pathogenesis of white matter injury/PVL, are particularly vulnerable to **free radicals** that are generated in response to ischemia-reperfusion. The role of infection and cytokines in the pathogenesis of PVL might be related to effects on cerebral hemodynamics, to the generation of reactive oxygen species/free radicals, or to **direct toxic effects** on vulnerable oligodendroglial precursors.²⁶⁻²⁸

Babies with **meningitis** are noted to have motor deficits, seizures, hydrocephalus, vision, hearing and cognition problems. Neonatal meningitis can have **severe long-term sequelae** (CP, significant learning problems (IQ < 55), global delay, need for special education) in **12–29%** of survivors and **milder impairment** (abnormality that impairs function without significant intellectual or developmental impairment: mild CP, mild learning problems (IQ 55–69)) of neurological function occurs in another **15–38%**. In **VLBW infants** this number increases to **40-50%**. A recent report from the United Kingdom noted a **4-fold increase in CP among VLBW infants with a history of neonatal sepsis** compared with infants with no history of neonatal infection.⁹ Similar outcomes were demonstrated in a large cohort study by Stoll et al involving more than 6000 **ELBW neonates**. Infected ELBW infants are associated with poor neurodevelopmental and growth outcomes in early childhood-CP, low Bayley Scales of Infant Development II scores on the mental development index and psychomotor development index and vision impairment. Infection in the neonatal period was also associated with impaired head growth, a known predictor of poor neurodevelopmental outcome.³² Hearing impairment was more frequent among children who survived neonatal sepsis or sepsis/NEC, especially if they were infected with gram-negative agents or had polymicrobial bacteremia or multiple infections.

Outcomes in **relation to organisms** have not been consistent. A few studies have shown poorer outcome in gram negative infections as compared to GBS.

EPIDEMIOLOGY OF SEPSIS¹⁻⁵

The term neonatal sepsis is used to describe a disease of infants who are younger than one month of age, are clinically ill, and have positive blood cultures. The presence of clinical manifestations differentiates this condition from the transient bacteremia observed in some healthy neonates. Neonatal sepsis is the largest cause of morbidity and mortality in newborns

particularly in the preterm/low birth weight babies. The incidence is 1-5/1,000 live births in term babies and increases by 3-10 folds in preterm. It is complicated by meningitis in many neonates and the incidence of meningitis is 0.2-0.4/1,000 births in term neonates and much higher in preterms. The data from our own country as published in National Neonatal Perinatal Database reflects a much higher incidence of neonatal sepsis.

DIAGNOSIS

In early onset sepsis, the maternal history may provide important information about maternal exposure to infection, maternal colonization and obstetric risk factors (prematurity, prolonged ruptured membranes, maternal chorioamnionitis). The signs and symptoms of neonatal late onset sepsis are often nonspecific,¹⁻⁵ and sepsis should be considered in any sick neonate.

INVESTIGATIONS

No single laboratory test has been found to have sufficient specificity and sensitivity and therefore, laboratory information must be used in conjunction with risk factors and clinical signs.¹⁻⁵

MICROBIOLOGIC TESTS: CULTURES

Blood

- It is the gold standard for the diagnosis of septicemia. Definitive diagnosis of neonatal sepsis can be made only with a positive blood culture.
- Minimum one, but ideally >1 blood culture. Blood cultures should be obtained from peripheral skin punctures.

Cerebral Spinal Fluid (CSF)

- **Meningitis can be often missed clinically.** Consider performing a lumbar puncture if there are any signs of sepsis in a neonate.
- Repeat lumbar puncture at 24-48 hours.

Complete 2 weeks of antibiotics in gram-positive meningitis and 3 weeks in gram-negative infection after CSF is sterile.

Blood cultures may be sterile in 10-15% of infants with early onset and in one-third of infants of VLBW with late-onset meningitis. **Lumbar puncture (LP) is indicated in all cases with positive blood culture and symptomatic (stable) neonates being started on antibiotics on strong clinical suspicion.**

CSF should be obtained before starting antibiotics and sent for cell count, differential count, and chemistry determinations as well as for

Gram stain and culture. CSF culture is the only reliable diagnostic marker of meningitis. In a study in VLBW babies with meningitis, **spinal fluid abnormalities were sparse**, regardless of etiologic organism. Of 38 non-bloody spinal fluid taps ($<1,000$ erythrocytes/ mm^3), only 6 had >30 leukocytes/ mm^3 , 5 had protein >150 mg/dl%, and 6 had glucose <30 mg/dL (1.67 mmol/L). Only 10 infants (**26%**) **had 1 or more of these spinal fluid abnormalities**. “Meningitis” survivors as determined by CSF cultures, had a higher rate of major neurologic abnormality (41% vs 11%, $p<0.001$) and subnormal (<70) Mental Development Index (38% vs 14%, $p<0.001$) than non-meningitis survivors.⁸⁰

Other Cultures

Other cultures (urine, pus, limited utility for ET, catheter tip cultures) should be obtained as indicated by clinical findings. One must also check maternal cultures before and after delivery.

OTHER LABORATORY TESTS

Excluding cultures, none of the laboratory tests when used alone are sensitive or specific enough to diagnose or exclude neonatal sepsis. Many investigators have evaluated the predictive values of panels (combination) of tests for diagnosing sepsis.

Leukocyte Counts

The ratio of immature to total neutrophils (I/T ratio) is 0.16 at birth and declines to a peak value of 0.12 after 72 hours of age. I/T ratio of >0.20 is suggestive of infection. Total WBC less than $5,000/\text{mm}^3$, absolute neutrophil count less than $1,000/\text{mm}^3$ and bands/ polymorphonuclear ratio greater than 0.2 have been shown to have good predictive accuracy and sensitivity for sepsis.

Acute-Phase Reactants³⁴⁻⁵²

Of the many different acute phase reactants C reactive protein has been most extensively used and investigated. Serial determinations of CRP at 12-hour intervals after the onset of signs of sepsis has been found to increase the negative predictive value of CRP, in excluding sepsis. Nonbacterial infections can have a variable CRP response. CRP has a low positive predictive value and should not be used alone to diagnose sepsis.³⁴⁻⁴⁷ Serum procalcitonin has been claimed to be superior to other acute phase proteins, including CRP, with sensitivity and specificity ranging from 87 to 100%.⁴⁸⁻⁵²

Cytokines⁵³⁻⁶⁶

Cytokines are the chemical mediators of inflammatory pathway and are detectable long before acute phase reactants or hematological changes occur in response to bacteremia. They have been extensively studied in the last decade—IL-6,⁵³⁻⁵⁵ IL8,^{56,57} CD64,⁵⁸⁻⁶¹ CD11b,⁶²⁻⁶⁶ and many others. They all suffer from limitations of use in clinical settings, and more importantly have not been able to improve accuracy of diagnosis of sepsis to the clinicians needs.

DETERMINANTS OF OUTCOME—NEONATAL MENINGITIS

A retrospective study of 101 cases of neonatal bacterial meningitis admitted between 1979 and 1998 identified early predictors of adverse outcome at 1 year of age (death or moderate/severe disability). Twelve hours after admission the important predictors of adverse outcome were presence of **seizures, presence of coma, use of inotropes, and leucopenia** 5000×10^9 (sensitivity 68%, specificity 99%). Ninety six hours after admission, predictors of adverse outcome were seizure duration of >72 hours, coma, use of inotropes, and leucopenia (sensitivity 88%, specificity 99%). There was no difference in outcome by pathogen, consistent with other reports. The study excluded infants <35 weeks of gestation and infants with criteria for intrapartum asphyxia, and thus cannot be used in assessing the risk of disability in such infants. Prospective validation of the model is required.

A retrospective study assessed the value of the electroencephalogram (EEG) in cases of neonatal meningitis. Infants who had normal or mildly abnormal EEG backgrounds had normal outcomes (at a mean of 34 months), whereas those with **notably abnormal EEGs** died or had severe neurological sequelae.

TREATMENT

Early recognition and treatment of neonatal sepsis and supportive therapy probably account for recent improvements in outcome and survival.¹⁻⁵ **When a toxic newborn or young infant presents with fever and lethargy or irritability,** it is important to consider the diagnosis of meningitis even if the classic localizing signs and symptoms are absent. Cerebrospinal fluid should be obtained (unless lumbar puncture is clinically contraindicated) to enable initial therapy to be planned. Initial results of cerebrospinal fluid testing may not conclusively differentiate between aseptic and bacterial meningitis, and antimicrobial therapy for all likely organisms should be instituted until definitive culture results are available. Comprehensive therapy, including **antibacterial and antiviral agents,** should continue until a

cause is identified and more specific therapy is initiated, an etiology is excluded or the patient improves considerably and the course of antimicrobial therapy is completed.

TREATMENT SUMMARY

ANTIBIOTIC THERAPY

Empirical antibiotic therapy should be instituted immediately after obtaining samples for culture rather than waiting for the culture results. The choice of empirical therapy should be based on several factors: the timing and setting of the disease, the microorganisms most frequently encountered, the susceptibility profile for these organisms, the site of the suspected infection and the penetration of the specific antibiotic to that site and the safety of that antibiotic.

- Empirical therapy for meningitis after the first week of life
 - Repeat lumbar puncture at 24-48 hours
 - Continue antibiotic therapy (intravenously) for at least two weeks (GBS and *Listeria*) or three weeks (Gram-negative bacteria) after sterilization of CSF cultures
 - Consider longer duration of therapy if focal neurological signs persist at two weeks, if >72 hours required to sterilise CSF, or if obstructive ventriculitis, infarcts, encephalomalacia, or brain abscesses are found by neuroimaging studies. A repeat lumbar puncture may help guide duration of therapy in these circumstances.
- B. Supportive care of the sick neonate has an equally important if not more than antibiotics and adjuncts.
- C. Immunotherapy

Currently there is insufficient evidence to support the routine administration of exchange transfusion, granulocyte transfusion, granulocyte colony stimulation factor and intravenous immunoglobulin (IVIG) in treatment or prevention of neonatal sepsis. Pentoxifylline, a phosphodiesterase inhibitor has been found to reduce mortality in preterm neonates with suspected late onset sepsis.

IMAGING

If CSF culture positive at 48-72 hours and/or suspicion of neurological complications perform cerebral ultrasound and/or computed tomography. Neuroimaging is recommended to detect the complications of meningitis. Complications should be suspected when the clinical course is characterised by shock, respiratory failure, focal neurological deficits, a positive CSF culture after 48-72 hours of appropriate antibiotic therapy, or infection with certain

organisms. *Citrobacter koseri* and *Enterobacter sakazakii* meningitis, for example, are frequently associated with the development of brain abscesses, even in infants who have a benign clinical course. The most useful and non-invasive method early in the course is ultrasonography, which will provide information regarding ventricular size and the presence of haemorrhage. Computed tomography will be useful in detecting cerebral abscesses and later in the treatment course in identifying areas of encephalomalacia that may dictate prolonged therapy.

MANAGEMENT PRACTICES IN A NEONATE WITH SUSPECTED SEPSIS

While the treatment of the sick/symptomatic neonate is less controversial, the same cannot be said for the asymptomatic baby. Currently, decision to initiate treatment and selection of antibiotic are both empirical. Protocols may be devised for the unit and audited for utility (e.g. Perinatal risk score by Bhakoo et al).

PREVENTION OF NEONATAL SEPSIS

Antibiotics given to mother with pre-labor rupture of membranes reduces the risks of infection in mother and baby (ORACLE trial), the choice of antibiotic may be decided on local epidemiology of the unit. Some antibiotics may be associated with increased risks, e.g. amoxicillin-clavulonate is associated with risk of NEC after birth.

Each unit will have to evaluate practices and develop stringent protocols for prevention of sepsis, e.g. Kilbride et al have commented on evaluation and development of potentially better practices to prevent neonatal nosocomial bacteremia.⁶⁷ These include:

- Reducing line and line connections (hubs) contamination will decrease risk of bacterial entry and nosocomial bacteremia.
- Hand hygiene is the primary means to limit potential colonization and nosocomial infections in high-risk newborns.
- Standardized assessment of nosocomial infections will limit unnecessary antibiotic treatment of contaminated blood cultures (False positives).
- Use maximal barrier precautions for insertion of central catheters.
- Selected use of topical application of preservative-free ointment in preterm infants.
- Decrease the number of skin punctures.
- Reduce the duration of IV lipid use.
- Limit the number of days that percutaneous deep lines are in place to 21.

ADJUNCT THERAPIES

Discussed elsewhere in the book.

KEY POINTS – reducing NDD due to sepsis

1. Sepsis mediates NDD by meningitis (loss of cerebral blood flow auto-regulation, increased permeability of BBB, direct cytotoxic injury) and indirect effects—hypoxia and perfusion problems. In VLBW and ELBW babies, sepsis without meningitis also increases risk of NDD (mediated by inflammatory cytokines). In intrauterine infection, chorioamnionitis is associated with white matter injury in preterm.
2. As many as one-third of term babies and half of VLBW babies with meningitis have serious NDD.
3. **Lumbar puncture (LP)** is indicated in all neonates with positive blood culture and symptomatic (but medically stable) neonates being started on antibiotics on strong clinical suspicion.
4. CSF should be obtained before starting antibiotics. **CSF culture and Gram stain** are the most reliable tools in diagnosis of meningitis, especially in VLBW.
5. **Seizures, duration of coma, need for inotropes, leucopenia and delayed sterilization of CSF** are predictors of NDD.
6. **EEG**— A normal or mildly abnormal EEG is a predictor of good outcome in meningitis.
7. **Neuroimaging** is recommended to detect the complications of meningitis. Complications should be suspected when the clinical course is characterized by shock, respiratory failure, focal neurological deficits, positive CSF culture after 48–72 hours of appropriate antibiotic therapy, or infection with certain organisms- *Citrobacter koseri* and *Enterobacter sakazakii*.
8. **Screening and treatment** of asymptomatic neonates at risk of infections is currently empirical, algorithms/protocols may be devised for the unit.
9. **Diagnosis**—Cultures are the only definitive diagnostic tools for sepsis, all other lab tests are not sensitive/specific to be used alone, and mostly tests are combined as panels.
10. **Management**—If a neonate presents with encephalopathy, the baby must be started on appropriate broad spectrum antibiotics in anti-meningitic doses until the diagnosis of sepsis – meningitis is excluded. If viral infections are likely, antiviral drugs may also be started, till CSF viral studies are available.
11. **Supportive care** and adjunct therapies must be initiated as appropriate.
12. **Prevention of sepsis**—Strict hygiene and house keeping protocols must be adhered to, and regular monitoring of cultures for nosocomial infections is necessary.

FAQ's⁶⁸⁻⁷⁹

Q-1. What is the role of vancomycin for prophylaxis against sepsis in preterm neonates?

A-1. The limited data available suggests that the use of prophylactic vancomycin in low doses reduces the incidence of nosocomial sepsis in the neonate with insufficient evidence to ascertain the risks of development

of vancomycin resistant organisms. However, **the current consensus does not recommend routine antibiotic prophylaxis.**

Q-2. What is the status of use of topical ointment for preventing infection in preterm infants?

A-2. The rationale for this practice is that topical emollient therapy decreases dermatitis and fissuring, thus decreasing the entry of bacteria into the bloodstream. Randomized, controlled trials of emollient application have demonstrated improved skin grading scores and decreased numbers of bacteria cultured from the skin. However, the practice of routine ointment application remains controversial because a more recent randomized trial demonstrated an increase in CONS in preterm infants who received twice-daily petrolatum ointment application. The routine application of emollients may actually increase colonization, with no added benefit for patients who have intact skin. The group consensus is that **emollients have a place in maintaining skin integrity, but routine application for intact skin is unnecessary and the risks may outweigh the benefits.**

Q-3. Is there a difference of prophylactic versus selective antibiotic use for term asymptomatic babies born to mothers with risk factors?

A-3. There is insufficient data from randomized controlled trials to guide clinical practice. A large randomized controlled trial is needed in asymptomatic term infants born to mothers with risk factors for infection in their babies, which compares the effect of prophylactic versus selective antibiotics on morbidity, mortality and costs.

Q-4 What is the role of prophylactic intravenous antifungals to prevent fungal infections in preterm VLBW babies?

A-4. Recent meta-analysis found some evidence that prophylactic intravenous fluconazole reduces mortality prior to hospital discharge in very low birth weight infants. The meta-analysis suggests that there will be one fewer death in every nine infants treated with this intervention, but the 95% confidence interval around this estimate of effect is wide. The longer term neurodevelopmental consequences for infants exposed to this intervention remain to be determined. It will be important to identify any subgroups of very low birth weight infants that receive the most benefit from this intervention. There is also a need for further data on the effect of the intervention on the emergence of organisms with stable antifungal resistance.

Q-5. Is there a role of prophylactic antibiotics to reduce morbidity and mortality in neonates with umbilical venous/arterial catheters?

A-5. There is insufficient evidence from randomized trials to support or refute the use of prophylactic antibiotics when umbilical venous catheters are inserted in newborn infants. There is no evidence to support or refute continuing antibiotics once initial cultures rule out infection in newborn infants with umbilical venous catheters.

Q-6. Are there any vaccines which can be given to the mother to prevent neonatal infection?

A-6. There are trials going on in early phases with GBS vaccines. There are also trials with pneumococcal vaccine to prevent pneumococcal infection in neonates. Currently, there is insufficient evidence to support pneumococcal vaccination during pregnancy to reduce infant infections.

Q-7. Vaccination after birth.

A-7. Besides routine vaccination, *Hemophilus influenzae* B vaccine and pneumococcal conjugate vaccines given after birth reduce the risk of meningitis in early infancy.

Q-8. What is the role of pentoxifylline in neonatal sepsis?

A-8. Current evidence suggests that the use of pentoxifylline as an adjunct to antibiotics in neonatal sepsis reduces mortality without any adverse effects. But the number of neonates studied has been small. Hence, these results should be interpreted with caution. Researchers are encouraged to undertake large well-designed trials to confirm or refute the effectiveness of pentoxifylline to reduce mortality and adverse outcomes in neonates with suspected or confirmed neonatal sepsis.

Q-9. What is the role of IVIg in neonatal sepsis?

A-9. There is insufficient evidence to support the routine administration of IVIg preparations investigated to date to prevent mortality in infants with suspected or subsequently proved neonatal infection.

Q-10. Is there any role of IVIg in preventing sepsis in preterm infants?

A-10. Recent meta-analysis showed that IVIg administration resulted in a 3% reduction in sepsis and a 4% reduction in any serious infection, one or more episodes, but was not associated with reductions in other important outcomes: sepsis, NEC, IVH, or length of hospital stay. Most importantly, IVIg administration did not have any significant effect on mortality from any cause or from infections. Prophylactic use of IVIg is not associated with any short term serious side effects. From a clinical perspective a 3-4% reduction in nosocomial infections without a reduction in mortality

or other important clinical outcomes is of marginal importance. The decision to use prophylactic IVIG will depend on the costs and the values assigned to the clinical outcomes.

Q-11. What is the current evidence on use of granulocyte transfusions in neonatal sepsis?

A-11. Currently, there is inconclusive evidence from RCTs to support or refute the routine use of granulocyte transfusions in neonates with sepsis and neutropaenia to reduce mortality and morbidity.

Q-12. What is the role of various colony stimulating factors in management of neonatal sepsis?

A-12. There is currently insufficient evidence to support the introduction of either G-CSF or GM-CSF into neonatal practice, neither as treatment of established systemic infection to reduce resulting mortality, nor as prophylaxis to prevent systemic infection in high risk neonates. No toxicity of CSF use was reported in any study. The limited data suggesting that CSF treatment may reduce mortality when systemic infection is accompanied by severe neutropenia should be investigated further in adequately powered trials which recruit sufficient infants infected with organisms associated with a significant mortality risk.

WEB LINKS

1. <http://www.cochrane.org/reviews/>
2. http://www.gfmer.ch/Guidelines/Maternal_neonatal_infections/Neonatal_infections.htm
3. <http://www.neonatology.org/neo.clinical.html>

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Section 7

Interventions

- 14. Pain and Analgesia**
- 15. Neonatal Transport**
- 16. Perinatal Steroids**
- 17. Mechanical Ventilation**

Pain and Analgesia

Pain is defined as ‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage’. Neonates endure many painful procedures during their stay in the neonatal intensive care unit (NICU). The use of pain relieving interventions has been sparse due to the **misconception that neonates do not feel pain**. There is now sufficient evidence that neuro-anatomical and neuro-endocrine systems in a viable fetus are sufficiently mature for transmission and perception of painful stimuli.¹⁻⁴

PATHOPHYSIOLOGY

Nociceptive pathways develop very early in fetal life. As early as 6 weeks gestation, dorsal horn cells in the spinal cord form synapses with the developing sensory neurons. These sensory neurons grow peripherally to reach the skin of the limbs by 11 weeks, the rest of the trunk by 15 weeks and the remaining cutaneous and mucosal surfaces by 20 weeks. At full term, the density of nociceptive nerve endings in the newborn skin is at least as great as that of the adults. Myelination of nociceptive thalamo-cortical radiations is complete by 37 weeks. In contrast, descending inhibitory tract, which suppress the transmission of noxious stimuli, are not fully functional at term. The **lack of descending inhibition** from higher centers increases afferent nociceptive transmission in the spinal cord. Although nociceptive connections are immature in the preterm, the larger receptive fields, the immaturity of the descending inhibitory pathways, and the ability of “non C nerve fibers” to transmit nociceptive inputs into the dorsal horn (facilitated by “sub-threshold C-nerve fibers”) results in **under damped, poorly discriminated and exaggerated responses**. This concept is derived from Fitzgerald’s observations on the cutaneous withdrawal reflex.⁵

WHAT ARE THE COMMON PAINFUL PROCEDURES IN NEONATAL PERIOD?

Painful procedures commonly performed in the neonatal intensive care unit are:

Diagnostic

- Arterial puncture
- Heel lancing
- Lumbar puncture
- Retinopathy of prematurity examination
- Suprapubic bladder tap
- Venipuncture
- Bronchoscopy
- Endoscopy.

Therapeutic

- Bladder catheterization
- Central line insertion/removal
- Chest tube insertion/removal
- Chest physiotherapy
- Dressing change
- Feeding tube insertion
- Intramuscular injection
- Peripheral venous catheterization
- Mechanical ventilation
- Postural drainage
- Removal of adhesive tape
- Suture removal
- Tracheal intubation/extubation
- Tracheal suctioning
- Ventricular tap

Surgical

- Circumcision
- Other surgical procedures.

HOW DOES A NEONATE REACT TO PAINFUL STIMULI?

Both term and preterm neonates exhibit physiologic and hormonal responses to painful stimuli - increased sympathetic activity, increased catecholamine production, **hyper dynamic circulation, increased oxygen demand, insulin resistance, increased gluconeogenesis, and a catabolic state.** The responses may be exaggerated when compared with older

children and adults. Major stress e.g. surgery without analgesia can result in serious complications and contribute to surgical mortality.

Acute Effects of Pain

The acute effects of nociception are

- *Hemodynamic response*: Rise in mean arterial pressure
- Rise in intracranial pressure
- Hormonal responses
- *Greater nitrogen loss, post surgery*: Delayed post-operative recovery.

Long-term Effects of Pain

- Post-injury hyperalgesia
- Allodynia
- Persistence of immature pain response.

Immediate Neurological Consequences of Pain

Acute hemodynamic changes caused by painful or stressful stimuli are implicated in causation or subsequent extension of early intraventricular hemorrhage (IVH) or the ischemic changes leading to periventricular leukomalacia (PVL).⁶

Long-term Consequences of Pain

There is evidence that untreated pain experienced in early life may lead to an exaggerated response to subsequent painful episodes. Infants circumcised without anesthesia demonstrate exaggerated response to vaccination. This hypersensitivity may be a consequence of painful stimuli during critical period of brain development, leading to structural and functional changes in the nervous system.

Non-noxious stimuli during these periods of hyperalgesia increase painful experiences. Long-term follow-up of preterm neonates may substantiate the preliminary data associating **repetitive painful experiences with neurobehavioral and developmental sequelae.**

ASSESSMENT OF PAIN IN NEONATES

Pain assessment tools in neonates depend on **subjective evaluation of physiological and behavioral responses.** (Table 14.1)

PREVENTION AND MANAGEMENT OF PAIN IN NEONATES—PRINCIPLES

1. Pain in newborns is often unrecognized and under-treated. Neonates do feel pain, and analgesia should be prescribed when indicated.

Table 14.1: Commonly used methods for assessment of pain in newborn

	<i>Premature Infant Pain Profile (PIPP)</i>	<i>Neonatal facial Coding Scale (NFCS)</i>	<i>Neonatal Infant Pain Scale (NIPS)</i>	<i>CRIBS score</i>
<i>Variables assessed</i>	Gestational age Behavioral state Heart rate Oxygen saturation Brow bulge Eye squeeze Naso-labial furrow	Brow bulge Eye squeeze Naso-labial furrow Open lips Stretch mouth Lip purse Taut tongue Chin quiver Tongue protrusion	Facial expression Cry Breathing patterns Arms Legs State of arousal	Crying Requires Increased oxygen demand Expression Sleeplessness
Reliability data	Inter-rater and intra-rater reliability >0.93	Inter-rater and intra-rater reliability > 0.85	Inter-rater reliability >0.92	Inter-rater reliability >0.72
Forms of validity established	Face, content, construct (in preterm and term neonates)	Face, content, construct, and convergent (r = 0.89)	Face, construct, and concurrent (r = 0.53-0.84)	Face, content, discriminant, and concurrent (r = 0.49-0.73)
Clinical utility	Feasibility and utility established at bedside	Feasibility established at bedside	Not established	Nurses preferred CRIBS over another scale

2. If procedure is painful in adults, it should be considered painful in newborns, even if they are preterm.
3. Compared with older age groups, newborn may experience a greater sensitivity to pain and are more susceptible to the long term effects of painful stimulation.
4. Adequate treatment of pain may be associated with decreased clinical complications and decreased mortality.
5. The appropriate use of environmental, behavioral, and pharmacological interventions can prevent, reduce, or eliminate neonatal pain in many clinical situations.
6. Sedation does not provide pain relief and may mask the neonate's response to pain.
7. Health care professionals have the responsibility for assessment, prevention, and management of pain in neonates.
8. Clinical units providing health care to newborns should develop written guidelines and protocols for the management of neonatal pain.

TREATMENT MODALITIES FOR PAIN

1. Pharmacological
 - a. *Opioids*: Morphine, fentanyl, codeine
 - b. *Non opioids*: Paracetamol, sucrose, midazolam
 - c. *Anesthetic agents*: EMLA, lidocaine, ketamine, thiopental.

2. Environmental
 - a. Minimizing painful interventions
 - b. Clustering of painful interventions
 - c. Decreased handling
 - d. Reducing ambient noise and light
 - e. Establishing day – night cycle.
3. Behavioral
 - a. Gentle sensory stimulation of visual, tactile, auditory, and taste sensation
 - b. Oral sucrose
 - c. Kangaroo mother care.

Pharmacological Treatment Modalities (Table 14.2)

Morphine: Morphine, fentanyl and codeine are the most commonly used opioids in NICU. Morphine is the historical gold standard against which other analgesics are compared.

- **Evidence:** Cochrane review⁷ on opioids for neonates receiving mechanical ventilation. Thirteen studies, 1505 infants. Infants given opioids showed reduced premature infant pain profile (PIPP) scores compared to the control group (weighted mean difference -1.71 ; 95% confidence interval -3.18 to -0.24). However the studies were significantly heterogeneous. Meta-analysis of mortality, duration of mechanical ventilation, and long and short term neurodevelopmental outcomes showed no significant differences. Very preterm infants given morphine took significantly longer to reach full enteral feeding than those in control groups.
- **Short term neuro-developmental outcome:** Only one study⁶ assessed the neurodevelopmental outcome at 36 weeks corrected age using neurobehavioral assessment of the premature infant (NAPI score). After adjusting for differences in neonatal medical index (sickness score) and gestational age, no significant differences were noted in the NAPI score, between the morphine and placebo group.
- **Long term neuro-developmental outcome:** When assessed at 5-6 years age, there were no significant differences in the morphine and non-morphine groups in disability, combined death and disability rates, intelligence, motor impairment or behavioral problems.
- **Incidence of IVH:** A meta-analysis showed no significant difference (relative risk 0.84; 95% confidence interval 0.60 to 1.17) in the incidence of “all grades of IVH” between morphine and placebo groups. The lone study on very preterm infants,⁶ also showed no significant effect of analgesia on the incidence of “any grade IVH”. The meta-analysis did not find a difference in incidence of “severe IVH” between morphine and placebo groups.

- **Incidence of PVL:** A meta-analysis of studies including very preterm babies, showed no significant difference in incidence of PVL between morphine and placebo groups.
- **Conclusion:** There is insufficient evidence to recommend routine use of opioids in mechanically ventilated newborns. **Opioids should be used selectively**, as indicated by clinical judgment—pain scales.
- **Doses:** In ventilated babies, an intravenous loading dose (50-150 microgram/kg) is required to achieve effective analgesia, followed by an infusion rate between 5 and 20 microgram/kg/hour. However, as tolerance develops, the infusion rate may need to be increased. Morphine should be given with caution in the spontaneously breathing neonate.
- **Unanswered questions:** need for further research on long term neuro-developmental consequences of morphine. Currently, no recommendation can be made on its routine use.

Midazolam: Midazolam is a short acting benzodiazepine. It is preferred over other benzodiazepines because of its water solubility and rapid clearance. The safety and effectiveness of intravenous midazolam as a sedative in critically ill neonates is not well established.

The Cochrane review⁸ showed higher level of sedation in the midazolam group compared to the placebo group, although there was no difference in sedation level between midazolam and morphine. Jacqz-Aigrain found lower blood pressure in babies receiving midazolam than in placebo group.⁹ Anand et al showed a **higher incidence of adverse neurological events** (death, grade III-IV IVH, PVL) in the **midazolam group compared with placebo and morphine group**.⁶

- **Conclusion:** There are insufficient data to promote the use of intravenous midazolam infusion as a sedative for neonates in intensive care units. **If sedation is required, morphine is safer than midazolam.**
- **Further research:** effectiveness and safety of midazolam in neonates.

Sucrose: The administration of sucrose with and without non-nutritive sucking (pacifiers) is the most studied non-pharmacological intervention for relief of procedural pain in neonates. The effects of sucrose are thought to be mediated by both the endogenous opioids and non-opioid systems. These mechanisms may be additive or synergistic but most likely depend on normal functioning of central nervous system.

In Cochrane review, sucrose, used in a wide range of dosages, was found to improve physiologic (heart rate) and behavioral (the mean percent

time crying, total cry duration, duration of first cry, and facial action) pain indicators and composite pain scores in neonates undergoing heel stick or venepuncture. Premature infant pain profile was significantly reduced in infants who were given sucrose compared to the control group. Long term neuro-developmental outcomes were not reported in any of the study.¹⁰

- **Conclusion:** Sucrose is safe and effective for reducing procedural pain from single painful events (heel lance, venepuncture).
- **Doses:** there is an inconsistency in the dose of sucrose that is effective, in available studies (dose range 0.012 g to 0.12 g). There is a dose dependent effect, but optimum dose is not known.
- **Unanswered questions:** The effect of repeated administration of sucrose in neonates need to be investigated, also, the right dose needed when combined with behavioral (e.g. facilitated tucking, kangaroo care) and pharmacologic (e.g. morphine, fentanyl) interventions. Efficacy in very low birth weight neonates who are unstable and/or ventilated also needs to be studied.

Breastfeeding or breast milk: There are several proposed mechanisms by which breast milk or breast feeding acts as an analgesic-presence of a comforting person (mother), physical sensation (skin to skin contact with comforting person), diversion of attention and sweetness of breast milk. Compared to artificial formulas, breast milk contains a higher concentration of tryptophan, a precursor of melatonin. Melatonin is shown to increase the concentration of beta endorphins and could possibility be one of the mechanisms for the nociceptive effects of breast milk.

In a systemic review by Shah et al,¹¹ neonates in the breastfeeding group were found to have lesser increases in the heart rate and reduced proportion of crying time compared to swaddled group or pacifier group. Neonates in the breastfeeding group had a significant reduction in duration of crying compared to fasting (no intervention group), but there was no significant difference when compared to glucose group. PIPP scores were significantly different between the breastfeeding group when compared to placebo group and the group positioned in mother's arm. However these scores were not significantly different in the breastfeeding and glucose group.

- **Conclusion:** If available, breastfeeding or breast milk should be used to alleviate pain in neonates undergoing a single painful procedure.
- **Further research:** The effectiveness of breast milk for repeated painful procedures is not established and further research is needed.

Kangaroo mother care (KMC): In a clinical trial by Ludington-Hoe SM et al,¹² heart rates and length of cry in response to pain were significantly reduced during Kangaroo Care as compared to when infants were in the warmer. In another study by Johnston CC et al.¹³ Premature Infant Pain Profile scores across the first 90 seconds from the heel-lancing procedure were significantly lower during KMC.

EMLA and pain relief for circumcision: EMLA is a water-based cream that contains 2.5% lidocaine and 2.5% prilocaine. The efficacy of EMLA in treatment of procedural pain in children and adults is well established. Apprehension in using EMLA in neonates is due to risk of methemoglobinemia from prilocaine metabolites (oxidize hemoglobin). Preterm infants may be at greater risk of toxicity because of immaturity of skin that enhances percutaneous absorption of drugs.

In the Cochrane review,¹⁴ EMLA was compared with dorsal penile nerve block (DPNB) and placebo for circumcision. Compared to placebo/no treatment, DPNB demonstrated significantly lower heart rate, decreased time crying and increased oxygen saturation. EMLA also demonstrated significantly lower facial scores, decreased time of crying and lower heart rate. Erythema and mild skin pallor were observed with the use of EMLA. Methaemoglobin levels evaluated in two trials of EMLA were within normal limits. **Conclusions;** DPNB was the most frequently studied intervention and was the most effective for circumcision pain. Compared to placebo, **EMLA was also effective, but was not as effective as DPNB.** Both interventions appear to be safe for use in newborns. None of the studied interventions completely eliminated the pain response to circumcision.

EMLA for lumbar puncture: A randomized controlled trial from Delhi.¹⁵ compared EMLA with placebo for pain relief in lumbar puncture. When compared with placebo, **EMLA significantly attenuated the pain response**, as shown by a lower heart rate, a lower behavioral score particularly at needle insertion and needle withdrawal. **Conclusion:** Lumbar puncture in newborns is associated with pain. Eutectic mixture of local anesthetics is an efficacious agent for reducing the pain associated with needle insertion and withdrawal during lumbar puncture in newborns.

EMLA vs sucrose for venepuncture: A randomized controlled trial by Abad F et al¹⁶ found that **24% oral sucrose solution compares favorably with EMLA cream** as a safe and cheap analgesic procedure to decrease pain responses to venepuncture in newborns. There was no added advantage of EMLA cream over sucrose solution.

Venepuncture versus heel lance for blood sampling in term neonates: Heel lance has been the conventional method of blood sampling in neonates for screening tests or measurement of serum bilirubin or glucose. Sick neonates admitted to neonatal intensive care units undergo this procedure repeatedly as part of routine care. A systematic review compared pain associated with heel lance and venepuncture.¹⁷ All included studies showed statistically significant lower pain scores for venepuncture as compared to heel lance. A meta-analysis of the NIPS scores during the first minute of the procedure was statistically significantly lower in the venepuncture group compared to heel lance group. The study concluded that, **venepuncture, when performed by a skilled phlebotomist, appears to be the method of choice for blood sampling** in term neonates.

Pre-medication for Endotracheal intubation: Most NICUs do not have a policy on pre-medication for intubation. The systemic review by Shah et al 2002 concluded that wake intubation is probably inappropriate in most newborn infants.¹⁸

Table 14.2: Recommended analgesia in neonates¹⁹

Agent	Intermittent dose	Infusion dose	Local/ Topical
Opioid analgesics			
Morphine sulfate	0.05-0.1 mg/kg IV	0.01-0.03 mg/kg/hr 0.5-2 µg/kg/hr
Fentanyl citrate	0.5-3 µg/kg IV	
Anesthetic agents			
Lidocaine (local/topical)	2-5 mg/kg IV 0.5-1 mg/kg endotracheally
EMLA(local/topical)	0.5-2 mg/kg IV	0.5-1 mg/kg per hour	0.5-2 g under occlusive dressing 1 hour before the procedure
Ketamine hydrochloride (Systemic)	2-5 mg/kg IV	
Other agents			
Acetaminophen	10-15 mg/kg orally; 20-30 mg/kg rectally
Sucrose	12%-24% solution given orally 2 min before the procedure, 2 ml for term neonates and 0.1-0.4 ml for preterm neonates

FURTHER RESEARCH

1. Long term neurodevelopmental assessment of neonates undergoing painful procedures and receiving various pharmacological and non pharmacological interventions is still not available and further research is required.
2. Environmental interventions for reduction of pain, e.g. clustering of painful interventions, decreased handling, reducing ambient noise and light and establishing day night cycle has not been studied in detail and requires further research.

KEY POINTS – reducing NDD related to pain and adverse effects of analgesia

1. Neonates have pain sensation – they have functional neuro anatomic and neuro endocrine pain pathways at very early gestations.
2. Preterm babies may have exaggerated pain sensation; their descending pain suppressing pathways may not be mature, although the pain sensing ones are.
3. Pain causes several physiologic and hormonal responses - increased sympathetic activity, hyper dynamic circulation, increased oxygen demand, insulin resistance, increased gluconeogenesis, and a catabolic state.
4. Painful stimuli are implicated in causation and extension of IVH and PVL in preterm babies.
5. Repeated painful experiences modify subsequent reaction to pain. Pain may have a role in modifying neurological and behavioral outcomes.
6. There are not enough studies on long term outcomes of medication/non pharmacological methods used for analgesia in painful procedures.
7. Morphine is considered safer than midazolam if analgesia is necessary. But, even morphine should be used sparingly in very preterm babies and babies already in shock.
8. Ideally pain assessment should guide need for analgesia and routine use is not currently recommended. Pain assessment scales combine physiologic and behavioral parameters.
9. Sucrose, breast milk, Kangaroo Mother Care and non-nutritive suck are effective non-pharmacologic methods that reduce pain.
10. Venepuncture by trained personnel is associated with less pain than heel lance.
11. Local application of EMLA reduces procedure related pain – canulation, lumbar puncture etc.
12. A consistent effort must be made to reduce, club painful procedures and use appropriate pharmacological and non pharmacological measures.

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Neonatal Transport

Sick neonates are transported routinely after birth from the maternal unit (labor room) to the neonatal facility (**intra-hospital transfer**). Sometimes, **inter-hospital transport**, from a primary hospital (level 1) to a better-equipped center (level 2/level 3 units) immediately after birth and later when the neonate is seriously sick, becomes necessary. The commonest reasons for transport are respiratory distress, perinatal asphyxia, seizures, preterm delivery and a newborn needing surgery.

IN-UTERO TRANSPORT¹⁻¹¹

Transferring women at risk of very preterm birth, or previously identified complication of pregnancy, that necessitates better care for the neonate, decreases neonatal mortality.^{3,8} The National Neonatal-Perinatal Database (NNPD) for the year 2002–2003 showed a striking **6.7 fold higher risk of death in extra-mural neonates** (born outside and referred to tertiary facility), as compared to NICU babies born in the tertiary institute (intra-mural). This does not include those infants who do not reach the regional center. In-utero transport decreases major neonatal complications and hence, short term (grade III and IV intra-ventricular hemorrhage) and long-term neuro-developmental disabilities are fewer.²

IMPACT OF NEONATAL TRANSPORT ON OUTCOMES

Higher risk for **grade-III or IV intra-ventricular hemorrhage** have been documented in VLBW infants born at level-I hospitals and transported to the tertiary care center, as compared with those born at the level-III facility.¹⁰ In a study reported from Canada, infants delivered at the community hospitals had a higher prevalence of neuro-sensory impairments compared with infants delivered at the tertiary care center (37% vs 14%,

$p < 0.05$). Countries like UK, Australia, Canada, Ireland and Norway have established national neonatal transport programs and have demonstrated dramatic improvements in clinical outcome, as well as reduction in infant mortality.

The reason for better outcomes include better

- prenatal care (e.g. antenatal steroids)
- resuscitation at birth
- access to specialist support
- infra-structure including safer intra-hospital transfer.

The **type of tertiary facility** to which the infants are transferred may influence outcomes. For example, Shah et al⁹ demonstrated that Canadian, out-born, premature (<32 weeks) infants admitted to perinatal centers had a lower risk of death, compared with those admitted to free-standing pediatric hospitals (adjusted odds ratio 2.25; 95% CI 1.20–4.20); staff and management policies in such facilities may not be equipped or accustomed to the needs of premature infants. After birth, out-born infants may be compromised by the speed and efficiency with which eventual transfer to an appropriate tertiary center is accomplished.

NEONATAL TRANSPORT

In India, most of the time, it is the distressed parents who transport their sick newborns in an auto-rickshaw, bus, car and if lucky in a private ambulance with just an oxygen source at the best. The following are crucial for improving outcomes of transported neonates.

EARLY RECOGNITION

A delay in management of illness – hypoxia, hypo perfusion, metabolic problems like hypoglycemia and jaundice, all can cause increased risk of disability. Units must have simple and easy to follow guidelines to recognize severity of illness and facilitate early and safer transfer.¹⁹

PATIENT SELECTION

It may not be beneficial to transfer all babies, difficult to manage at the primary level, to a referral centre. Babies likely to have poor outcomes, e.g. extreme preterm babies, severe incurable malformations, HIE grade-III, etc. may not benefit by transfer. For example only infants weighing more than 800 gm at birth showed a significant improvement in disabilities at 3 years corrected age (49% vs 22%, $p < 0.001$).⁷

RESPONSIBILITIES OF REFERRING CENTER

Parents should be counseled about the need for transport and the risks involved and consent be taken. Document the mother's and infant's case histories and investigations (including radiograph plate) should be made available to the transport team. All referring hospitals should have facilities for **resuscitation and initial stabilization** of critically ill, newborns.

STABILIZATION BEFORE TRANSFER

There is no need to rush the baby from the referring hospital. This increases the risk of physiological deterioration during the transport. Keeping the baby warm at birth and before transport is the responsibility of the referring clinician. In the community skin-skin to contact is effective (if warmers not available). The newborn should be given oxygen, IV glucose and appropriate antibiotics if required.

LOGISTIC ISSUES IN TRANSFER OF NEONATES—DURATION OF TRANSPORT

In a study from India,¹² showed that neonates with a long duration of transport had 79% higher odds of death than those transported for a short duration, even after adjusting for confounders of the 4966 neonates those transported for >90 minutes had more than twice the rate of neonatal death (RR 2.26, 95% CI: 1.26-4.04), and evidence that those transported for between 60 and 90 minutes had an 80% higher rate of neonatal death (RR 1.81, 95% CI: 1.07-3.06) as compared with those transported for between 30 and 60 minutes.¹²

MONITORING DURING TRANSFER

In unorganized transport or self-transport, by the time the neonate reaches referring hospital he is cold, hypoglycemic, poorly perfused, cyanosed and acidotic. **Even babies transported by paramedics were unstable, half the time**, showing that in the absence of sensitization to newborn care, babies may be transferred sub-optimally. When the baby is being transferred (intra or inter hospital), there should be **good monitoring and appropriate interventions to prevent hypothermia, hypoglycemia, hypoxia, hypo-perfusion**, all of which have implications on long-term morbidity and developmental outcome.

NETWORKING

Organization of referrals based on availability of beds (networks) improves outcomes of extreme preterm babies.

COMMUNICATION

Between parents, referring specialist and referral unit can minimize medical and social issues.

REVERSE TRANSFER

This feedback will improve the neonatal care practices of referring unit. It also takes care of a major inhibition for transport and referral i.e. loss of patient confidence in referring unit.

STANDARD PROTOCOLS FOR NEONATAL TRANSPORT

There is a need for protocols on safer transport and this must also cover legal issues. The National Neonatology Forum of India has developed a module for training on neonatal transfer.

ETHICS

It is very important to avoid criticizing the management of referring hospital. Also it is important to speak to the parents before you start any procedures on the baby.

DOCUMENTATION

Documentation of clinical status on leaving the referring hospital, during transport and arrival is very important.

ORGANIZATION OF A NEONATAL TRANSPORT SERVICE**NEONATAL TRANSPORT TEAM**

Transport of sick, newborn infants is a challenging job and should not be left to the most junior member of team. The transport team should consist of; (i) a specially trained doctor, (ii) an experienced nurse and (iii) a trained ambulance driver. The doctor and nurse should be able to recognize and initiate treatment of complications, administer required medications, resuscitate, keep stable, and maintain communication with team leader (Neonatologist).

TRANSPORT AMBULANCE

Ideally should be able to house and stabilize transport incubator. There should be source of oxygen, enough light, back up energy source, etc. Power source should be compatible with the medical transport equipment.

EQUIPMENT

Equipments and drugs for transport should be kept in state of readiness. Equipment should be regularly checked to ensure that batteries are charged,

gas supplies are adequate and emergency drugs and disposables present. There should be a checklist, which the transport nurse uses before going for transport services. Transport incubator with transport ventilator would have:

- **Monitor:** Multi channel monitor with ECG, NIBP with cuff, SpO₂ monitoring, Thermometer, Stethoscope
- **Airway:** Self inflating bag and mask (all sizes), Endotracheal tubes (all sizes), 2 Laryngoscopes, Oxygen cylinders, suction catheters and portable suction device, nasogastric tube, chest drain, etc...
- **Circulation:** Intravenous syringe pump, IV catheter, tubing and connectors, Three way taps, IV solutions, Umbilical catheter, syringes
- **Others:** Sterile gloves, cleaning solutions, IV cut down pack, suture materials.

DRUGS

Resuscitation drugs, Adrenaline 1:10,000, Calcium gluconate 10% solution, Dextrose 10% solution, Phenobarbitone, Phenytoin; Cardiovascular drugs, Dopamine, Dobutamine, Adenosine, Frusemide, Prostaglandin E₂, Antibiotics – Ampicillin, Amikacin, Cefotaxim, Metronidazole; Sedatives/muscle relaxants – Morphine, Midazolam; Others – Vitamin K, Heparinized saline.

CARE DURING TRANSPORT

RESPIRATORY CARE

We need assess the neonate's ability to maintain airway during the transport. Anticipate physiological deterioration during transport. Clear airway secretions and position the baby with slight neck extension. Neonates who have mild distress can be managed with an oxyhood. All infants with significant respiratory distress should be intubated, before transfer is very difficult to intubate in the ambulance. To prevent long-term consequences the neonate should be adequately oxygenated and if ventilated, they should have adequate sedation and analgesia to prevent the baby from fighting ventilator, tube dislodgement, hypoxia, risk of intra-ventricular hemorrhage (preterm) and PPHN (Term Meconium Aspiration syndrome). Check for pneumothorax at all times. Emptying the stomach before transport reduces the risk of aspiration.

CIRCULATION

Check heart rate, capillary refill, quality of peripheral pulses, color, temp of skin. If perfusion is poor or blood pressure is low give 10 ml/kg of normal saline and repeat if necessary. Start inotropes if required. See that the newborn is normotensive before you start the journey and through transport.

THERMAL CARE

Minimize draughts and keep ambulance warm (25°C). Wrap the baby in cling wrap and cover with blanket. If skin temperature is below 36°C, then re-warm the baby before transport either in the radiant warmer if available in the hospital or shift to transport incubator. Avoid opening the transport incubator canopy and maintain incubator temperature in thermo-neutral range. Hypothermia can lead to hypoxia and hypoglycemia.

Neonates who are hypothermic are at risk of developing necrotizing entero-colitis and pulmonary hemorrhage. In the community setting temperature maintenance could be achieved by skin to skin contact (kangaroo mother care), using warm blanket, cotton wool, hot water bottle in a carrycot (avoid direct touch or leakage), thermocol box with holes, etc.

BLOOD SUGAR

Check heel-prick blood sugar, commence IV infusion with a syringe pump. From sub-centers and PHC if IV access is difficult give 10 ml/kg of EBM or 5–10% dextrose orally. Infants who have **altered level of consciousness or seizures with low blood glucose** level are at risk of adverse long-term neurological outcome. In case of suspected sepsis, antibiotics need to be started after collecting blood culture. Delay in antibiotics with progression of sepsis into septic shock or meningitis have long-term implications in terms of neurological outcome.

KEY MESSAGES – reducing NDD by appropriate neonatal transport

1. In-utero transport is safer; recognize high-risk pregnancy, and transfer mother to tertiary care before delivery
2. Early recognition and referral of sick neonate, before they are too sick for safe transfer
3. Appropriate patient selection, avoid referral of babies unlikely to benefit from transfer
4. Stabilization before transfer, Monitoring during transfer
 - a. Airway and oxygenation
 - b. Perfusion
 - c. Euglycemia
 - d. Thermal regulation
5. Communication between referring, receiving team and parents is crucial
6. NNF module on neonatal transport need to be followed and regularly upgraded by experiences from different centers.

FURTHER READING

1. Neonatal transfer and Transportation: NNF training module.

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Perinatal Steroids

Premature infants are treated with a number of drugs in the NICU despite a lack of long-term studies proving their safety, especially on the developing brain. Of particular recent concern is the data that the use of postnatal dexamethasone in VLBW infants is associated with abnormal neurodevelopmental outcome.

Chronic lung disease (CLD) in preterm infants including the previously commonly used term bronchopulmonary dysplasia (BPD), is an important cause of mortality and is associated with long-term morbidity, including delayed growth, recurrent respiratory infections, impaired pulmonary function, and neurodevelopmental delay. In the past, several randomized trials have demonstrated the usefulness of postnatal dexamethasone in short-term respiratory outcomes, although there was no actual impact on the survival (Table 16.1). These have included early extubation and baby going off oxygen earlier. Unfortunately long courses of very high dose dexamethasone had been used for years despite the lack of follow-up studies on the safety of such a potentially risky drug. Initial short-term studies have shown poor weight gain and poor head growth in neonates treated with early postnatal dexamethasone. The results of larger long-term follow up studies have, now, conclusively proved that use of **postnatal dexamethasone is strongly associated with neuromotor delay (upto 40%), cerebral palsy (CP) (2 fold) and PVL (Table 16.2).**

The **early (<96 hours) regimen of dexamethasone was associated with greater risk of neurodevelopmental problems than moderately early (7–14 days) or delayed (> 3 weeks) regimens.** The mechanism of injury could be dexamethasone-induced suppression of the release of brain-derived neurotrophic factor, which is vital for neuronal development. Apart from having direct neuronal toxicity, dexamethasone may also impair mechanisms that protect against hypoxia and hypoglycemia. It is possible

Table 16.1: Benefits of postnatal corticosteroids

<i>Outcome</i>	<i>Timings</i>	<i>RR(95% CI)</i>	<i>NNT(95% CI)</i>
CLD at 28 days	E	0.85 (0.79, 0.92)	14 (9, 25)
	M	0.87 (0.81, 0.94)	9 (6, 20)
CLD at 36 weeks corrected age	E	0.69 (0.60, 0.80)	11 (8, 20)
	M	0.62 (0.47, 0.82)	4 (3, 8)
	D	0.76 (0.58, 1.00)	6 (3, 100)
Mortality at 28 days	E	1.05 (0.90, 1.22)	
	M	0.44 (0.24, 0.80)	17 (10, 50)
Mortality before discharge	E	1.02 (0.90, 1.17)	
	M	0.66 (0.40, 1.09)	
	D	1.03 (0.71, 1.51)	
Failure to extubate at 7 days	E	0.76 (0.66, 0.88)	8 (6, 17)
	M	0.62 (0.46, 0.84)	3 (2, 7)
	D	0.69 (0.58, 0.82)	4 (3, 7)
PDA	E	0.75 (0.68, 0.83)	10 (7, 14)

D = delayed (>3 weeks); E = early (<96 hours); M = moderately early (7–14 days); NNT = number needed to treat.

Table 16.2: Adverse effects of postnatal corticosteroids

<i>Outcome</i>	<i>Timings</i>	<i>RR(95% CI)</i>	<i>NNH(95% CI)</i>
Hyperglycemia	E	1.36 (1.23, 1.51)	9 (7, 13)
	M	1.51 (1.20, 1.90)	8 (6, 20)
Hypertension	E	1.84 (1.54, 2.21)	10 (8, 14)
	M	2.73 (1.25, 5.95)	20 (13, 100)
	D	2.61 (1.29, 5.26)	17 (10, 50)
Hypertrophic cardiomyopathy	E	4.33 (1.40, 13.40)	3 (2, 6)
	M	3.29 (1.50, 7.20)	5 (3, 11)
GI hemorrhage	E	1.90 (1.35, 2.66)	17 (11, 33)
	M	1.74 (1.02, 2.98)	17 (9, >200)
Infection	M	1.35 (1.06, 1.71)	11 (7, 50)
Growth failure	E	6.67 (2.27, 19.60)	2 (1, 2)
Abnormal neurological exam	E	1.81 (1.33, 2.47)	10 (7, 20)
CP	E	1.69 (1.20, 2.38)	17 (9, 50)
Death or CP	E	1.16 (1.00, 1.34)	17 (8, >200)

D = delayed (>3 weeks); E = early (<96 hours); M = moderately early (7–14 days); NNH = number needed to harm.

that dexamethasone is uniquely neurotoxic amongst the corticosteroids, maybe contributed partly by the preservatives used. People have used later, shorter and smaller doses of dexamethasone in evolving BPD, however clear cut evidence of long term benefits or safety has not been studied. Steroids other than dexamethasone have been studied that could provide pulmonary benefits without harming the developing brain. Betamethasone, methylprednisolone, inhaled steroids and hydrocortisone has been found to be safer, but efficacy and follow up studies are awaited.

It therefore appears that there is little role of postnatal steroids and should be used as a part of studies where neurodevelopmental outcome

is the primary endpoint. **Dexamethasone should not be used in the first 4 days** and very limited steroid use may still be justified later in life-threatening situations, to improve lung inflammation and improve lung function.

The European association of perinatal medicine has recommended:

1. Corticosteroids should be avoided
2. No indication to give postnatal dexamethasone in the first 3–4 days of life
3. Spontaneously breathing neonates should not be given steroids
4. Corticosteroids might be indicated for very ill, ventilator dependent patients
5. The lowest possible dose for the shortest possible duration should be used.

It has been suggested that dexamethasone could be started at doses as low as **0.2 mg/kg/day initially for 2 days and later tapered to 0.1 mg/kg/day and 0.05 mg/kg/day for 3 days each**. The greatest benefit of steroids is seen when used in 2nd week of life. Babies exposed to steroids should have RBS and BP monitored and should have neurodevelopmental follow up.

Compared to postnatal steroids, single course of antenatal steroids is of great benefit in reducing the incidence of IVH and improving neurodevelopmental outcome. Antenatal steroids are widely recognized for their ability to increase maturity of the fetal lung. But as the improvements in lung function were not sustained beyond a week, multiple courses of antenatal steroids were given to the mothers. However, mounting evidence suggests that **repeated courses of antenatal steroids given to stimulate lung maturity is physiologically (poor lung growth) and developmentally (poor brain growth and adverse neurodevelopmental outcome) hazardous to premature infants**. Therefore

Table 16.3: 2000 NIH consensus statement recommendations on antenatal corticosteroids

- All pregnant women between 24 and 34 weeks gestation who are at risk of preterm delivery within 7 days should be considered candidates for treatment with a single course of Antenatal corticosteroids.
- Standard treatment consists of 2 doses of betamethasone ,12 mg, intramuscularly 24 hours apart or 4 doses of 6 mg of dexamethasone intramuscularly 12 hours apart
- As a result of insufficient scientific data from randomized clinical trials (RCTs) regarding efficacy and safety, other regimens and **repeat courses of corticosteroids should not be used routinely**, but reserved only for patients enrolled in RCTs.

repeated courses of antenatal steroids are unproven and potentially harmful. The NIH guidelines are given in Table 16.3.

However in a recent study from Chandigarh, multiple doses of antenatal steroids resulted in improved NICU survival, without any endocrine, somatic or neurodevelopmental adverse outcomes in babies followed till 22 months (Table 16.4).

Table 16.4: Long-term outcomes of antenatal steroids—Chandigarh study

	Multiple courses (n=25)	single course (n=28)	P
Mean age at follow-up	21.1 months	23 months	0.08
Neurological outcome			
suspect	6	4	0.37
Abnormal	2	0	0.12
BSID scores-abnormal MDI	2	2	0.91
weight <5th centile	16	19	0.77
length<5th centile	4	10	0.1
OFC<5th centile	5	12	0.08

In general, drugs in the NICU should be used judiciously, after carefully reviewing the literature and consensus statements. Periodic drug updates are published in peer reviewed journals and one should keep abreast of this. An effort should be made to follow the babies treated with potentially risky drugs for their developmental outcome. Minimizing interventions, gentle brief ventilation, developmentally supportive care and intensive monitoring would definitely decrease the need for drugs in NICU.

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Mechanical Ventilation

Availability of newer and better machines for ventilation and better care of sick neonates has resulted in a great improvement in survival of ventilated neonates. Ventilation strategies are currently targeted at minimizing lung injuries. There is a paucity of data on neurodevelopmental implications of **different ventilation strategies**.

HOW INAPPROPRIATE VENTILATION CAN CAUSE BRAIN INJURY?

The cause of brain injury in ventilated neonates is multifactorial but **perturbations in cerebral blood flow** are considered to be of central importance.^{11,15,16} Cerebral circulation is very sensitive to changes in PaCO₂ and pH. Babies on mechanical ventilator are vulnerable to both insufficient corrections of homeostasis and also to inadvertent “over-ventilation”.

FACTORS IN MECHANICAL VENTILATION THAT AFFECT NEURODEVELOPMENTAL OUTCOMES

PaCO₂

CO₂ extremes result in changes in cerebral blood flow. Low CO₂ decreases cerebral blood flow and high CO₂ increases cerebral blood flow.

Studies on hypocapnea and preterm brain injury: In a study monitoring PaCO₂ levels, extremely low PaCO₂ levels (<17 mm Hg) during first three days of life were associated with significantly increased risk of moderate to severe periventricular echodensities, large periventricular cyst, grade III or IV intracranial hemorrhage and cerebral Palsy (CP).¹

In another study, a lowest PaCO₂ of > 20 mm Hg was not associated with an increased risk of adverse neurological outcome. In this study, there was **no correlation between CO₂ changes beyond the third day of life and brain injury** (neurosonographic or neurodevelopment

abnormalities). In the absence of perinatal complications (like APH, asphyxia) there is **strong correlation between severe hypocapnea (PaCO₂ <20 mm Hg) and cystic PVL.**²

The duration as well as the severity of hypocapnea has been associated with adverse neurodevelopment outcome. A retrospective study comparing preterm infant with cystic PVL with matched controls showed that, infants with cystic PVL had both lower mean PaCO₂ levels and **longer period with PaCO₂ levels < 25 mm Hg.**⁴

High frequency jet ventilation (HFJV) places the baby at high risk of hypocarbia. Wiswell prospectively evaluated preterm infants undergoing HFJV with serial neurosonograms, and assessed the cumulative effect of hypotension, acidosis, hypoxia and hypocarbia. Using logistic regression analysis it was found that infants with cystic PVL were more likely to have **cumulative hypocapnea below a threshold level of 25 mm Hg during the first day of life.** However in a prospective randomized controlled trial performed by the same investigator in which HFJV was compared to conventional ventilation in preterm infant with RDS, hypocapnea was not found to independently predict an adverse outcome.^{3,5}

Permissive Hypercapnea

The association between hypocapnea and adverse neurodevelopmental morbidity has resulted in greater interest in the practice of allowing higher PaCO₂. Data available from the two studies in the Cochrane review do not support the use of permissive hypercapnea to prevent morbidity/mortality in ventilated new born infants. There are **no serious adverse effects reported with permissive hypercapnea** (minimal ventilation strategies) in the studies included. Therefore, it can be concluded that hypercapnea at least in the range targeted (up to 60 mm Hg) is not harmful in the short term. Long term neurodevelopmental evaluation is yet to be seen. Gentler ventilation strategies are likely to result in **shorter duration of ventilation** and lesser lung and possibly other organ injuries.⁶

Until more evidence to support the safety and benefit of hypercapnea strategy is available, it would seem wise to **avoid exposure of ventilated newborns to either severe hypocapnea (<20 mm Hg) or hypercapnea (>55 mm Hg).**

pH

Sensory neural hearing loss is more common in infants with PPHN treated with **alkalosis** and extracorporeal membrane oxygenation (ECMO). More than half (53%) of surviving infants with PPHN treated with **hyperventilation** and respiratory paralysis had hearing impairment.^{7,19}

Metabolic acidosis may be an indicator of tissue hypoxia and should be corrected by treating the appropriate cause. The use of sodium bicarbonate to treat even the severest of acidosis (except in select circumstances) is considered harmful. Respiratory acidosis, high CO_2 is associated with increased cerebral perfusion and risk of IVH.

PaO₂

Hypoxia

It would be unethical to have studies comparing outcomes of babies with hypoxia and those with appropriate therapy. It is still not known as to how low levels of PaO₂ would definitely be associated with brain injury. Indirect evidence of tissue hypoxia (metabolic acidosis, lactate, etc). may be a guide to oxygenation status at tissue level.

Hyperoxia

ROP awareness has mandated closer monitoring of oxygenation. With continuous pulse oxymetry monitoring and judicious use of blood gases low/high PaO₂ can be avoided. Keep saturations between 87–93 % in preterm babies. PaO₂ should be between 60–80, use minimum FiO₂ to achieve above targets. Although direct brain injuries are not described, hyperoxia is associated with ROP and BPD/CLD.

MEAN AIRWAY PRESSURE AND OPTIMAL LUNG VOLUME

Hypoxia and acidosis are understandably responsible for poor neuro-developmental outcomes. Delay in ventilation, or conservative ventilation strategies (under-ventilation) and consequent hypoxia/hypercapnea and low pH can be detrimental to brain. The initial trials on HFV that used conservative mean airway pressures resulted in increased IVH and that too severe grades. Recent optimal lung volume strategies employing higher mean airway pressures have supported both elective and rescue HFV.

In an event of hypoxemic brain injury, body compensates by increasing cerebral perfusion, and hence, severity of brain injury is minimized. Overzealous ventilation to improve oxygenation will lead to **high mean airway pressures** or tidal volumes. This increases intra-thoracic pressure and results in **decreased venous return** and filling pressures in the heart.⁹

Current ventilation targets “**optimal lung volumes**” and avoids complications of under/over ventilation. It is mandatory to observe **central venous pressure (CVP) and invasive blood pressure** in a sick baby requiring high airway pressures on ventilator. Lack of such close monitoring and dependence on clinical observations for **hemodynamic status** of a baby may result in poor neurological out come.

ASYNCHRONOUS BREATHING

Asynchrony during ventilation of a preterm baby with RDS can result in fluctuating cerebral blood flow which is a precursor of IVH.¹⁰ Increased respiratory efforts cause fluctuations affecting both systolic/diastolic components of perfusion. To avoid arterial blood pressure fluctuations, synchrony needs to be achieved. This can be achieved by increasing ventilator support, use of synchronized mechanical ventilation, or sedation and muscle paralysis.

Synchronized Ventilation

Use of SIMV and SIPPV especially after the acute phase (in weaning) reduces duration of ventilation and oxygen dependency.

Neuromuscular Paralysis

Cochrane review has shown that paralyzing with pancuronium reduces the incidence of IVH in babies fighting the ventilator. But paralysis is known to adversely affect other aspect of ventilation and long term outcomes have not been addressed in these studies. Currently, **paralysis is not routinely recommended.**¹²

Sedation

Morphine: Neo pain trial suggested that **pre-emptive morphine infusions do not reduce IVH** among mechanical ventilated babies. Morphine use in **extreme preterm babies and babies with poor perfusion** are at increased risk of disability.¹³

Midazolam: Studies, where midazolam was used for sedation of sick ventilated babies, showed statistically increased incidence of adverse neurological events (death, grade III/IV IVH and PVL). Cochrane systemic review concludes insufficient evidence for the use of midazolam: lack of clinical benefit and increased risk of poor neurological out come.

NURSING ISSUES

Both, Tracheal suctioning and chest physiotherapy are considered risk factors for IVH. Vigorous deep tracheal suctioning produces fluctuations in blood pressure leading to risk of IVH.

DURATION OF VENTILATION

There is a documented relationship between number of days on the ventilator and adverse developmental outcomes.

ACUTE COMPLICATIONS—PNEUMOTHORAX

Results in sudden and severe fluctuations in cerebral circulation. In preterm and unstable neonates, pneumothorax increases risk of IVH.⁸

CLD/BPD

Longer duration of ventilation and oxygen dependency increases risk of NDD in preterm babies. Currently the effect of ventilation strategies, fluid, nutrition, adjunct therapies like steroids, vitamin A, aerosolized and systemic diuretics on incidence and severity of CLD and consequent NDD are inconclusive.

VENTILATION STRATEGIES

- a. nCPAP—a less invasive form of ventilation, reduces the number of days baby remains intubated. Currently, not enough data to show difference in neurodevelopmental outcomes on nCPAP vs conventional ventilation
- b. HFV—There were initial concerns of increased IVH with HFV. With use of optimal lung volumes, HFV is now considered safe and a preferred mode of ventilation when high mean airway pressures are required on conventional ventilation
- c. Volume targeted ventilation—with improving ventilators, it is now possible to fine tune the targeted tidal volume at each breath and thus possibly keep the CO₂ tightly controlled. Duration of ventilation and incidence of pneumothorax is reduced.^{17,18}

ADJUNCTS—SURFACTANT

Although drop in pulmonary pressure and increased cerebral perfusion have been demonstrated, no increase in IVH rates and incidence of disability are noted on long term follow up. Improved survival of smaller babies (due to surfactant and ventilation) has not added to a greater proportion of handicapped babies. It is only logical that reduced severity of lung disease, less air leaks and shorter ventilation would indirectly act through several mechanisms and reduce NDD.¹⁴

SUGGESTIONS TO MINIMIZE VENTILATION ASSOCIATED BRAIN INJURIES

1. Use antenatal steroids in preterm labor. This reduces incidence and severity of RDS and hence, need for ventilation. ANS also decreases NDD through several other mechanisms

2. Appropriate use of Surfactant will reduce severity of lung disease and need for ventilation
3. Monitor oxygenation – avoid hyperoxia, keep saturations between 87–93% in preterm babies. PaO₂ should be between 60–80, use minimum FiO₂
4. Avoid hypocarbia – gentler ventilation, early extubation, use of nCPAP,
5. nCPAP – non invasive ventilation, early extubation are lung friendly, but neurodevelopmental outcomes are not reported
6. Permissive hypercapnea – allowing CO₂ to rise above previously targeted “normal ranges” is not tested enough to be recommended
7. Volume targeted ventilation, although new, promises to control CO₂ tightly and optimize ventilation
8. Synchronized ventilation is likely to reduce ventilator associated lung injury, duration of ventilation and reduce fluctuations in cerebral circulation.

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Section 8

Neurodevelopmental Assessment

18. Risk Stratification for Neurodevelopmental Disability
19. Clinical Examination Protocol
20. Screening Protocol

INTRODUCTION.....

Optimal perinatal care is the most important determinant of neurodevelopmental outcomes.

Appropriate follow up of these high risk neonates after discharge from NICU is another “opportunity” to modify outcomes.

The understanding of neurodevelopment assessment has made significant advances. But, the lack of a “**user friendly standard-protocol**” that can be practiced at all levels of care has been the limiting factor to “best-clinical practices”. This chapter attempts to organize currently available knowledge on neurodevelopmental follow up – who should be assessed, how, when, what to look for and who would be responsible.

OBJECTIVES OF A FOLLOW UP PROGRAM.....

Reduction of childhood disability by:

- **Providing anticipatory guidance to parents/families** of high-risk infants
- **Guiding pediatricians/primary care physician** on “assessment and follow up”
 - Provide simplified algorithms on assessment, follow-up and referral
- **Providing developmental experts** with best practices and integrating follow up with medical care

• **Quality assurance**—assign responsibilities at various levels of care
The risk stratification, clinical examination, screening, follow-up, early stimulation and specific interventions (next section) are detailed in a sequence in the book for purpose of easy reading. But, in clinical practice many of the processes are simultaneous and may be in a sequence as determined by the pediatrician of the baby.

Risk Stratification for Neurodevelopmental Disability

Throughout this chapter,

Green color represents babies at **minimal risk** of NDD, **Yellow color** represents babies at **moderate risk** of NDD and **Red color** represents babies at **high risk of NDD**.

NEED FOR RISK STRATIFICATION

ANTICIPATORY GUIDANCE TO PARENTS

Plotting of risk factors of the high risk neonate on the color chart forms an easy-to-understand visual display of the babies “risk” that can guide parents at various stages, e.g. before birth, at admission to NICU, at occurrence of risk events, a discharge and so on. For example

	< 2500 gm	< 1500 gm	< 1000 gm
Risk of CP (%)	0.8-1.4	6-14	9-17
Risk of MR (%)	0.8-1.4	2-8	22.3-37

Risk of CP in general population is 0.02%. It is evident that a baby born at <1000 gms is at a greater risk.

ASSIGNING LEVEL OF FOLLOW UP

All babies need to be assessed for their growth and development. This is the primary responsibility of a pediatrician/any primary care physician who cares for children.

In order to **optimize utilization of available resources** it is necessary to identify babies/infants at increased risk of neurodevelopmental disabilities (NDD) and stratify their assessment, follow up and intervention based on expected outcomes. The perinatal risk factors for NDD have been

detailed in the previous chapter. The previous chapters on high risk newborn are summarized in the Table 18.1.

Table 18.1: Risk stratification (encircle risk factors), chose the column of maximum severity as indicated by risk factors

<i>Mild risk for NDD</i>	<i>Moderate risk for NDD</i>	<i>High-risk for NDD</i>
Antenatal risk factors	Fetal growth abnormalities	Fetal distress
Prelabour ROM, prolonged labor	Outborn/Sub-optimal Perinatal care	Sub-optimal Neonatal transfer/care
Preterm	Gestation < 33 weeks	< 28 week
< 2500 Gm	Birth weight < 1500 gm	< 1000 gm, preterm with SFD, 10th centile
> 1 abortion, infertility treatment	Multiple births (twins/triplets)	Metabolic disorders, Intra-uterine infections, congenital anomaly (nervous system/ multiple), teratogens exposure
Perinatal asphyxia/mild NE	Moderate Neonatal encephalopathy (NE) Levene grade 2	Severe NE ** – Levene Grade 3, Prolonged encephalopathy > 2 weeks, multi organ injury
Transient hypoglycemia	Hypoglycemia, blood sugar < 25 mg/dL, > 3 days	Symptomatic hypoglycemia, seizure
Suspect sepsis (screen negative)	Sepsis (culture +ve/ clinical and screen +ve)	Meningitis
Neonatal jaundice needing phototherapy	Neonatal jaundice leading to Exchange transfusion	Kernicterus
IVH grade 1 or 2, no abnormality at 40 weeks	Intraventricular Hemorrhage (IVH) > grade 2 on Neuro-sonogram	Ventriculomegaly and/or cystic periventricular leukomalacia (at 40 weeks), hydrocephalus
NICU admission	Complex medical course – NEC and PDA (needing surgery), CLD	Severe hypoxia (ventilation > 7 days, apnoea requiring resuscitation), hypotension
Normal neurologic exam at discharge	Severe/prolonged encephalopathy Any cause	Abnormal neurologic examination at discharge/ Suspect finding on neurodevelopmental Follow Up
Good home + follow up	Sub-optimal Home Environment (Parent coping poor/ low socio-economic)	Parent/physician concern for NDD

Clinical Examination Protocol

PHYSICAL EXAMINATION—POINTERS TO NDD (RED FLAGS) ...

MAXIMAL OCCIPITO FRONTAL CIRCUMFERENCE (OFC) (HEAD CIRCUMFERENCE)

One of the Best Studied/Simple Tools in NDD Prediction

Measure OFC—Use a narrow tape with a small metallic end. Measure OFC by “overlap” technique to avoid the artifact produced by the non pliable metallic end.

Measure length—Use an infantogram.

Plot OFC and length on standard growth charts; **compare centiles** of OFC in relation to length (In low birth weight babies use special growth charts, and use corrected age on standard charts after the preterm babies cross the expected date of delivery).

Exclude familial variations in OFC (measure maternal/other family members OFC before labeling abnormal).

Exclude measurement errors when looking at serial OFC—try and use the same tape/infantogram.

Microcephaly

- OFC centile << length centile
- Static/dropping OFC centile (in relation to length centile) on serial follow-up

Macrocephaly

- OFC centile >> length centile
- Increasing OFC centile (in relation to length centile) with/without hydrocephalus

ASSESS GROWTH

Measure weight and length; plot on appropriate growth chart and compare centiles.

- Poor growth— weight \ll length centile
- Growth centiles less than expected for gestation/dropping on serial follow up
 - Severe growth retardation (symmetric) with dysmorphism points to genetic origin
 - Poor growth may point to medical problems that can affect Neurodevelopment
 - Poor growth may be seen in babies with NDD as the feeding is not optimal

COMPLETE HEAD-TO-TOE EXAMINATION (FOR ABNORMALITIES THAT MAY POINT TO NDD)

- a. **Dysmorphic facies** (Chromosomal anomalies)
Slant of eye, placement of ears, and philtrum of upper lip etc. may be morphologically different and point to specific syndromes/chromosomal anomalies. **Do not commit on dysmorphic facies on first day of life** (effect of delivery process) and **without seeing the face of parents/family members. Preterm babies may appear dysmorphic.** It would be appropriate to wait and reassess before diagnosis are made.
- b. **Abnormal Dermoglyphics** (chromosomal anomalies)
- c. Neuro cutaneous markers (NCM)
In dark skinned babies a careful search may be necessary in-order to not miss these NCM. For the same reason the newborn period (while the skin is still not fully pigmented) is the best to make a note of café-au-lait spots.
- d. Examine for murmurs
- e. **Abnormal genitalia**
- f. **Intra-uterine infections markers**—IUGR, congenital heart disease, hepatosplenomegaly, cataract, petechiae (thrombo-cytopenia), microcephaly
- g. **Sacral dimple/midline defect** (above level of natal cleft)—for occult spinal defects.

HIP EXAMINATION FOR DEVELOPMENTAL DYSPLASIA OF HIP (DDH)

- a. Desirable—to screen all neonates/infants for DDH
Perform clinical examination of hips on first 2 days of life and all immunization/well baby visits till 1 year for signs of DDH. If—

- i. Ortolani/Barlow positive or asymmetry or suspect click-clunk on assessment—retest at 2 weeks.
- ii. Refer to orthopedician by 2 weeks—USG at 3 to 4 weeks of life (X-ray if greater than 4 months age).
- b. Risk group—breech, girl, family h/o. Consider need for routine Ultrasound screening.

NEUROBEHAVIOR

In neonates, predictive power of isolated neurological signs is not great. An overall impression of suspicious/abnormal neurological status is more useful—**tone, suck, feed, cry and activity** (movements)—5-fold increase in incidence of CP.

An overall impression of abnormal/suspicious neurobehavior is very useful in prediction of (neurodevelopmental) outcomes.

<i>Neurological signs in neonate (mostly term)</i>	<i>Increased risk of CP</i>
Abnormal Tone—limb, neck, trunk	12-15 fold
Diminished cry for > one day	21 fold
Weak or absent suck	14 fold
Need for gavage or tube feeding	16-22 fold
Diminished activity > one day	19 fold

Collaborative Perinatal Project of National Institutes of Health

Important—neonate should not be sedated, should be medically stable at time of examination.

NEUROBEHAVIORAL ASSESSMENT

Neurobehavioral assessment is a useful tool for assessment of young infants—from preterm (> 32 weeks) to one month corrected age

- Research tools for assessment of neurobehavior
 - NAPI (Neurobehavioral Assessment of Preterm Infants)
 - APIB (Assessment of Preterm Infants Behavior)
 - BNBAS (Brazelton Newborn Behavior Assessment Scale)
- Simple clinical tools assessment of neurobehavior
 - Levene’s Grading for encephalopathy (for term babies) (Table 19.1)
 - Simple KIMS* score

NAPI (Neurobehavioral Assessment of Preterm Infants)

Research tool for assessment of neurobehavior. Can be used for babies between 32 weeks gestation and term. Requires training. It includes assessment of—

* Kerala Institute of Medical Sciences

- Motor development and vigor
- Scarf sign
- Popliteal angle
- Alertness and orientation
- Irritability
- Vigor and crying
- Percentage sleep ratings

Also score rating scales for **quality of spontaneous movements, crying and visual behavior.**

VLBW and ELBW babies who had CP, had low scores of NAPI.

Table 19.1: Perinatal asphyxia—Levene's modification of Sarnat and Sarnat score#

Grade 1	Grade 2	Grade 3
No seizure	Seizure	Prolonged seizure
Irritable	Lethargy	Comatose
Hypotonia mild	Marked tone abnormal	Severe hypotonia
Poor sucking	Requires tube feed	Needs ventilation##

Levene MI, Lornberg J, Williams THC. The incidence and severity of post-asphyxial encephalopathy in full term infants. *Early Human development* 1985; 11:21-26.

Fails to maintain spontaneous respiration

Simple KIMS Score**

Lethargic baby defined as

- Decreased spontaneous movements
- Decreased tone
- Poor responsiveness to touch
- Poor cry

If the baby is lethargic (abnormal signs mentioned above) for more than 24 hours—consider HIE, meningitis, IVH—do Neuro imaging, CSF analysis. In sick babies, lethargic for more than 24 hours, there is an increased risk of adverse outcomes (death/NDD) by 13 times.

*Constantinou JC, Adamson- Macedo EN, Mirmiran M, Ariagno RL, Fleisher BE. Neurobehavioural Assessment predicts differential outcome between VLBW and ELBW preterm infants. *J Perinatol* 2005;25(12):788-93.

** Naveen Jain. Predictors of adverse outcomes in sick neonates, abstracts. *Neonol* 2004.

NEUROLOGICAL EXAMINATION

- a. Optimality score has made neurological examination of newborn easy and objective. (The neurological assessment of the preterm and full term newborn infant, 2nd ed. Clinics in Developmental Medicine Series, vol. 148. Dubowitz LMS, Dubowitz V, Mercuri E).
- b. Some abnormal signs that point to NDD are cited in Table 19.2.

Table 19.2: Abnormal neurological examination findings in newborn

<i>Item</i>	<i>Abnormal</i>
Head size	</> 2SD
Fontanel	Wide
Pupils	Asymmetric, slow reaction
Position of eyes	Strabismus, nystagmus, sun-setting
Fixation and horizontal tracking (30 degree)	No
Acoustic response	No eye open/frighten
Glabellar tap	Weak/asymmetric
Posture	Lies flat on table, hands closed
Spontaneous movements	Decreased/increased
Tremors	Fine in hands, chin, coarse limb
Muscle tone (rest)	Asymmetric, decreased
Muscle tone (against resistance)	Increased/decreased
Traction response	Head lags, flaccid, arms fully extended (no flexion at elbow)
Palmar/plantar grasp	Absent, interrupted, tremor
Knee/ankle/biceps jerk	Exaggerated/absent
Moro stage 1	Absent, exaggerated (full extension) (Normal - extension of elbows)
Moro stage 2	Absent adduction, flexion of elbows
Cry	Weak/groaning/high pitch
Asymmetry	Present
Cranial nerve	Abnormality
Responsiveness	Diminished/hyper excitable

NEUROIMAGING

May be done as Initial assessment of neurodevelopment (Before discharge/ first assesment of a young infant)/or decided on follow up based on abnormal clinical findings.

NEUROSONOGRAM

Indications

- Preterm \leq 32 weeks gestation, \leq 1500 grams weight at birth
- Preterm with abnormal Neurobehavior/examination—seizures, lethargy, apnoea, sudden onset pallor, bulging anterior fontanel, tight popliteal angles.

Protocol—1st assessment at 3 to 5 days (desirable), 2nd assessment at 40 weeks corrected gestation (mandatory).

Look for evidence of brain atrophy as in ventriculomegaly/cystic Peri-Ventricular Leukomalacia (PVL)—white matter disease (WMD)

CT SCAN

Indications

- Moderate (Grade 2, Levene)/prolonged or unexplained encephalopathy
- Encephalopathy and Seizures
1st scan as clinically indicated (1st 2 weeks of life, before discharge), 2nd at 2 to 6 weeks age (more useful for prognostication)
Look for Marked diffuse hypo density or major intra cerebral hemorrhage/ calcification/malformations/evidence of strokes (infarcts)
CT is not superior to Neurosonogram in picking up PVL.
- In sick preterm infants, neurosonogram is preferred, as it is portable, can come to NICU, rather than baby move, and can be repeated serially without risk of radiation hazards (in contrast to CT).

MAGNETIC RESONANCE IMAGING (MRI)

The neuro-radiologist interpreting newborn MRI must be aware of milestones of myelination on the MRI.

Advantages

Sensitivity of MRI in diagnosis of brain atrophy in preterm neonates is higher than neurosonogram (specificity similar). Diffusion weighted MRI can prognosticate outcomes early (within minutes after the asphyxial insult) in perinatal asphyxia. MRI is generally superior to CT in delineation of many pathologies; but CT is superior to MRI in delineation of intracranial calcification.

Practical Difficulties

Deep sedation needed for MRI, difficulty in monitoring (metal incompatibility of MRI) makes it unsafe in these at-risk babies.

EEG

The EEG of a baby must be evaluated keeping in mind the gestation; EEG maturation and changes have been demonstrated at various gestations. Always include a quiet sleep EEG in evaluation of newborns; abnormalities may be apparent only in this period.

Impairment of EEG developmental maturation persisting for more than 3 weeks of life (often associated with major EEG abnormalities) is predictive of abnormal outcomes.

Major EEG abnormalities

- Disordered development
- Depression/lack of differentiation
- Burst suppression pattern
- Electro cerebral silence
- Unilateral depression of background activity
- Periodic discharges
- Multifocal sharp waves
- Central positive sharp waves
- Rhythmic generalized/focused alpha activity
- Hypsarrhythmia

PHYSIOLOGICAL BRAIN IMAGING

Positron emission tomography (PET) provides information regarding cerebral blood flow, oxygen and glucose consumption, also the spatial distribution and also quantitative details. Currently this is a research tool.

Screening Protocol

RETINOPATHY OF PREMATUREITY (ROP) SCREENING

For Preterm Infants (before discharge/on follow-up if discharged before screening complete).

INDICATIONS—WHO TO SCREEN?

Preterm baby < 33 weeks gestation/<1500 gm birth weight (some Indian studies have reported ROP at older gestation/weights—the protocols may be modified at individual centers, based on local experience. Most Indian experts suggest \leq 34 weeks).

Any preterm baby with severe cardio-respiratory compromise.

WHEN TO SCREEN?

Start at 4 weeks of life or after 31 weeks gestation (which ever is later)
Screen 1/2/3 weekly as per ICROP guidelines and more frequently if “plus disease” noted.

HOW OFTEN TO FOLLOW-UP?—FOLLOW-UP AFTER

- 1-week or less, if
Stage 1 or 2 ROP: zone I, stage 3 ROP: zone II
- 1 to 2-week, if
immature vascularization; zone I—no ROP, stage 2 ROP: zone II,
regressing ROP: zone I

- 2-week follow-up
stage 1 ROP: zone II, regressing ROP: zone II
- 2- to 3-week follow-up
Immature vascularization: zone II—no ROP, stage 1 or 2 ROP: zone III, regressing ROP: zone III

WHAT TO LOOK FOR?

Severe ROP—for laser photocoagulation/cryotherapy.

WHEN CAN THE BABY BE DISCHARGED FROM ROP SCREEN?

No risk of ROP needing treatment.

Findings that suggest that examinations can be curtailed include the following:

1. Zone III retinal vascularization attained without previous zone I or II ROP (if there is examiner doubt about the zone or if the postmenstrual age is less than 35 weeks, confirmatory examinations may be warranted);
2. Full retinal vascularization;
3. Postmenstrual age of 45 weeks and no pre-threshold disease (defined as stage 3 ROP in zone II, any ROP in zone I) or worse ROP is present; or

Regression of ROP (care must be taken to be sure that there is no abnormal vascular tissue present that is capable of reactivation and progression).

WHO CAN SCREEN?

- Indirect ophthalmoscopy by trained ophthalmologist, after pupillary dilation using binocular indirect ophthalmoscopy to detect ROP (desirable).
- Direct ophthalmoscopy by trained pediatrician (in absence of trained ophthalmologist).

WHEN TO TREAT?

The presence of “plus disease” (defined as dilation and tortuosity of the posterior retinal blood vessels) in zones I or II suggests that peripheral ablation, rather than observation, is appropriate.

Threshold ROP, as defined in the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity, may no longer be the preferred time of intervention.

Treatment may also be initiated for the following retinal findings:

1. Zone I ROP: any stage with plus disease
2. Zone I ROP: stage 3—no plus disease
3. Zone II: stage 2 or 3 with plus disease

Treatment should generally be accomplished, when possible, **within 72 hours** of determination of treatable disease to minimize the risk of retinal detachment.

ROP—Policy Statement

Screening Examination of Premature Infants for Retinopathy of Prematurity.*

ROP is a pathologic process that occurs in immature retinal tissue and can progress to a tractional retinal detachment, which can result in functional or complete blindness. Peripheral retinal ablative therapy using laser photocoagulation has resulted in the possibility of markedly decreasing the incidence of this poor visual outcome, but the sequential nature of ROP creates a requirement that at-risk preterm infants be **examined at proper times** to detect the changes of ROP before they become permanently destructive.

“The International Classification of Retinopathy of Prematurity Revisited” (Arch Ophthalmology 2005) should be used to classify, and record retinal findings at the time of examination.

The schedule of follow up is determined by stage of disease, plus disease and zone.

HOW DO WE DILATE?

The recommended eye drops are tropicamide 0.5-1% with phenylephrine 2.5%. Two to three instillations of each of these drops, five minutes apart are usually sufficient to dilate the pupils in 15-20 minutes; and the effect remains for 30-45 minutes. Cyclopentolate 0.5% to 1.0% can also be used safely. Care should be taken to wipe (with sterile cotton/tissue) any eye drops that spills onto the cheeks, as they can be absorbed from the skin of the babies and cause increased heart rate. It is not advisable to use 10% phenylephrine or atropine (drops or ointment) in premature babies for screening, as severe tachycardia, and fatal hyperthermia and dehydration can occur due to systemic absorption. Use of any dilating eye drops (or even antibiotic or corticosteroid eye drops) in premature babies can be life threatening and should not be taken casually. [Note: In India only 10% (and sometimes 5%) phenylephrine is available commercially. A 10% solution needs dilution in 1:4 ratio. To prepare 2.5% solution, dilution can be done with methylcellulose eye drops or commercially available distilled water.]

*Section of Ophthalmology American Academy of Pediatrics; American Academy of Ophthalmology; American Association of Pediatric Ophthalmology and Strabismus. AAP policy statement: Screening Examination of Premature Infants for Retinopathy of Prematurity. Pediatrics 2006;117(2):572-6

SCREENING FOR HEARING IMPAIRMENT ****WHO TO SCREEN?**

Desirable—all neonates, mandatory—all babies admitted to NICU/risk factors for hearing impairment (see overleaf).

WHEN TO SCREEN?

Desirable—before discharge from NICU, Mandatory—within 3 months of life.

Hearing Assessment—Risk Group

- Craniofacial anomalies
- Family h/o of hearing impairment
- Intracranial hemorrhage
- Neonatal Jaundice (needing exchange)
- Amino glycosides, frusemide
- Asphyxia
- Meningitis
- Ventilated
- < 1500 gms
- IU infections

Babies who have risk factors for hearing loss should have a **diagnostic** hearing test at 1 year chronological age (even if passed the screening test).

HOW TO SCREEN?

Oto-Acoustic emissions (OAE)—for all babies

Brainstem Evoked Response Audiometry (BERA)—babies who fail repeat OAE.

Babies at high risk of hearing impairment must undergo both (OAE misses sensory-neural hearing impairment).

WHO CAN SCREEN?

Any trained personnel can do OAE.

BERA must be done and interpreted by an audiologist.

If hearing impairment is detected, the infant should have intervention for hearing impairment before 6 months of age to optimize language development.

OAE

Evoked otoacoustic emissions (OAE) are acoustic signals generated from within the cochlea that travel in a reverse direction through the middle ear space and tympanic membrane out to the ear canal. These signals are generated in response to clicks or tone bursts. The signals may be detected with a very sensitive microphone/probe system placed in the external ear canal. The OAE test allows for individual ear assessment,

** Michael Cunningham, ND and Edward O. Cox MD. The committee on practice and ambulatory Medicine and the section on otolaryngology and Bronchoesophagology. Hearing Assessment in infants and Children: Recommendations Beyond Neonatal Screening Pediatrics 2003;111(2):436-40

is performed quickly at any age, and is not dependent on whether the child is asleep or awake. Motion artifact does not interfere with test results. The OAE is an effective screening tool for inner and middle ear abnormalities. At hearing thresholds (30 dB), there is no OAE response. The OAE test does not further quantify hearing loss or hearing threshold level. The OAE also does not assess the integrity of the neural transmission of sound from the eighth nerve to the brainstem and, therefore, will miss auditory neuropathy and other neuronal abnormalities. Infants with such abnormalities will have normal OAE test results but abnormal BERA test results.

BERA

BERA is an objective means of evaluating hearing. This instrument measures evoked responses in response to sound clicks at frequencies greater than 1000 Hz. The automated screener provides a pass-fail report and no test interpretation by an audiologist is required. Automated BERA can test each ear individually and can be performed on children of any age.

Motion artifact interferes with test results. For this reason, the test is performed best in infants and young children while they are sleeping or, if necessary, sedated.

The BERA and OAE are tests of auditory pathway structural integrity but are not true tests of hearing. Even if BERA or OAE test results are normal, hearing cannot be definitively considered normal until a child is mature enough for a reliable behavioral audiogram to be obtained. Behavioral pure tone audiometry remains the standard for hearing evaluation.

Children as young as 9 to 12 months can be screened by means of conditioned oriented responses (CORs) or visual reinforced audiometry (VRA).

SCREENING FOR CONGENITAL HYPOTHYROIDISM***

WHO TO SCREEN?

Desirable: screen all neonates, Mandatory: screen at least babies at risk of NDD.

WHEN TO SCREEN?

Beyond day 3 and before 1 week of life.

If discharged earlier, take samples before discharge from hospital

***American Academy of Pediatrics; Rose SR; Section on Endocrinology and Committee on genetics, American thyroid Association; Brown RS; Public Health Committee, Lawson Wilkins Pediatric Endocrine Society; Foley T, Kaplowitz PB, Kaye CI, Sundarajan S, Varma SK. Update of Newborn Screening and therapy for Congenital Hypothyroidism. Pediatrics 2006;117(6):2290-2303.

HOW TO SCREEN?

Desirable method: TSH and Free T₄, Mandatory: at least TSH alone (cost-effective, can miss some cases).

WHAT TO LOOK FOR?

TSH > 20 in 1st 2 weeks of life, TSH > 10 after 1st 2 weeks of life are abnormal.

(If the screening test is suggestive, full work up should be completed and treatment started within 2 weeks).

Congenital Hypothyroidism (CH)

The overall incidence of CH ranges from **1 in 3000 to 1 in 4000** newborn infants. Newborn screening and thyroid therapy started **within 2 weeks of age** can normalize cognitive development.

Initial dosage of 10 to 15 µg/kg levothyroxine (LT₄) is recommended. The goals of thyroid hormone therapy should be to maintain total/free thyroxine in the **upper half of the reference range** during the first 3 years of life and to normalize the serum thyroid-stimulating hormone concentration.

The goal of therapy is to **normalize T₄ within 2 weeks and TSH within 1 month.**

Although T₃ is the more biologically active Thyroid Hormone (TH), most brain T₃ is derived from local monodeiodination of T₄, so T₃ should not be used.

The pill should be crushed and suspended in a few milliliters of formula, breast milk, or water. Care should be taken to avoid concomitant administration of soya milk, fiber, iron supplements, or anticonvulsants;

During TH therapy, 4 or more episodes of insufficiently suppressed TSH (>5 mU/L) after the age of 6 months were the most important variables associated with school delay.

A failure of the serum free T₄ concentration to increase into the upper half of the reference range by 2 weeks and/or failure of the TSH concentration to decrease to less than 20 mU/L within 4 weeks after initiation of L-T₄ administration should alert the physician that the child may not be receiving adequate L-T₄ regularly.

Infants need to undergo frequent laboratory and clinical evaluations of thyroid function, growth, and development to ensure optimal Free T₄ dosage and adherence to their therapy regimen. Serum Free T₄ and TSH measurements should be performed: at 2 and 4 weeks after the initiation of L-T₄ treatment, every 1 to 2 months during the first 6 months of life; every 3 to 4 months between 6 months and 3 years; every 6

to 12 months until growth is completed; and at more frequent intervals when compliance is questioned, abnormal values are obtained, or dose or source of medication has been changed; FreeT₄ and TSH measurements should be repeated 4 weeks after any change in L-T₄ dosage.

The aim of therapy is to ensure **normal growth and development** by maintaining the serum total T₄ or Free T₄ concentration in the upper half of the reference range in the first year of life.

SCREENING FOR METABOLIC DISORDERS

WHO SHOULD BE SCREENED FOR METABOLIC DISORDERS?

Desirable—All neonates. Mandatory—All neonates at risk of NDD.

POINTERS TO METABOLIC DISORDER

- Unexplained encephalopathy.
- “Sepsis like picture” with labs not supporting—cultures and sepsis screen and response to antibiotics not suggesting sepsis.

Baseline Tests

Serum ammonia, blood gas analysis (for anion gap acidosis), urinary ketones.

Special Test

Serum, urine (stored cold during transfer), CSF for biochemical analysis to metabolic lab.

Section 9

Neurodevelopmental Follow-up

- 21. Discharge Protocol
- 22. Follow-up Protocol
- 23. Organization of Neurodevelopmental
Follow-up

Discharge Protocol

DISCHARGE PLANNING

ROLE OF TREATING PEDIATRICIAN/NEONATOLOGIST

- Plan discharge well ahead; document all risk factors for NDD, clinical course in NICU and interventions
- Identify a local primary care physician for purpose of follow-up and communicate effectively
- Involve the development therapist in pre-discharge counseling
- Co-ordinate multi-specialty consults
- Integrate follow-up with medical follow-up
- Communicate with family, specialists and primary care physician.

ROLE OF DEVELOPMENTAL THERAPIST

- Babies at moderate/high risk of NDD should be initiated on an early stimulation program before discharge.

ROLE OF PRIMARY CARE PHYSICIAN

- Counseling parents educating/guiding on need for follow-up
- Link between specialists and family
 - Co-ordinate appointments—tests, interventions
 - Conveniences of family (family friendly)
 - Periodic preventive assessments with medical visits.

CHECK LIST BEFORE DISCHARGING A HIGH RISK NEONATE

1. Summary of baby's neonatal hospital course (copy to primary physician)
 - Date of birth and expected date of delivery

- Gestational age at birth
 - Birth weight
 - Risk factors for NDD
 - Antenatal risk factors
 - Neonatal risk factors (diagnosis, medications/interventions, referrals)
 - Discharge weight (and weight gain over last week), approximate 1% of birth weight per day
 - Discharge OFC (growth over last week), 0.75 to 1.25 cm/week for preterms till term, 0.5 cms per week there after (and for term babies)
 - Date and results of
 - last metabolic screen (Ca, P, ALP)
 - last hematology assessment (Hb)
 - last ROP check
 - hearing screen (if done)/proposed date of test if not done before discharge
 - last neurosonogram report
 - ~ worst/significant abnormality on USG
 - Dietary intake at discharge (breast milk/formula/other supplements, as per medical prescription)
 - Immunization status
 - Environment assessment (HSQ) (assess parent preparedness/socio-economic).
2. Risk stratification for NDD based on risk factors and initial assessment of neurodevelopment
 - In-clinic FU (low/no risk)
 - Developmental unit (Moderate risk)
 - Child development center (high-risk).
 3. Pre-discharge counseling
 - Danger signs- how to contact in case of emergency?
 - Need for neurodevelopmental follow-up
 - Plan of follow-up till one year
 - Role of parents in stimulation of child
 - Parent observed development assessment (e.g. development observation card, DOC).
 4. Follow-up appointments
 - ROP
 - Appointment for hearing screen (if not done)
 - Newborn unit (medical)
 - Lab tests
 - Neurodevelopmental assessments.
 5. Immunization.

CHECK LIST OF NDD WITH DEFINITIVE THERAPY

(Make sure these are not missed, these are definite opportunities to improve babies outcomes)

- ROP treatment—laser photocoagulation/cryotherapy
- Squint correction/surgery/refractory error correction
- Hearing intervention—hearing aid/speech therapy/cochlear implant
- Hypothyroidism treatment with L—thyroxine
- Seizures medications, hypertonia medications
- Developmental stimulation
- Physical and occupational therapy
- Pediatric surgery interventions—hernia, GERD surgeries
- Ortho consults
- Hydrocephalus shunt
- ENT consult—swallowing, oro-motor problems.

DDST—report as **normal**—review after 3-6 months, **abnormal**—state interventions, **questionable**—repeat after 3-4 weeks.

DASII—report as **DQ and score**—If more than 85 reviews after 3-6 months. If less than 85—repeat after 3-4 weeks and intervention.

Neuro exam—report as **normal tone/hypertonia/hypotonia/patterns**—diplegia, quadriplegia, hip shoulder girdle hypotonia, hemiplegia.

REASSESS—IF NO DEFINITE OPINION POSSIBLE

Hearing—a baby passing a hearing test states hearing is normal on that day, acquired hearing loss can result in hearing impairment later.

Parents to note. Each of the tests takes a lot of time and hence, tests **may not be possible without prior appointment.** Parents also need to confirm availability of the appointment one-day prior, as appointments are made well ahead and unforeseen situations may make a particular service unavailable on that day. A good mood of the baby is essential for all tests/sedation may be required for some—hence completion of test is subject to cooperation/sedation.

A normal report indicates that no abnormality is detectable on that day. Brain of babies is still acquiring complex functions and hence, the future course cannot be predicted by these tests—and are **not guarantees of normal future** and hence, repeated testing—surveillance is necessary, the tests only help to plan any interventions on that day. The parents are the best development specialists and if they note any unusual behavior they may report to the development unit. Plan of follow-up after 1-year age will depend on the baby's development assessment.

KIMS –CDC follow-up schedule

Name
DATE OF BIRTH

Hospital No.
EDC

Corrected age DATE	Term (CA)	1 month	2 months	4 months	8 months	12 months
Growth (weight, OFC for length, corrected age)						
Neurobehavior/ personal social (DDST)						
Neurologic exam (Amiel Tison)	Limited utility before 3 months Use DDST for moderate risk (done by developmental pediatrician) Use DASII for high- risk done by developmental therapists					
Gross motor (DDST)						
Fine motor (DDST)						
Language (DDST)						
DASII score MoDQ						
DASII score MeDQ						
CDC grading						

NB: some centers prefer to follow a schedule of 3, 6, 9 and 12 months

Corrected age DATE	Term	1 month	3 months		12 months
Ear (OAE/BERA)		*	*		* (repeat in risk high)
Labs (Hb, Ca, P, ALP),	*	* Calcium	MV till (3.5-4.5kg)	Clinical and lab assessment for iron- deficiency anemia	Iron

Eye (ROP/squint nystagmus/ refraction) DATE By ophthalmologist	4 weeks after birth/ 31 weeks (if later)	As per ophthalmologists advice—1/2/3 weekly or more frequently in plus disease	45 WEEKS/ completed vascularization	9-12 months— Refraction/ squint

ASSESSMENT OF THE CHILD’S HOME ENVIRONMENT

Assessed at all visits to neurodevelopment clinic.

WHAT IS HOME ENVIRONMENT?

Assessment of parents/extended family - coping/parenting skills/opportunities for stimulation of infant.

TOOLS

- **Social environment scale**

The social status of the family is a simple measure of environment, but not a completely reliable predictor of the outcomes in an at-risk infant.

- **HOME inventory**

Objective tool for assessment of home environment in relation to baby's development.

- **Home screening questionnaire**

Simpler to do in clinical practice.

HOME (Home Observation for Measurement of Environment)

Betty M Caldwell, Robert H Bradley

Objective method of describing the quality of home environment.

The inventory scores the environment on following areas:

- Emotional and verbal responsiveness
- Acceptance of child behavior
- Organization of physical and temporal environment
- Provision of appropriate play materials
- Parent involvement with the child
- Opportunities for variety in daily stimulation.

Dr Anand Pandit et al, clearly demonstrated that the intelligence quotient (IQ) of LBW and VLBW decreased (more so in later) with decreasing maternal education—demonstrating the effect of environment on neuro-developmental outcomes.

Follow-up Protocol

If the infant is being assessed for the first time beyond neonatal period please check whether initial assessment is complete.

INTRODUCTION—CONCEPT OF CORRECTED AGE

For assessment of “**milestones**” in preterm infants, there is unsettled controversy of whether to “**correct for prematurity**” and if so how much to correct (full or half) and till what age?.

If correction is not made for prematurity, an extreme preterm infant may miserably fail all developmental tests in early infancy. On the other hand, correction overestimates child's cognitive abilities (especially important ≤ 35 weeks) and may fail to identify infants who would benefit from early interventions.

It appears that earlier exposure to extra-uterine environment may have greater effect on language (component of cognition) than on motor development. Preterms with language and cognitive abilities consistently below their age corrected for prematurity should be evaluated and initiated on early intervention.

Most developmental experts agree to correct for prematurity till at least two years of age.

Correction for prematurity—full correction: calculate the infants age from the “expected date of delivery” (for the purpose of neurodevelopmental follow-up), rather than from the actual date of birth.

GROWTH, NUTRITION AND MEDICAL ASSESSMENT

- Head circumference should be plotted at every health maintenance visit until the age of 2 years (LOE 2).
- Height and weight should be measured and plotted at regular intervals.

A poor weight gain <20 gm/day during the first month after discharge should be investigated.

Use preterm growth charts for preterm babies.

NUTRITION

Encourage breast-feeding even in VLBW, ELBW babies. There is no evidence to recommend fortified formula over breast-feeding, if breast milk is available sufficiently

- Mothers must express breast milk for the sick preterm baby from as early as possible (breast pumps may be used).
- Even in very preterm (< 32 weeks corrected age)—practice non-nutritive sucking and kangaroo mother care.

All preterm infants (<35 weeks) should receive supplements

- Iron - starting at 4-6 weeks (can start at 2 weeks) till 1-year of age (3 mg/kg/day of elemental iron)
- Calcium (as phosphate salt) - start when on full feeds—150 mg/kg/day of elemental calcium till term (Monitor Hb, Ca, P, alkaline phosphatase, nearing 40 weeks corrected age)
- Multi-vitamin supplementation till approximately 3.5 kg (approximate, expert opinion)
- Protein supplementation -using human milk fortifiers or special formula for preterms has demonstrated only short term growth advantages, the advantage of supplementation does not carry into childhood (Indication—poor linear growth poor and by medical prescription only).

Weaning may start early (at 4 months corrected age) in preterm babies.

GENERAL CARE/MEDICAL ISSUES

- Advice on thermoregulation (kangaroo mother care)
- Advice on prevention of infections (hand wash, avoid visitors)
- Schedule of feeding (demand feeding even for VLBW once stable enough to discharge)
- Immunization—BCG, OPV can be given after discharge from NICU (after 34 weeks gestation), hepatitis B—if mother recorded HBsAg negative, immunize as per national schedule starting with first DPT (can be given if baby ready for discharge and gaining weight). In case the mother is Hep B positive, or status unknown, Hep B vaccine can be administered even in extreme preterms immediately after birth. Other **vaccines as per chronological age** (from actual date of birth, not expected date of birth)

- Constipation—common in preterms, may use lactulose
- Inguinal hernia—advice surgical consult/umbilical hernia reassurance
- Examine for murmurs after 2-3 weeks of life on a regular basis (Left to right shunts manifest earlier in preterm)
- Watch for hepatosplenomegaly, cataract, (IU infection)
- Repeat any abnormal lab tests till normal (e.g. hemoglobin, platelet count, renal and liver function tests).

NEUROLOGICAL EXAMINATION

A structured, age-appropriate neuro-motor assessment should be performed and assessed by **corrected age**

- at least once during the first 6 months
- once during the second six months
- and once between ages 1 and 2, 2 and 3 and 4 and 5 years (LOE 3).

ASSESSMENT OF PASSIVE TONE

Assessment of passive tone (Amiel Tison, Infant Motor Screen) in the first year of life is a useful tool for early detection of motor developmental disability (Reported even better than BSID at 3, 6, 9 months).

Test schedule –desirable: 3, 6, 9, 12 months (some prefer 2, 4, 8, 12), mandatory - 3 months, 12 months.

Adductor and popliteal angles are best studied. Adductor and popliteal angle are measured with a goniometer.

Months	3	6	9	12
Adductor angle	40-80	70-110	100-140	130-150
Popliteal angle	80-100	90-120	110-160	150-170

Word of Caution

It has been seen that, tight angles at 4 months (<2000 gm birth weight) do not always predict abnormal outcome, many of which become normal, where as persisting hypertonia at 8-12 months is associated with poor outcomes.

What to look for

- a. Tone abnormalities
 - Normal tone
 - Hypotonia (mild/severe)
 - Hypertonia (mild/severe).

- b. Pattern of tone abnormalities
 - Diplegia
 - Quadriplegia
 - Hemiplegia.
- c. Look for asymmetry.
- d. Serial assessment of tone abnormalities
 - Transient
 - Persistent.

ACTIVE TONE

There should be no head lag at 3 months of age, should be possible to pull to sit by 6 months and pull to stand by 9 months age.

ABNORMAL NEUROLOGICAL SIGNS ON NEWBORN

Explained in previous chapters.

PRIMITIVE REFLEXES AT 3 MONTHS

- Palmar grasp
- Automatic walking
- Moro reflex
- Asymmetric tonic neck reflex.

All **disappear by 3 months** in Indian infants.

Primitive reflexes are **difficult to interpret** even by experts. In infants with diffuse bilateral cerebral injuries, stronger, sustained reflexes with **no signs of habituation** (stereotyped, not decreasing with repeated elicitation) are obtained.

POSTURAL REFLEXES AT 9 MONTHS

- Parachute
- Lateral propping

Postural reactions are relatively easier to interpret, and a **slow appearance** indicates delay in acquiring postures and hence, CNS injury. Vojta's system of kinesiological diagnosis (based on the evaluation of 7 postural reactions) enables one to identify infants at risk for neurodevelopment delay as early as 3 months of age with 100% accuracy when 3 reactions were abnormal.

CRANIAL NERVE EXAMINATION

Refer text of pediatric neurology.

RED FLAGS

- Frog legs—hypotonia

- Scissoring—hypertonia
- Early rolling 1-2 months (hypertonia)
- Persistent fisting at 3 months of age
- Pulling directly to stand at 4 months (instead of to a sit)
- Delay in appearance of postural reactions
- Hand dominance prior to 18 months.

DEVELOPMENTAL ASSESSMENT

Developmental assessment is defined as obtaining information about the skills and potentials of individuals (next section for details).

RECOMMENDED SCHEDULE

For Babies at Mild Risk of NDD/All Babies

- Trivandrum Development Screening Chart (TDSC)
- Development Observation Card (DOC), Schedule: 2, 4, 8, 12 months at well baby/immunization visits.

For Babies with Moderate Risk Factors for NDD

Mandatory:

A multidimensional development-screening test (Denver Development Screening Test (DDST/Denver II) should be documented **using standardized instruments (LOE 3)**

- At least once during first 6 months
- At least once during next 6 months
- Once every year till 5 years.

Desirable

Formal developmental evaluation (Development Assessment Scale for Indian Infants –DASII) be performed (limited utility before 6-8 months corrected age)

- At least once between 9 and 15 months
- At least once between 21 and 30 months corrected age
- Within 2 months of a abnormal/questionable DDST.

For Babies with High Risk Factors for NDD

- Mandatory—DDST every 3-4 months
- Desirable—DASII every 3-4 months by developmental therapist.

BEHAVIORAL PROBLEMS/LEARNING DISORDERS

These disabilities result in poor adaptation to society and poor self-esteem.

- There is an increase in the psychological problems. Attention Deficit Hyper kinetic Disorder (ADHD) and only awareness of the problem can result in early diagnosis and intervention

- It is recommended that all babies < 28 weeks, < 1000 gms undergo a psycho-educational assessment between the ages 3 and 5 (LOE 3)
- Learning problems (borderline IQ) is a great area of concern as unlike the major disabilities, they are often not recognized and result in poor school performances and behavioral problems.

FUNCTION ASSESSMENT

For the purpose of rehabilitation—assessment of functional loss/adaptation is more useful than diagnosis of Neurodevelopmental disability. An example is—

1. Walks without restrictions; limitations in more advanced gross motor skills.
2. Walks without assistive devices; limitations walking outdoors and in the community.
3. Walks with assistive mobility devices; limitations walking outdoors and in the community.
4. Self-mobility with limitations; children are transported or use power mobility outdoors and in the community.
5. Self-mobility is severely limited even with the use of assistive technology.

Organization of Neurodevelopmental Follow-up

Infants should be assigned to risk groups (mild, moderate or severe) based on severity of perinatal problems, the interventions received in NICU and assessment of family preparedness.

FOR BABIES AT LOW RISK OF NDD

It is sufficient to follow-up in the usual well baby clinic – “In Clinic” follow-up.

Objective: Screening for growth and development deviation and referral.

Provider: All pediatricians/primary care physicians (level 1 care).

Prerequisites

- Familiarity with growth charts, TDSC
- Aware of indications to seek NDD consult.

FOR BABIES AT MODERATE RISK OF NDD

It would be appropriate to follow-up such babies in a specially planned-**“Developmental unit”**

Objective: Comprehensive ND FU, early developmental stimulation and referral.

Provider: all centers with NICU (level 2 care).

Prerequisites

- Pediatrician familiar with good clinical practices in neonatology
- Developmentally sensitized pediatrician (knowledge of special growth charts, protocols for neurodevelopmental follow-up)
- Developmental therapist trained in DDST (or equivalent development screening test), Amiel Tison (equivalent neurological examination)

- Early stimulation program
- Radiologist (familiar with neurosonography of preterms)
- Trained ophthalmologist for ROP screens
- Audiologist/ENT specialist (OAE)
- Physical and occupational therapist
- Social worker.

FOR BABIES AT HIGH RISK OF NDD

These babies are a serious risk of disability and screening would be inappropriate. They should have follow-up at a multi-specialty diagnostic and intervention center—"Child development center".

Objective: Serial comprehensive NDFU: Diagnostic tests and interventions.

Provider: tertiary care centers.

Prerequisites: (desirable)

- Neonatologist (uses standard risk definitions for NDD)
- Developmental pediatrician (uses special growth charts, formal neurologic examination), developmental therapist trained in DASII (or equivalent formal development tests), DDST (or equivalent development screening test), Amiel Tison (equivalent neurological examination screening test), early stimulation program
- Counselor for genetic disorders (familiar with dysmorphology)
- Pediatric neurologist
- Radiologist (trained in neurosonogram CT, MRI and EEG in newborn/preterm)
- Trained ophthalmologist/retina expert
- Audiologist/ENT specialist (OAE, BERA)
- Endocrinologist (familiar with management of congenital hypothyroidism)
- Metabolic disorders expert (tandem mass spectroscopy)
- Physical and occupational therapist
- Psychologist for behavioral problems
- Expert in learning disability management
- Neurosurgeon, pediatric surgeon
- Social worker

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Section 10

Developmental Evaluation

24. Developmental Evaluation

Developmental Evaluation

Developmental assessment is defined as obtaining information about the skills and potentials of individuals.

THE PURPOSES OF ASSESSMENT

Assessment of individual children might serve one of the following purposes:

1. To determine the existence of a developmental delay
2. To identify strengths and needs
3. To develop strategies for intervention
4. To determine progress on significant developmental achievements
5. To serve as a basis for reporting to parents

WHAT IS DEVELOPMENTAL ASSESSMENT

- Every baby follows his or her own unique schedule of development within fairly broad limits
- Assessment may take on special significance in a suspected developmentally abnormal infant.
- The score obtained is not an IQ score, but rather a relatively short-term, best estimate of developmental progress.
- It can prove useful in detecting the precursors of later impairment.
- Despite limitations assessment techniques continue to be effective means of identifying infants at risk for developmental disabilities.
- Identification of risk status can lead to early intervention services aimed at prevention and amelioration of potential problems.
- Infant assessors must be well trained professionals who not only have a sound background in child development but have training in the use of the measures and understand their strengths and limitations.

DEVELOPMENTAL ASSESSMENT — BELOW 2 YEARS**TEN COMMANDMENTS IN ASSESSMENT**

1. Assessment must be based on an integrated model of child development, which includes developmental domains and child's functional capacities. It is necessary to observe the child over a time period and in different contexts.
2. Assessment involves multiple sources of information and multiple components.
 - Developmental history
 - Parents perceptions of child's strengths and needs
 - Direct observation of the child, including interactions with caregiver
 - Observations and interaction with the family regarding family's needs and capabilities. Focused observation of the child in different areas of functioning is a must.
3. Assessment should follow a certain sequence.
 - Build an alliance with the parent/caregiver
 - Obtain developmental history
 - Observe the child in the context of unstructured play with caregivers
 - If appropriate, observe child in play with evaluator/clinician
 - Conduct specific assessments of individual functions
 - Integrate all the data to create picture of the whole child, and convey assessment findings in the context of an alliance with the parents.
4. The child's relationship and interactions with his or her caregiver should form the cornerstone of the assessment. Children will generally reveal their highest level of skills in the context of spontaneous, motivated interactions with caregivers. The evaluator can build on these interactions by coaching the parent to elicit certain competency or by joining in the interaction.
5. An understanding of the sequences and timetables in typical development is essential as a framework for the interpretation of developmental differences among infants and toddlers. Given the considerable variation in the normal range of development during the early years, professionals must have sound knowledge in the typical sequence and timetable for different areas of development.
6. Assessment should emphasize attention to the child's level and pattern of organizing experience and to functional capacities, which represent an integration of emotional and cognitive functioning. The basic capacities of relating, interacting and thinking will directly have impact on the specific developmental skills under consideration. It is not

- just a question of whether a particular skill exists or not, but how does the environment support the child's developmental functioning.
7. The assessment process should identify current competencies and strengths, as well as identify the next step in the developmental sequence in order to facilitate growth. It is more useful to think about how to build on the child's current capacities, than to merely describe deficits or lags in development. Too often an assessment focuses on the delay in development.
 8. Assessment is a collaborative process. Building an alliance with the primary caregivers is essential to the process. All the professionals involved with the child have an important role to play in the evaluation.
 9. Assessment should be viewed as the first step in a potential intervention process. The process of screening and assessment has an impact on the family and child regardless of whether intervention services will be provided. It is important to recognize the impact of the process on the family.
 10. Reassessment should occur in the context of daily family or intervention activities. Formal reassessment should occur in the context of the child's daily activities and be conducted by those who are working with the family and child.

TOOLS AND TECHNIQUES IN DEVELOPMENTAL ASSESSMENT

The large majority of developmental delays in the first year could be identified by using cut off points for four simple motor developmental milestones namely, social smile, head holding, sitting and standing.

The major tools and techniques that can be used for developmental screening are:

1. Trivandrum Developmental Screening Chart (TDSC)
2. Developmental Assessment Scale for Indian Infants (DASII)
3. Denver Developmental Screening Test (DDST)
4. Neurological evaluation—Amiel-Tison Passive Angles method
5. CDC grading for motor milestones
6. Developmental Observation Card (DOC)
7. Assessment of Vision Impairment in Early Infancy
8. Assessment of Hearing Loss in Early Infancy

TRIVANDRUM DEVELOPMENTAL SCREENING CHART (TDSC)

What is TDSC?

This is a simple developmental screening test designed and validated at the Child Development Centre, Trivandrum. There are 17 test items in

the chart, carefully chosen after repeated trial and error. The age range for each test item is taken from the norms given in the Bayley Scales of Infant Development (BSID).

Age range—0-2 years.

Test Material

TDSC is a simple tool which doesn't require a developmental kit. A pen and a bunch of key are probably the things required.

Who can do it?

The Trivandrum Developmental Screening Chart is a simple tool that can be administered by anganwadi workers or any person with minimal training. There is an over representation of items near one year of age because one year is an ideal age for formal developmental assessment in a community setting.

Through the Integrated Child Development Scheme (ICDS) routine developmental assessment of infants of children less than two years of age is routinely done in Kerala using Trivandrum Developmental Screening Chart (TDSC), a simplified form of Bayley Scales of Infant Development. Since the norms for TDSC is taken from Bayley Scales, the universally accepted developmental scale for children below 30 months, TDSC may be used in other states also.

DEVELOPMENTAL ASSESSMENT SCALE FOR INDIAN INFANTS (DASII)

Age Range-till 2.5 Years

DASII developed by late Ms. Pramila Phatak, Baroda University based on Bayley Scales of Infant Development (BSID). Bayley Scales are designed to provide a tripartite basis for the evaluation of a child's developmental status in medical, psychological and social aspects in the first two and half years of life.

DASII consists of 2 scales viz; mental scale and motor scale.

- i. *The mental scale:* This is designed to assess sensory-perceptual acuties, discrimination and the ability to respond to these, the early acquisition of 'object constancy' and memory, learning and problem solving ability; vocalizations and the beginnings of verbal communications; and early evidence of the ability to form generalizations and classifications, which is the basis of abstract thinking. Results of the administration of the mental scale are expressed as a standard score, the MDI, or Mental Development Index.

- ii. *The motor scale*: This is designed to provide a measure of the degree of control of the body; coordination of the large muscles and finer manipulatory skills of the hands and fingers. As the motor scale is specifically directed toward behaviors reflecting motor coordination and skills, it is not concerned with functions that are commonly thought of as ‘mental’ or ‘intelligent’ in nature. Results of the administration of the motor scale are expressed as a standard score, the PDI, or Psychomotor Development Index.

Denver Developmental Screening Test–II

Age range	: 2 weeks to 6 years
Purpose	: A screening tool to detect developmental delays
Publication dates	: 1967-1990
Publisher	: Denver Developmental Materials, Inc.

Description

This instrument was designed to be a quick and simple screening tool to be used in clinical settings by people with little training in developmental assessment. The test is comprised of 125 items, divided into four categories:

- Gross Motor
- Fine Motor/Adaptive
- Personal Social
- Language

The items are arranged in chronological order according to the ages at which most children pass them. The test is administered in 10–20 minutes and consists of asking the parent questions and having the child perform various tasks. The test kit contains a set of inexpensive materials in a soft zippered bag, a pad of test forms, and a reference manual. The manual includes instructions for calculating the child’s age, administering and scoring each item, and interpreting the test results.

The test items are represented on the form by a bar that spans the age at which 25%, 50%, 75%, and 90% of the standardization sample passed that item. The child’s age is drawn as a vertical line on the chart and the examiner administers the items bisected by the line. The child’s performance is rated Pass, Caution, or Delay depending on where the age line is drawn across the bar. The number of Delays or Cautions determine.

Neurological Evaluation

Generally in children who present with symptoms of CP, the earliest manifestation is the abnormalities in the muscle tone. It may be either

hypertonia or hypotonia. The variations in tone can be picked up early by the method of evaluation devised by Amiel-Tison. It has simplified the approach to motor difficulties, grouping them within a simple framework with a dual goal: to simplify the explanations to the family who want to understand, for example, why cerebral damage would lead to orthopedic treatment of the hips; the second, to simplify the classification of motor problems for the doctor and the physiotherapist. Repeated neurodevelopmental assessments at 2 years, 3 years, 5 years, 7 years etc. only can give the complete picture of all possible abnormalities including problems at school.

The major advantage of following the method of Amiel-Tison in preference to other neurological evaluation techniques is that there is an individual objective for each of the baby in terms of monthly evaluations and corrective therapy. At the end of one year no attempt is made to give any score. The babies are grouped into:

- i. Normal babies.
- ii. Babies with patterns of transient abnormalities.
- iii. Babies with patterns of persistent abnormalities.

AMIEL-TISON Passive Angles Details

- i. *Adductor angle*: With the infant lying supine, the legs are extended and gently pulled as far apart as possible. The angle formed by the legs at this point is called the adductor angle. Asymmetry between the right and left leg should be noted.
- ii. *Heel to ear*: With the infant lying supine, the legs are held together and pressed as far as possible towards the ears. The pelvis must not be lifted from the table. The arc extending from the infant's heel to the table represents the angle. Increased resistance on one side is an indication of asymmetry, but it might be difficult to apply equal pressure to both sides.
- iii. *Popliteal angle*: The thighs are flexed laterally at the hip along both sides of the abdomen. While holding the infant in this position, the examiner presses the lower leg as far as possible towards the thigh. The popliteal angle, which is formed by the calf and the thigh is estimated in both legs simultaneously. In contrast to the maneuvers described above, it is easier to apply equal pressure to both sides when examining the popliteal angle; therefore, estimation of asymmetry is more objective. Significant asymmetry is indicated by a difference of 10 to 20 degrees between the right and left angles.
- iv. *Dorsiflexion angle of the foot*: The examiner holds the infant's leg straight and flexes the foot towards the leg. This is accomplished

by applying pressure with the thumb to the sole of the foot. The dorsum of the foot and the anterior aspect of the leg form the dorsiflexion angle.

- v. *Scarf sign*: The infant is held in a semi reclining position supported by the examiner's palm. At the same time, the examiner takes the infant's hand and pulls the arm as far as possible across the chest towards the opposite shoulder. Four positions are possible in describing the position of the elbow in relationship to the umbilicus.
1. The elbow does not reach midline (not cross)
 2. The elbow across the midline (cross)
 3. The arm encircles the neck and the elbow reaches axilla
 4. The arm encircles the neck like a scarf and elbow is beyond axilla.

CDC GRADING FOR MAJOR MOTOR MILESTONES

The grading for 3 major motor milestones developed by CDC is widely used for developmental assessment.

Grading—for what ?

- To form a common opinion about the developmental status of the child.
- Make out the improvements in the therapy procedures.
 - To convince the mother about the improvements in the development of her child.

Head Holding: Completed 4 Months

Grade 0	: No head holding at all
Grade I	: Head erect and steady momentarily
Grade II	: Dorsal suspension—lifts head along with body
Grade III	: Prone position—elevates on arms, lifting chest
Grade IV	: Holds head steady while mother moves around
Grade V	: Head balanced at all times.

Sitting: Completed 8 Months

Grade 0	: No sitting at all
Grade I	: Sit momentarily
Grade II	: Sit 30 seconds or more leaning forward
Grade III	: Sit with the child's back straight
Grade IV	: While sitting, can turn around and manipulate a toy
Grade V	: Raises self to sitting position

Standing: Completed 12 Months

- Grade 0 : Not standing well
 Grade I : Stands holding onto a furniture momentarily
 Grade II : Take few steps with both hands supported
 Grade III : Can stand alone with legs apart
 Grade IV : Come to standing position with support of a stool
 Grade V : Without support takes few steps.

Interpretation of CDC Grading

- Grade 0, I, II - abnormal for that age
 Grade III, IV, V - normal for that age
 Grade 0 means poor developmental status
 Grade V means better developmental status.

If a baby has apparently Grade-III head holding (only lifting head without raising on arms) without Grade-II, this is to be considered abnormal, because this may be due to neck extensor hypertonia. Occasionally it may be possible that Grade-IV standing is achieved before the child is able to stand alone (Grade-III) and this is not abnormal.

DEVELOPMENTAL OBSERVATION CARD (DOC)

Developmental disabilities are often seen in infants with no apparent risk factors. Hence it is ideal to have some sort of developmental evaluation for all babies. This is now possible using Developmental Observation Card, a self explanatory and simple card that can be used by the parents. The DOC developed at Child Development Centre, Thiruvananthapuram is now being used in our developmental screening clinic. The large majority of developmental delays could be identified using cut off points for 4 simple developmental milestones. Developmental Observation Card developed at Child Development Centre (CDC) Kerala could be used effectively by distributing the same in postnatal wards.

DOC—Major Milestones

- Social Smile** - achieved by completed 2 months.
(Baby smiling back in response to your smile)
- Head holding** - achieved by completed 4 months
*(Keeping head steady when baby is held upright)
 (Lifts head and shoulder supported on fore arm in prone position)*
- Sitting alone** - achieved by completed 8 months.
(Baby is able to sit alone with back straight, no support).

Standing alone - achieved by completed 12 months.
(Baby is able to stand bearing weight on both legs with minimal or no support).

Make sure that the child can see, hear and listen. Those who fail these simple milestones must have a formal developmental assessment.

ASSESSMENT OF VISION IN EARLY INFANCY

Early detection of visual and hearing problems is not a special service to be offered by ophthalmologists and ENT surgeons. Anybody and everybody who comes in contact with the baby, especially the mother should be encouraged to make sure that the baby can see, hear and even more important can listen. If an adult becomes blind or deaf he can cope with the situation because his brain has already developed and matured and he has had all life's experiences.

An infant with visual and hearing impairment from birth unless supported adequately may develop developmental delay due to a lack of orientation, mobility and experiences. Significant visual and hearing impairment will affect all areas of development because the child's awareness of environment and the ability to interact with it are limited and different from their normal counter parts.

VISUAL DEVELOPMENT

- At birth—babies show visual perception and will follow a moving person with his eyes. Baby can follow a dangling ring with difficulty.
- 3-4 weeks—will watch mother intensely as she speaks to him, fixating on her face.
- 4 weeks—can follow in a range of 90 degrees.
- 4-6 weeks—begins to smile at mother's face.
- 3 months—can follow a range of 180 degrees and can fixate well on near objects.
- Before 6 weeks there is little convergence.
- 4 months—can fix his eyes on a half-inch brick.
- The eyes of the newborn tend to move independently. Binocular vision begins at 6 weeks and is well established by 4 months
- 12-20 weeks—hand regard starts as he lies on his back
- 5 months—excited when his feed is being prepared.
 - 6 months—adjusts his position to see objects. Bending back to see things he is interested in also starts at this age.

VEP (Visual Evoke Potential)

VEP is electrical response to a standardized visual stimulus. The test is used for assessing visual acuity and visual processing disorder.

Method—it is recorded by putting electrodes over occipital scalp. Visual stimulus is given by a light flash through red light emitting diodes in goggles placed over infants eyes. An alternative or generally preferable stimulus is given by shift or reversal of checkerboard pattern.

Response

- First negative wave is seen at the age of 24 weeks of gestation.
- The positive wave appears between 32-35 weeks of gestation.
- The completely defined pattern is seen by 40 weeks of gestation.
- The latencies of both positive and negative waves decreases in linear fashion with increasing maturation.
- Waking and sleep states may alter the latency of VEP.
- Testing is recommended in quiet sleep and can be done as early as 3 months.

Role of VEP in Newborn

Experience is limited, because obtaining data requires newborn to fix eyes on visual display.

Clinical condition	Response
1. Severe hypoximia in PT	Loss of VEP (response is regained on normalization of gases)
2. Asphyxia in term	Impaired VEP (severity of abnormality correlates well with poor neurological outcome)
3. Posthemorrhagic hydrocephalus	Abnormal response (due to dilatation of occipital horn. Improvement seen follow V-P shunt.)
4. PVL	Abnormal response seen.

Role in Children

1. To determine prechiasmal, chiasmal and postchiasmal lesion.
2. Demyelinating disorder of visual pathway.
3. Monocular VEP can be of help in evaluation of visual acuity and refraction.

ASSESSMENT OF RETINOPATHY OF PREMATURITY (ROP)

It is a postnatal multifocal vasoproliferative retinal disorder. It affects eyes of certain premature babies. It is a preventable cause of blindness.

Incidence

80–90% less than 1000 gm birth weight

50–65% 1000–1250 gm birth weight.

Incidence and severity increases with decreasing gestational age and birth weight. Onset of ROP correlates well with postconceptional age rather than chronological age. The mean age of onset of ROP is around 34 week's postconceptional age.

ASSESSMENT OF HEARING LOSS IN EARLY INFANCY***Hearing Development***

The ear is fully developed at birth and sound perception is possible in utero. Recognition of voice and speech perception is present shortly after birth. Language development begins at birth. It is known that babies learn to speak by mimicking what they hear.

This sequence of development of sound localization (according to Murphy) is described when a sound is made approx. 18 inches from the ear. It is as follows.

- 3 months—the infant turns his head to the side to which the sound is heard.
- 3–4 months—the infant turns his head towards the sound and the eyes look in the same direction.
- 5–6 months—turns his head to one side and then downwards if the sound is made below the ear.
- About 6 months—he turns his head to one side and then upwards, when the sound is made above the level of the ear.
- 6–8 months—turns his head in a curving arc towards the sound source.
- 8–10 months—the head is diagonally and directly turned towards the sound (correctly localizes).

A baby may initiate sounds by 6 months. By 7 months he may respond to his name. By the age of 9–12 months he knows the meaning of several words. From about 9 months the baby learns to control and adjust his response to sound. By the first year the ability to localize a sound source is almost as good as in older children and adults. He may listen to hear sounds again and not attempt to localize it.

Although infants can locate sounds their skill at doing so is somewhat limited. Experts suggest that infants have a natural preference for females—that is high-pitched human voices. In fact it is more accurate to say that infants prefer sound in the middle range of pitch, which is the range most similar to human voices—male or female.

Points to be Remembered

- Babies cannot speak if they cannot hear
- If the problems of hearing are undetected it will cause problems with speech, language and cognitive development
- It is important to have the baby's hearing tested as early as possible, if there are risk factors for a hearing abnormality
- Hearing loss may not be apparent until children show signs of developmental delay, often in their speech and language.

Early Detection of Hearing Abnormalities

Check whether the baby is progressing as per the normal speech, language and hearing developmental stages. Ensure that the baby is acquiring these milestones.

Around 2 months of age

- Starttles to loud noises
- Quiets to familiar voices
- Makes vowel sounds like "ohh" and "ahh"

Around 4 months of age

- Looks for sounds with his eyes
- Starts babbling
- Uses a variety of voice sounds, such as squeals, whimpers and chuckles.

Around 6 months of age

- Turns head toward sound
- Begins to imitate speech sounds
- Babbles (ba-ba and ga-ga)

Around 9 months of age

- Imitates the speech sounds of others
- Understands "no-no" and "bye-bye"
- Turns his head towards soft sounds

Around 12 months of age

- Correctly uses "ma-ma" or "da-da"
- Gives a toy when it is asked for
- Responds to singing or music
- Locates sound in all directions

Simple Ways to Check for Hearing Impairment

The best age for a formal hearing test is at 8-10 months and not before 6 months or after 15 months. All babies should have a formal hearing test at 8 months of age.

AUDIOMETRY AND BERA

Audiogram

Incidence of bilateral hearing loss is around 1.5-2.0/1000 children under six years of age, in developed countries. In India the incidence is believed to be still higher than that. Early detection and treatment is critical to speech, language and cognitive development. The most efficient combination for early detection of hearing loss is OAE & BERA. Audiogram provides only fundamental description of hearing sensitivity.

Indications for Audiometry

<i>Age</i>	<i>Speech</i>
1 year	No vocal imitation or babbling.
1.5 year	No use of single word.
2 year	Single word vocabulary less than

PURE TONE AUDIOMETRY (PTA)

Method

The air conduction is tested by delivering pure tones ranging from 250-8000 Hz through an ear phone. The bone conduction is tested by an oscillator placed on mastoid or forehead.

Interpretation

1. Air and bone conduction threshold are same in normal ear and in ear with sensory neural deafness.
2. In conductive hearing loss there is difference between air and bone conduction threshold.
3. In mixed hearing loss both air and bone conduction thresholds are abnormal.
4. In children with functional hearing loss the test is not valid.

Visual Reinforcement Audiometry

The test is useful in children between 5 months to 2.5 years. The technique incorporates head turning response with activation of a mechanical toy reinforcer. It does not provide ear specific information.

Behavioral Observation Audiometry

This test is useful in children below 5 months of age. It tests unconditioned reflexive response to complex test sound (noise, speech, music etc).

Response varies widely within and across infants. Test is less sensitive therefore mainly used as a screening test.

BRAINSTEM EVOKED RESPONSE AUDIOMETRY (BERA)

The test is useful in diagnosis of auditory dysfunction and other disorders of auditory pathway. The electrical response is recorded by putting two electrodes across mastoid and vertex. The test can be performed under sedation or anesthesia.

There are total seven waves, which represents different areas of auditory pathway.

- Wave I Eighth nerve
- Wave II Cochlear nucleus
- Wave III Superior olivary nucleus
- Wave IV Lateral lamniscus
- Wave V Inferior colliculus
- Wave VI Thalamus
- Wave VII Thalamic radiations

Developmental Changes

Waves I, III and V are better featured at birth.

Wave I stabilizes by 3 months and wave V by 1.5 years.

With age, amplitude of wave increases while threshold decreases.

The time difference between wave I and wave IV-V complex is dependent upon transmission through brainstem auditory pathway.

<i>Character of BERA</i>	<i>Site of disorder</i>	
	<i>Periphery</i>	<i>Brainstem</i>
Wave I (threshold)	Elevated	Normal
Wave I (latency)	Prolonged	Normal
Wave V (latency)	Prolonged	Prolonged
I-V Interval	Normal	Prolonged

Section 11

Early

Developmental

Stimulation

- 25. Early Stimulation in NICU
- 26. Early Stimulation after Discharge
- 27. Early Stimulation Protocol

Early Stimulation in NICU

By early ‘infant stimulation’ programs we mean early interventional therapy for babies at-risk for developmental delay and periodic developmental assessment, in motor development, cognitive functioning, language development or adaptive functioning.

WHY IS EARLY STIMULATION IMPORTANT IN TODAY’S WORLD?

1. All parents want their infants to develop to their maximum potential.
2. Nowadays advanced perinatal care have improved chances of survival of newborns who would otherwise have succumbed. These survivors are identified with problems later on. Often such problems are identified quite late, may be at school age, when only some rehabilitation measures can be taken which do not necessarily bring out the best in the child.
3. Parents are adapting small family norms and every child is precious and they want a high degree of quality in their child. Planned and highly individualistic intervention programs after a detailed developmental assessment is the answer to this.

AIMS OF EARLY STIMULATION

1. Stimulating the child through the normal developmental channels
2. Prevention of developmental delay
3. Prevention of asymmetries and abnormalities.
 - to prevent atrophy of muscles
 - to prevent fixity of joints
 - to prevent contractures of the joint
 - to decrease the tone of the muscle
 - to prevent tightening of tendons

4. Detection of transient abnormalities and minimization of persistent abnormalities.

IMPORTANCE OF EARLY STIMULATION

Early stimulation is important both for the growing brain and body. Adequate nutrition and the presence of both parents during the early years are also crucial to a child's well being. All these factors contribute towards a normal healthy adult. The stimulation the child receives depends on life at home and the family structure.

A newborn baby's life may appear to be nothing but a cycle of sleep and feedings. From this age itself, a baby's personality begins to evolve. Some babies are very lively, others are slow to react. But all need to be cuddled, spoken to gently and stimulated. Stimulation plays an important part in child development. Various easily available age appropriate toys are advised and the optimum time for stimulation is when the child is most active and playful. Stimulation should be given to normal babies as well.

Proponents of early interventional therapy are suggesting that multidisciplinary structured intervention by highly trained interveners should be provided for infants who are at risk for neuromotor disorders as soon as possible to minimize future handicaps and successfully rehabilitate the child. Early stimulation and early intervention can be applied remarkably to infants in order to arouse their actions and feelings ultimately giving them a normal experience of development.

Parents of newly diagnosed children with mental retardation often refuse to accept that their child is not "normal". This leads to a delay in instituting early therapy and often results in the child developing some set patterns, which are difficult to change. Therefore special schools prefer to start a program by age 3 or 4 and may not accept children at ages above 6 or 7. The need therefore is to approach institutions in your vicinity at the earliest.

Unlike a normal baby a brain damaged baby is an at risk baby requires more attention of the family members in an effort to prevent mental subnormality setting in, by anticipatory action.

These goals rest on the delivery of developmentally supportive individualized care geared to enhance the strengths of each infant and family. This alliance listens to the language of the infant's behavior and uses the dialogue between the infant, family and the professional caregiver to guide care.

Early intervention improves not only medical outcome but also neurodevelopment outcome by preventing active inhibition of the central

nervous system pathways due to inappropriate input, and supporting the use of modulating pathways during a highly sensitive period of brain development. Developmentally supportive care may be associated with improved cortical and specifically frontal lobe development from early on. This may begin to explain the positive lasting effects into school age that are beginning to be documented in preterm children who received developmental care.

EARLY INTERVENTION AND PARENTS

- Increasing the knowledge, skills and experience of parents by improving parental perceptions of their infant's abilities and by improving parenting skills.
- Parents can utilize the developmental care framework long after the child has been discharged from the neonatal intensive care unit.
- Parents need the skills to understand and interact with their small infant appropriately.
- Longer term positive effects have been seen on the ways that mothers may interact with their infants and on the infants cognitive development.
- Interventions require individualized care plans centred on the infant's behavioral organization, the mother-child interaction, and the parent's needs.
- Parent participation in decision-making and actual hands-on experience in caring for their child in preparation for their role as full-time parents is recommended as essential and is the key to successful developmental intervention.

WHO NEEDS EARLY STIMULATION

ALL BABIES

Need stimulation to grow physically and even more for cognitive and intellectual development by arousing their feelings.

ALL AT RISK BABIES

It is compulsory to provide early stimulation for at risk babies in a planned and systematic manner in order to arouse their feelings, through interaction with the mother and the environment and to prevent mental sub normality setting in-by anticipatory action.

At risk babies are babies who have had problems during the pre-natal, natal and postnatal period i.e. before, at or after birth and are at risk for developing some sort of developmental problems later on.

The problems may be pre-maturity (born < 37 weeks of gestation), low birth weight (<2.5 kg at birth), birth asphyxia (lack of oxygen at birth), septicemia (infection of the blood), seizure (fits) etc. An at risk baby needs more attention from the family members with the aim of trying to prevent mental sub normality setting in- by anticipatory action. For them it has to be started from the NICU (Neonatal Intensive Care Unit). There should not be over stimulation. Studies have shown that babies did better with less stimulation in NICU.

OVER STIMULATION

- Babies cannot comfortably handle different modes of stimulation all at once.
- For all babies their neural system has to be mature to receive the stimulus given to them. While giving stimulation it should be essential to note that the stimulation is not beyond their capacity. There are cues to watch for the baby might
 - Just close his eyes and try to go to sleep.
 - May start to stick out his tongue as an aversion response, then yawn
 - And finally, start to show agitation by his body movements; arching his back, squirming to get away, fussing, crying etc.
- Playing with one's baby in ways that both parent and child enjoy is the best way to stimulate his senses and thinking. How much the parent enjoys the activities shared with the baby is the best stimulation for the child. When the parent is emotionally involved in the play, and not feeling bored or dutiful or anxious, the infant will be more involved too.

PRECAUTIONS

THINGS TO BE REMEMBERED WHILE GIVING STIMULATION

- Monitored stimulation with an awareness of and willingness to decrease environmental hazards is necessary.
- The stimulation provided has to be developmentally appropriate.
- The smallest babies need the quietest of places that can be provided.
- The quality of stimulation given is more important than the quantity of time spent.
- Stimulation should be introduced gradually followed by a developmental assessment.

- The younger the infant, the more disorganized his neurological systems are and the less likely he will be able to process stimulation, whether positive or negative.

SAFETY MEASURES TO BE TAKEN WHILE GIVING STIMULATION

- Stimulation should be given only under strict supervision.
- Care should be taken to prevent the baby from swallowing any of the small things used during stimulation.
- Avoid giving paint coated toys, it may be toxic if swallowed.
- Avoid toys with sharp edges and those which are fragile.

NEWBORN STIMULATION IN NICU

Early stimulation should start as early as possible in the NICU with a special emphasis on incorporating both the parents and medical people. There should be programs designed to increase parental awareness of infants abilities and individuality patterns. Stimulation given in NICU should be neither over stimulating nor under stimulating.

Infant has limited, individual but improving capacity for input filtering and perceptual analysis and state control. In NICU the child experiences often painful procedure, handling, noises, lack of contingent responses, irregular, inconstant social contact, and unstable comforting mechanisms. Infants toleration of and need for different modalities of stimulation can be estimated sequentially and it should be individualized and changed over time.

MODIFICATIONS THAT CAN BE MADE IN NICU

- Individual lightening units can be dimmed and adjusted to reflect the cycles of the days (specially during night).
- Reduce unnecessary noises from the neonatal environment. Heartbeat sounds, mother's voice and music can be recorded and the tape played near the baby at a low volume.
- Gentle massage and soft bedding promote tactile stimulation.
- Try to promote bonding whenever possible through kangaroo method.
- Rocking and oscillating waterbeds can be introduced in order to stimulate the kinesthetic/vestibular senses.
- Passive exercises for the joints in order to prevent muscle spasm.
- Each individual has his own individual reactions and a multi-sensory combination all the above can be applied accordingly.

Early Stimulation after Discharge

THE WAITING GUEST

Bringing the baby home from hospital is a time that the mother, the family and friends have been waiting for. However, it is important to remember that all this attention and love can be overwhelming.

BABIES NEED PEACE AND QUIET

Babies may exhibit distress when they are being overwhelmed. It can be difficult to explain to those who wish to see the baby, after weeks and months in hospital, that the baby may become tired very quickly. However, it is important that the mother and the baby are given a chance to truly get to know each other.

BABIES NEED 'WALLS' AROUND THEM

After discharge from the nursery, babies may be fussy and difficult to settle. Full term babies in the womb spend a lot of time curled up in a ball, legs and arms tucked in. If one's child is agitated, one can put him on his tummy on one's shoulder, and help get his legs and arms tucked in, his hands to his mouth, and wrap him in a blanket.

UNDERSTAND HER 'CUES'

At home the mother should be able to recognize additional individual signs of stress or distress. Being able to recognize and respond appropriately to these cues will help the mother become closer to her baby. It will also be very useful should the baby need to go back into hospital, as she will then have this extra knowledge about caring for her baby.

NEWBORN STIMULATION AT HOME**KEEP IN MIND THAT**

- Newborn babies are surprisingly alert. When the tummy is full, the bottom is dry and the body rested, newborns are busy looking, listening, and learning about their new world.
- Babies are hard-wired to learn. If parents understand the wiring a little better, they can target early play to help their newborns learn and develop. Keep the play gentle and the playtime short — just a few minutes at a time is probably plenty.
- Subtle environments; pastel colours, a feather on a string spinning in the breeze, a fish tank to watch, curtains blowing, lying under a tree, a candle flame, these foster deep attentiveness, long curious staring and wondering, which is good for development.

The following are some ways to begin playing with a newborn. Remember though that it is easy to over stimulate a newborn.

VISION

- Vision is one of the most primitive senses at birth—newborns can only focus about 8 inches away, and their sight is two dimensional. Because vision develops so quickly and so dominates the human sensory experience, it soon becomes the major means through which children learn about the people and properties of their world. The following are some ideas to stimulate the baby's developing sense of vision.

BOLD PATTERNS WITH STRONG CONTRAST

- Newborns are attracted to the edges of patterns where light and dark meet.
- Babies tend to look at the edges of shapes, so a baby is likely to scan one's hairline rather than gaze into one's eyes.
- Start with simple shapes—squares, circles, and bold black and white face shapes. Paste these shapes by the changing table, or cut them out and make a "Nursery Novel," a little book made up of different patterns. The newborn's eyes examine the edges and his brain learns to process simple visual information.

MAKING FACES

- The most intriguing object for newborns is the mother's or father's face.
- Try to catch the baby's attention and make a face— one can stick out the tongue, make an 'O' with one's lips, or raise and lower one's eyebrows.

- Newborns can mimic expressions.
- Remember to vary the expression: new babies have very short attention spans.

MOVING OBJECTS

- Vision involves the complex process of tracking objects as they move through space.
- Lay the baby on the lap. Take a toy, small picture, or one's hand and slowly move it in an arc from your baby's left to right, and then back again. Newborns cannot track the object as it moves across their centre line—this will develop in the first few months.

HEARING

- At birth the sense of hearing is considerably more advanced than vision. Although it is more advanced, hearing develops gradually.

PLAYING MUSIC

- Music stimulates more than just the auditory brain centers and connects powerfully to the baby's emotions.
- Test how music affects the baby—play a lively, fast-paced song, then a slow, soothing song.
- Babies have an innate response to music, which can be very useful when trying to soothe an overtired, over stimulated, or colicky newborn.
- Classical music is particularly good for the baby's developing brain; it is closely linked with an improved ability to solve spatial problems. Playing classical strains to the newborn could help lay down important spatial reasoning pathways, as well as connections within the auditory system.

TALKING AND IMITATION

- Language development begins from the moment the baby first hears voices.
- Talk to the baby often — when changing him, feeding him, or walking with him. Listen carefully to his little noises and repeat them; one can have baby 'conversations' this way, each taking a turn.
- Read to the baby — look for books with rhythmic, rhyming language.
- Even tiny babies will listen attentively to the sing-song cadences of poems and nursery rhymes.

TOUCH.....

Every time a baby is touched or cuddled, it shapes his growing brain. Touch experience is essential not only for the development of touch sensitivity but for general cognitive development as well.

BABY MASSAGE

The purposive, non-repetitive contact with human hands on the baby's bare skin is a soothing way to stimulate the baby's sense of touch. Routine massaging the baby is essential for her optimum growth and development. Ideally it should be done by the mother, father or grand parents. The masseur should be relaxed and unhurried and won't be interrupted. Don't massage the baby when he is hungry or full of stomach.

SETTING

Mother sit relaxed on the floor with baby on a towel or rubber sheet. Newborns like massaging for about 2-5 minutes and children over 2 months of age will like even more time.

TECHNIQUE

Application of oil before massaging reduces friction. Gentle firm strokes can be used. Apply at least 12 strokes to each area. Do not kneed or squeeze. The stroke should not be too light or else they will cause a tickling sensation to the baby that may be discomforting.

- Make tiny circles on the face, then smooth the baby's forehead with both hands at the centre, gently press outside as if stroking the pages of a book. Make small circles around the baby's jaw, massaging around the baby's mouth may comfort him during teething.
- Rub the hands to make them warm and gently stroke the baby's chest as if stroking the pages of a book.
- Stroke each arm alternately from central outwards, open the palms and massage each finger separately.
- Massage the tummy from baby's right side to the left in a clockwise direction.
- Stroke and massage each leg and foot separately.
- Stroke the baby's back— first back and forth across, then in long, sweeping lines from shoulders to feet. Always keep one hand on the baby.
- Stroke the buttocks in a circular motion.
- Gentle passive exercises can be given in the joints of both hands and legs by bending and stretching. Make sure the baby is enjoying the stimulation. Reassure him if he cries or protests and restart again. Continue massaging according to his wish and end up with a kiss.

ROCKING, WALKING AND SWINGING

- Why is it that babies calm down when they are rocked or gently bounced? Closely related to the sense of touch, the baby's vestibular system tells the baby where his body is in space—if he is reclining, sitting upright or moving.
- Every time the baby is walked, rocked, or swung, the vestibular system is stimulated.
- Infants who are comforted through vestibular stimulation show greater visual alertness than babies comforted in other ways. It's during these periods of quiet alertness that babies do their best learning, when they can most effectively absorb information about the world around them.

Baby swings are a good way to stimulate the vestibular system. If the baby is in a sling or front carrier, the natural motion provides plenty of vestibular stimulation. Sometimes the motion will help a baby to sleep, but often the baby will become quiet and watchful. This is an excellent time to talk or sing to the baby.

TOUCH THERAPY—WHAT IS IT?

Touch therapy is purposive, repetitive, non-medical contact with human hands on an infant's bare skin administered with a view to stimulating nature and stimulating normal growth and development. It is recommended that mothers and fathers participate for best results. In its broadest sense it involves massage (tactile-kinesthetic stimulation), non-nutritive sucking and skin-to-skin contact in any form. It is an appealing, pleasurable, culturally acceptable easily taught and understood form of interventional stimulation to the preterm infant but can be administered to term infants equally effectively and there is no cost involved.

WHY TOUCH

Touch is the natural extension of stimulation as it is an extension of what the baby has experiences in utero. Nature intended development to occur in an environment filled with stimulation and sensations. Tactile kinesthetic stimulation is continuously provided in utero as the mother moves, walks, sits and bends, the amniotic fluid creates a whirlpool like milieu which as both stimulating and protective to the actively developing fetus. Since the fetal volume increases and amniotic fluid decreases as the pregnancy near term, the opportunities for touch and contact with the placenta, uterine surfaces and the fetus, own body becomes greater in the last part of the pregnancy.

This constant tactile— kinesthetic stimulation has been shown to be essential for the developing brain in terms of positive feedback messages.

TOUCH-EFFECT ON INFANTS

- Non-nutritive sucking for LBW babies are associated with better oxygenation during feeding.
- Improves weight gain—by increasing growth hormones or better utilization of nutrients due to better production of gut hormones.
- Effect on neurodevelopment.

Early Stimulation Protocol

Early stimulation can be applied remarkably to infants at-risk during infancy itself, in order to arouse their actions and feelings, ultimately giving them a normal experience of development through interaction with the mother and environment. Unlike a normal baby a brain damaged baby has acquired inability to send adequate signals to the mother and the people around, for them to respond normally and adequately. This then means that an at-risk baby requires more attention of the family members in an effort to prevent mental subnormality setting in, by anticipatory action.

THE 0-2 MONTHS PERIOD

Babies will usually put their both hands to mouth in order to organize. If your child isn't doing this, help her; gently to hold her hands together and then put them to mouth. This is calming and organizing, thereby creating neural pathways in her brain that will be the building blocks for future complex activities.

AUDITORY

- Make the child listen to different sounds such as squeeze toy, rattle, bell, music, high pitched and low pitched human sounds etc.
- Always humming in a soft low voice.

VISUAL

- Hang brightly colour clothes (red/orange/fluorescent), shining mobiles, colour balls; B & W striped clothes etc across the crib. Don't interchange them frequently.
- Put the baby in a well-ventilated room having good light.

TACTILE

- Frequently change child's position. Put the child on his sides, on his back, on his tummy etc.
- Put the baby in different surfaces like soft mattresses, form rubber mat, on soft clothes, on mother's lap etc.

VESTIBULO/KINESTHETIC

- Gently rock the child, avoid fast changes of position
- Avoid sudden jerky movements, always support his head.

ACTIVITIES

- Always try to maintain eye-to-eye contact while communicating with the child.
- Cuddle the baby closely, making it a joyous interaction with the mother and the baby.
- Talk and sing to baby when you bathe him, dress him, and when you feed or rock him.
- Encourage and help the baby to turn his head towards the source of sound and sights.

THE 2-4 MONTHS PERIOD**AUDITORY**

- Sound producing toys are suitable for this age. Noisy toys/squeaky rubber toys etc. can be given.
- Parents should spend more time with child, keep on talking with the child, pointing out the name of objects shown will help the child to use more words when he starts talking.

VISUAL

- Hang brightly colored objects/shiny mobiles about 12-15 inches above the crib, this will enable the child to watch it constantly and slowly starts to babble.
- Maintain eye contact while talking with the child
- Show brightly colored clothes when the child is awake.

TACTILE STIMULATION

- Give the child various things to bite and suck and paper to crumble.
- Give your child the experiences of soft, hard, rough, cold, warm etc.
- During daytime place the child on a foam rubber mat on the ground and allow him to move freely.

GENERAL STIMULATION

- Always hold the baby at shoulder
- Child should be carried straight at shoulder with hand supported, on both sides (right and left) after the attainment of head control, he can be carried crossed astride the hips on both sides.
- Place the child on his tummy, with both hands supported. Shake a sound making rattle in front of his head and gently lift the rattle just a little to encourage the child to lift the head and upper chest. Make sure that the baby is watching the rattle.
- Rub small toys or rings across the palm of the baby's hand to help him to grasp it. As he wraps his fingers around the toy, let him hold it. This will promote the child to grasp things.
- Place things just out of reach of baby's hands. Stimulate him to reach out and grasp it.
- When talking the baby crossed astride the hip some babies have the tendency to turn their head towards one side only. Play with the child or show colourful toys or make noises from the opposite side. This will promote the child to turn head towards the desired side.

THE 4-6 MONTHS PERIOD

- At this age children like imitation and they learn a lot from that. Stimulation programme at this age should be based in this. They need a variety of stimuli, and the parents pay attention to organize the environment in such a way that it is stimulating for the child. They love to see their own images at mirrors and will look at this for a long period. Expose the child to outside people, siblings etc.

AUDITORY STIMULATION

- Babies will turn their head towards the source of sound at this age. Shake a bell or a squeaky toy over his head. Then slowly shake it near to the side of his head. Encourage him to turn his head and find the sound. Repeat on the other side also.

GENERAL ACTIVITIES

- Place the child flat on his back on the ground over a soft blanket. Sit near to him/her, showing a colorful toy, slowly turn him/her by flexing the far away leg, and assist him to turn over to her tummy. Repeat it on both sides.
- Sit the baby on your lap and gently bounce your knees, by singing songs. This will promote child's ability to locate sounds almost he bounce himself.

- Encourage reaching by showing an attractive toy, just out of reach of child's hands. With this increased interest the infant moves his hands towards it.
- Strengthen the leg muscles: put your hands under child's feet and move her legs up and down as if she were pedalling a bicycle. Stimulate her to push on your hands with her feet.

THE 6-8 MONTHS PERIOD

Keep your child in a safe area near to your work place, so that you can have a close watch at her and can communicate with her frequently. A childproof room, if possible can be arranged at home where the child can move freely and explore. Let the child sleep on foam rubber mat on the ground during daytime.

GENERAL ACTIVITIES

- Start calling the child by his name. He should be spoken to quite often. Banging toys such as drums, pans or pots can be given at this age.
- The child can be carried crossed astride at this age.
- Give the baby pieces of paper to tear. The paper can be made attractive by changing colors and textures. Talk with baby about what she is doing, how it feels and how it looks.
- As long as possible make the child sit; a walker can be used and the child can be made to sit comfortably.
- Lay the baby back on the floor over a mat. Show him attractive toys on one side. Encourage him to roll over on his tummy. Then stimulate him to roll on his back by gently pushing back the child's shoulder by folding the hand under his chest towards which he is turned and showing a colorful sound producing toy from front to back.
- Make the child on his tummy and put a roll under his chest. By showing a colorful toy above his head, stimulate him lift his head and rise up on his hands.
- Child lying flat on his back. Stabilize the legs by pressing the knees. Raise the child's right shoulder (directing the movement over to the left). Let him lean on his left shoulder, then on his elbow, then his hand, till finally he is able to sit. To make him lie down again, lean him on his hand, elbow and left shoulder. Repeat the same movement on other side also.
- Help the child to sit on the ground by giving support on his pelvis.

- Child can be made to sit on small chairs with hand rest on the sides so he can sit comfortably.
- Put the child in all fours over a roll. Gently move the roll from front to back, making the child lean alternating on his knees and hands. After a very short time, he will make active use of his hands and knees. This will stimulate him to rise on his knees.

THE 8-10 MONTHS PERIOD

Provide safe and hygienic objects for the child to play and handle. Family members should participate in his play and he enjoys such companies. Play peek-a-boo with the child.

ACTIVITIES

- Encourage the child to stand on by hold on furniture
- Put him in all fours on the ground. Bring the child's buttocks on to his heels with the upper part of his body erect. Show him a toy at shoulder level so that he turns from one side to the other. This will allow the trunk independent of the legs and also stimulate him to rise on his knees erect.
- Mother sit on the chair, make the child stand on mother's knees and bounce her legs gently up and down. Stimulate the child to support as much of her weight as she can help to strengthen her leg muscles.
- Encourage the child to clap hands by demonstrating while listening to music. Give him some banging toys and help him to bang it so as to produce sound.
- Give him a small container and encourage him to drop small thing into it.
- Encourage the child to produce monosyllables.
- Show him/her picture books of birds/flowers/animals and assist to turn the pages of books. The pages of the books should be harder enough for the baby to turn it.

THE 10-12 MONTHS PERIOD

At this age the child understand instructions. Acts of daily life can be made stimulating for the child by pointing out things with the aid of simple but exact words.

ACTIVITIES

- Allow the child to play with other children.
- Balls with different sizes, dolls, puppets, push and pull toys, rocking toys, small containers, pegboards, etc. can be used.

- Allow the child to move freely on the ground.
- Naming the body parts can be done while bathing the baby.
- Child can be carried out for a walk and different animals and birds can be shown on the way.
- Lightweight toys, colour balls, squeaky toys, mirror etc. can be given.
- Do simple actions in front of the child and encourage copying the actions like clapping hands, tilting head throwing ball, waving bye-bye.
- Encourage the child to crawl over and stimulate him to crawl over moving things by pulling a toy.
- Stimulate the child to stand up by keeping his favourite toy on a low stool. Encourage him to pull to stand by holding on the stool.
- Give toys with large holes to poke and to feel with fingers. Care should be taken to avoid dangers on fingers.

THE 12-15 MONTHS PERIOD

Provide opportunity for the toddler to explore and understand the world surrounding him. In this stage of exploration basic concepts such as 'in' and 'out' will be learned.

- Give baby picture books that have heavy, thick cardboard pages. As you look at each picture, talk about what you see and then let the baby turn the pages. You may have to help him turn the pages one at a time.
- The baby can be stimulated to see, hear and smell things.
- Dressing time can be made fun by pointing to the body parts, counting to her. Numbers can be emphasized while stimulating child to stack blocks, putting things into containers etc.
- Look out of the window. If the window is low enough, help the baby pull up to stand so that he/she can see. Talk about what the weather is like.
- Make the child sit in front of a mirror so that she can see herself. Sit behind her and start to sing about her eyes, nose, mouth and hair. Pat your nose and see if baby will copy you. If she doesn't help her to move her hand so that she pats her nose while you sing. Sing the song a few more times and change the body part each time. This stimulates child to copy a few simple actions and also to know body parts.
- While the baby stands holding on to a support, encourage him to stoop or bend over by dropping a noise-making toy on to the floor beside him and pick it up.

- Encourage the baby to stand up holding to a walker (three wheeled) and to walk by calling him in front.
- While the baby is watching, hide a favourite small toy under a cloth. Encourage the baby to grab the cloth, pull it away, and find the hidden toy.
- Cut and mount toy pictures from picture book that looks similar to child's own toys.
- Give the baby two or three blocks of different sizes to stack and knock down. Hand him the blocks one at a time and help him to pile them on top of each other. Make a game out of playfully knocking them down and laughing as you build them up again.
- Give the baby a fat crayon and some paper.
- Encourage the child to scribble by drawing a few lines while she is watching. Assist her scribble on her own. If she does not, gently hold hand and help her scribble.
- Encourage the baby to place things into a wide mouth jar and then to take things out of a container.
- Finally stimulate the child to gradually achieve independence in all areas. Let him make his own decisions and take his own time.

Section 12

Developmental Therapy

28. Motor Stimulation in Early Infancy

29. Vision and Hearing Stimulation in Early Infancy

Motor Stimulation in Early Infancy

Various physical therapy techniques have been used all over the world for children with motor delay with encouraging results but not supported by randomised controlled trials. But what has been clinically observed is that child's potential to achieve motor milestones, even if late by months or years is prevented by late onset of therapy and stimulation.

INTERVENTION FOR HEAD CONTROL

While giving intervention for head control delay, in prone position, concentrate on the following abilities.

- *Raise the head*
 - *Hold it for sometimes*
 - *Turn the head to both sides.*
1. Place the child in prone across your lap. To encourage the child to raise his head, attract his attention with brightly colored objects that make strange or pretty sounds (At first use toys in the centre and progress to each side of the child and move them slowly from center to side and from side to side)
 2. If he does not lift his head, gently stroke downwards over the neck muscles.
 3. Bring his shoulders back and inwards towards the spine (retraction of the shoulder girdle). This provokes him to raise head.
 4. The child flat on his stomach, head and shoulders reaching out over the edge of the table. With one hand, hold the child's buttocks, with other hand, support him under his forearms. Gradually, remove the support from under his arms.
 5. If the child turns his head to one side only, do weight bearing exercises for the upper limb on the other side. Always approach the child from that side towards which the baby does not turn.

6. Place the child in supine position. Encourage the child to lift and hold his head by pulling him to sitting position, holding under the axilla and supporting the neck only if needed. Gradually, bring him to sitting position and then slowly put him back to lying position.
7. Place the child over a soft roller. Gently tilt the roller to and fro.
8. Encourage the child to hold his head steady by carrying him in an upright position (supporting the head only as needed).
9. Make the child sit over his mother's lap. Mother tilts her leg up and down so that the child tries to balance his head.
10. If the baby makes almost no efforts to lift or hold his head, when you feed him, instead of putting the nipple or food into his mouth, barely, touch his lips with it and make him come forward to get it.
11. Place the child over a bed with 4-inch thickness with hand supported on the floor.
12. The child must be made to lie on his stomach and is guided on his elbows (a roll can be used if necessary). Encourage the child to lift and hold his head by showing a colorful toy. The head holding can then be maintained as long as the child enjoys and then gradually, the child is stimulated to rotate the head laterally by moving the toy.
13. Encourage the child to lift and hold head by pulling him to sitting position in a playful manner and then gradually, putting him back to lying position.
14. Hold the child at a distance from our body by placing one hand under his knee and other on the chest. Stand near to a mirror and encourage him to raise his head and shoulder.
15. Hold the baby crossed astride, give support to the neck if needed.
16. Weight bearing on forearms will also help the child's head control.

Use visual and auditory stimuli in these positions. Check that the child's forearms are well away from the body, with elbows at right angles to the body (Place a roll of towels between his body and upper arms) and if possible, hands open.

INTERVENTION TO PROMOTE ROLLING

If the child is very stiff, first help to relax him by swinging his legs back and forth

1. Attracts the child's attention by holding a rattle or toy in front of him. Then move the toy to one side, so the child turns her head and shoulders to follow it. Encourage him to reach sideways for the toy.

2. Bring one of his arms over to the opposite side with palm of his hand facing forward his face; or offer him a toy on the opposite side; this may lead to roll over.
3. Place the child on his back on a blanket. Hold each end of the blanket, (two adult may be needed) and suspend the child in the blanket just off the ground. Tip the child gently from side to side, waiting for him to complete his roll over. Do not do this with a child arches backwards.
4. Child in supine on a soft rubber mattress or inflatable bed. Press down on one side of his body, so that he tips over towards you and rolls.
5. Make an incline with pile of mattresses or sponge rubber and left gravity help the child roll downhill on his own.
6. Child lying on his back. Bend one hip and knee well over to the opposite side and wait for him to complete the roll over. Stretch the child's underneath arm out and upwards, if it gets 'caught'. Praise him each time he makes an effort.
7. Child lying on his back. Bend one hip and knee well over to opposite side, while holding his upper shoulder back. Release his shoulder for him to complete the roll. This treats the 'rolling in one piece' as in the neck righting reaction.

CREEPING

If the child can lift her head well when lying on his stomach, encourage her to begin creeping.

1. Put a toy or food the child likes just out of reach and encourage the child to move towards it.
2. If the child cannot bring her leg forward to creep, help her by lifting the hip.

INTERVENTION TO PROMOTE CRAWLING

1. Place the child on hands and knees over or your arms and when possible let him balance on his own. Encourage the child to balance with one limb off the ground using toys.
2. Suspend the child in a blanket. Hold each end of the blanket and tip the child in it so that his weight is taken more on one side releasing the other side for a step forward.
3. Child in prone position, bend the child's one leg and place it under his stomach. Raise the pelvis on the opposite side. The child begins to bear weight on the bent knee and moves the other knee forwards. Repeat this on other side also.

4. Child flat on his stomach. Bend one leg brings it forward and move the opposite side upper arms forwards. Repeat on the other side also.
5. Once the child have started crawling, encourage him to crawl on all surfaces.

INTERVENTION TO PROMOTE SITTING

1. Make the child sit leaning over one hand with his elbow straight. Stabilize his elbow and hand by holding firmly over his elbow and wrist (hands should remain open). Gently tip the child to this side so that his body weight is taken through his elbow and wrist. Hold it for about 10 seconds and release. Repeat the same over the other side also.
2. Make the child sit while stabilizing his pelvis if needed
3. Make the child sit across your knee. Raise the knees up and down alternatively, so he has to balance.
4. Make the child sit. Encourage the child to twist and reach side wards for toys.
5. Make the child sit. Just tilt the child forward, backward and sideways so that he begins to catch himself.
6. Once the child had attained sitting balance, make him sit on a tilting board.
7. Place the child on hands and knees over rolls or your arms. Encourage the child to maintain this position for sometime. Then slowly guide him to kneel sitting and then to side sitting position.
8. Mother sit with her legs straight and back supported against a wall.(long sitting). Place the child prone across her lap (hands on one side and legs on the other side). With one hand hold the child's both knee and help him to attain quadriped position. Repeat this by placing the child on the other side also.
9. Child lying on his back. Encourage him to attain sitting position by gently pulling on of his hand diagonally across the opposite side. Child comes to sitting bearing weight on the other hand. While doing this if the child's knees flex excessively, keep them straight by pressing over the knees with one hand.
10. Encourage the child to sit by putting him in an armchair in a sitting position supporting him with pillows as and when possible. This position can also be used during feeding.
11. While playing and talking with the child, encourage the child to sit with a wide base supported at the pelvis. If necessary help the child to maintain this erect sitting position by showing a colorful toy. Gradually

he can be stimulated to turn to either side by moving the toy and also to reach out.

12. During play child can be encouraged in side sitting position on both sides by supporting himself on the hand to the side, which he is sitting. For example, if right side then right hand can be used as the support.
13. Guide the child to support on his hands and knees (four point kneeling/ quadruped positions) during play. A roll or pillow can be used if necessary. Help the child to maintain this position by encouraging him through play. If needed minimal support can also be given. Then slowly guide him to sitting on one of his sides, supporting on that particular hand. Help the child to maintain this position for a while. Then guide him again on to his hands and knees and then gradually to side sitting on the other side.
14. Baby walker can also be used to stimulate and improve sitting. (under supervision).

INTERVENTION TO PROMOTE STANDING

While giving therapy for standing, note

- a. Bears weight equally over both legs
- b. Deformities are corrected
- c. Gradually withdraw support and encourage independent standing
- d. Encourage walking by shifting weight from one leg to the other.
 1. Guide the child on to his both knees (upright kneeling) during play time. Finally support him at the pelvis, if necessary even give support to the upper part of his body. Gradually, the support can be withdrawn and the child can be made to support himself by holding on to a low stool. This position can be maintained by directing the child's attention to any play activity.
 2. From the lying on the back (supine position), stimulate the child to pull to sit and gradually to the standing position during play time.
 3. First guide the child on to his knees supporting on a low stool with both hands, while directing his attention to a colorful toy through play. Slowly help him to raise one of his legs so as to stand on one foot and the other knee (Half-standing position.) Help the child to maintain this position while playing and talking with him. This position can be repeated on other side also. Meanwhile depending on the child's ability stimulate him to pull to standing position by himself, supporting on the stool.
 4. Make the child stand leaning against a wall. Give support on knees if needed.

5. Make the child stand with support on both hands and then to one hand.
6. Place the child on kneel standing holding to a support. Gradually bring one of his feet forward and place it in front, thus bring him to half kneeling position. Do the same on the other side also.
7. Make the child kneeling holding on to a support. Encourage the child to ride up to standing position, holding on to the support. If needed, help him by supporting his pelvis, while he attempts to stand.
8. Child stands first with and then without support. Just push him forwards, backwards and laterally. Encourage him to catch himself.
9. Help him too balance on an inclined surface.
10. Encourage him to stand on one leg with support on both hands.
11. Gradually, withdraw the support.
12. Help him to walk with support on both hands.
13. Encourage him to walk on a parallel bar.

INTERVENTIONS FOR DEVELOPMENT OF HAND FUNCTION

HAND REGARD AND BRINGING HANDS TO MIDLINE

Place the child in a half-lying or supported sitting position with arms held forward. The child should be made aware of his hands by your talk, shining a torch on them, putting sticky things like a jam or honey or playing with his figures.

OPENING OF HAND

1. Stroke the outer edge of hand from little finger to wrist.
2. Press the heel of his hand on a firm surface while keeping his shoulder and elbow straight.
3. Open hands when the child is leaning on hands while in prone, sitting or standing positions. Pull the thumb or fingers out from the base and not from there.
4. Once the hands are open, help the child to rub his palms together, touch his face and body and later clasp and unclasp hands.

HAND GRASP

1. Place an object in his hand, and bend his fingers around it. Be sure the thumb is opposite the figures. Gradually, twist the object from side to side and let go off hand. The object should be of a size that fit into the whole palm of his hand. Avoid toys that can be squeezed. Use objects of different shapes and textures (wooden, metal and plastic

objects, sand, dough, clay, etc).Name the textures for him as he feels it.

2. Encourage the child to reach and grasp an object that just touches his fingertips. First touch the back of his hand and then place it below the fingertips.
3. Hang interesting toys, bells and rattles around large hands grips, bars, handlebars of a cycle, etc.

PINCER GRASP

Begin with large objects. Then progress to smaller ones. Thumb and all finger tips are used first before thumb and index finger are used.

1. Use child's index finger to press in to sand. Later make lines and scribbles in sand.
2. Put paint on the child's fingertips and encourage him to make dots and scribble.
3. Encourage the child to pick up small objects like buttons or pebbles and place them in a container.
4. Make the child hold thick pencils or chalk for making marks on a paper.
5. Encourage the child to hold a small cup handle for drinking.
6. Use toys, which have buttons and knobs to press and turn.
7. Allow the child to attempt the activities on his own. If he cannot manage to isolate his index finger, hold his little, ring and middle finger flexed for him until he can do this alone.

TOYS TO ENCOURAGE STIMULATION

- In the first few years babies learn to use his hands and develop eye-hand co-ordination by simply watching and moving his own hands and fingers. Good and age-appropriate toys will help practice and perfect these newly acquired skills.
- When you are making or buying toys to encourage your child to learn things, follow the BBC code, i.e. big, bright and colorful.
- Big toys are easier for young babies to see. Older children can use magnification of small objects.
- Bright means presenting toys and play materials in the best possible light,

Colorful means choosing toys with good strong contrasting colours and making sure they do not merge into the background. Putting a nappy or a cot sheet over a heavily patterned carpet may be useful. Some children find shiny surfaces attractive, others prefer mat colors. Children usually

show by their reaction, which they prefer and will not be bothered with a toy if they do not find it interesting.

POINTS TO REMEMBER DURING THE SELECTION OF TOYS

- Toy should be age appropriate
- Toys should be safe – no sharp points and cutting edges
- Colored toys—the paint should be non-toxic
- Components of the toy should not be so small that the baby is able to push them into the mouth, nose and ears
- The child's interest, needs and abilities should be considered
- Washable and sturdy enough to withstand rough handling.

Vision and Hearing Stimulation in Early Infancy

The term ‘early intervention’ encompasses a wide variety of medical, educational, and psychological treatments for an at-risk baby or one with neurodevelopment abnormalities as well as socioeconomically disadvantaged children. The parents need to provide stimulation for their children that would otherwise have been missed, by giving emotional support, sensory input and by play methods. Encourage the mothers to show love, to handle and talk to their children more, to help the children to acquire independence all of which help to improve language and communication later on.

VISION

WHY IS VISION IMPORTANT?

There are some assumptions that are basic to an understanding of how the visual system contributes to early development and that must be understood if a foundation for stimulation is to be established.

Vision is the Primary Data—Gathering System of the Human Organism

Of all the senses, vision provides the most information to the brain. It is both a near and distance sense, and can integrate the information it gathers. Only vision can perceive shape, size, color, distance and spatial location— all in one glance. The other senses together cannot provide equal information to the brain.

Vision is the Feedback System for all Other Developing Systems in the Young Child

An infant’s early development depends on vision, since all the other systems require visual feedback for practice and refinement. When the visual system is impaired or dysfunctional, the other systems do not have a monitoring tool to assure their smooth and timely development.

We Cannot Wait Until a Loss of Vision has Caused a Development Delay

Early Stimulation may be based on a deficit model. The time to intervene is before delay occurs; the goal is to prevent the delay, if possible;

Vision Happens in the Brain Not in the Eyes

It takes both eyes and brain for vision to occur. When either system is dysfunctional or defective, the visual system becomes impaired and cannot provide adequate visual information to the infant. The two systems are interrelated, interconnected and interactive. This basic concept is essential to early stimulation.

Do not Conserve Vision by Not Using It

Vision must be used to be effective and we cannot “save” vision. Moreover, it must be practiced to become most efficient.

EARLY DETECTION OF VISUAL ABNORMALITIES IN YOUNG CHILDREN

- Check for eye fixation—note whether the baby is watching when one is looking at his face and when one talks or plays with him.
- Hold the baby in such a way that the baby faces the window, and then slowly turn him towards the darkest side of the room. Observe whether the baby is turning his head towards the window.
- Observe whether the baby’s eyeball wanders from one corner of the eye to the other while awake (after 6 weeks).
- Check for cataract (a white spot seen in the pupil).
- Note whether the baby has a strong family history of visual problems.
- Be cautious if a squint persists even after 6 months of age.
- Holding objects very close to the face while examining or looking at something is a warning sign.

VISUAL STIMULATION—WHY EARLY?

- Visual impairment affects the development of the brain. If vision is not dominant as the avenue of information, it does not get its normal representation in the brain cortex.
- Visual stimulation seems to be more useful during infancy and very early childhood.
- It may be more helpful to children with certain cases of blindness than for other children.
- Pairing the visual stimulation with other experiences is more useful. Incorporation of all the senses (touch, hearing, and smell) into visual experiences helps the child make better sense of visual images.

- The ultimate goal of visual stimulation is to motivate the child to make the best use of the vision he has and to identify those situations when the use of another sense would be more efficient.

By early stimulation of vision it means use of strong visual stimuli to make an infant or child aware of vision, since these children usually have very limited visual capabilities and no visually guided functions. Tactile and visual stimuli can be used simultaneously. If the infant gets strong visual input and at the same time tactile information is used to explore the surface qualities and form of the object, there is hope that the two different types of information can be integrated.

Visual stimulation is an integral part of play and therapy situations. The content of the stimulation is the same as for normally sighted children but the visual information is clearer with a good contrast so that it can be used for eye-hand coordination, eye-foot coordination, and development of spatial relationships. In these training situations the visually impaired infants often use tactile information for quite some time to explore the surface qualities and form of an object. Picture perception is one of the most difficult concepts to develop in a visually impaired child.

In some visually guided motor functions the child may not reach the usual milestones so these motor functions need special training. Visual stimulation and training are integrated in the child's early stimulation program.

STIMULATION TECHNIQUES FOR VISUALLY IMPAIRED CHILDREN

All children need to be encouraged to use their eyes and to think about what they see. For those who find it difficult to concentrate, or those who appear to take little interest in their environment, a special effort must be made to provide them with things they will really want to look at, as well as interesting things they need time to explore.

Many a child has natural curiosity. When he is shown a pretty thing which may be precious or old, has been taken to visit an interesting place, or simply has his attention drawn to a spectacular sunset, he may be building associations and memories which might influence his life more than can perhaps be imagined.

Techniques

Arrange a room that is bright, stimulating, and colorful—full of toys and materials that are both interesting and attention grabbing. Some decorative items for a room are helpful for increasing visual awareness.

Intervention to Promote Eye Focus and Following

Place the child supine. Help him to keep his head in the midline. Hold both his shoulders forward. Place shiny, colorful, noisemaking toys or

a torch light close to the child's eye. The mother can attract his attention by face-to-face singing or talking

Senses as Learning Tool

- In a visually impaired child other senses are potentially at a maximum (touch, taste, smell, and hearing). So, provision of an environment where the child can explore things and utilize his existing good senses is very important.
- Provide opportunities for the child to grasp information by touching with his hands and skin, hear a lot using his ears, to smell using his nose and to taste with his tongue.
- A blind child needs to be taught a lot. A child with partial visual impairment can perceive a whole lot of unclear images, but in a child with complete visual impairment the stimulation is very difficult.
- The child learns about his world through talking and touching mainly. 'What is the object made of? What is it for? How is it? What happens if?'—he learns through hearing information related to it.
- Shake the baby's arms and legs and keep repeating the name of the parts you touch.
- Music boxes or wind up toys coming toward the child from a distance may help perk-up attention to an approaching object. Balls with electronic sounds that do not roll very far are available. A ball with a sound that continues to play is very helpful for seek-and-find.
- A toy that rolls away should have a sound so the child can remember where it went.
- Toys with music and sounds activated by pushing a button are useful.
- Allow the baby finger play with dough.
- Place the baby on different surfaces, hold him frequently, lay him on the ground, over a mat—all these help.
- Hang small bells around the crib.
- Textured balls, large push and bump toys like cars, trucks and walking push toys can be made use of.
- All young children with some vision enjoy mirror play, but watch out for glare. Use them in diffused lighting.
- Provide him with opportunities for hearing other people's speech also. Put the baby on his mother's lap while she is communicating with others.
- Spread sound making toys in the sound proof room where he is playing?
- Provide the child with the sensation of different textures. Make the child walk barefoot on grass, on gravel, on sand, on the road, etc.

ENCOURAGING EXPLORATION

- Gently guide the baby's hand towards the sound of a toy and keep decreasing the amount of help offered.
- Use toys that light up or objects with reflective surfaces if light perception is present.
- Change the position of the baby frequently, put him on his back, turn him onto his sides, on his tummy, etc.
- Don't put the baby always in the crib.
- Hung strings of Christmas lights in baby's room to encourage visual attention.
- Hang noisy toys over the crib and guide his hands towards it. Assist him to reach for and then grasp it.
- Ask the mother to keep the child at her side and to keep on talking to him as she does her work.
- Attach different textures on the lower portion of walls to encourage the child to explore the walls.
- Make the child sit on a rocking horse or rocking chair.

BODY IMAGE

- Draw the child's attention to different body parts. Place a small pillow over his legs and encourage him to knock it off.
- Place an over sized plastic ring on the baby's wrist or ankles and encourage him to remove the ring.
- Guide the baby's hand to each part of the body as related nursery rhymes are sung.

OBJECT PERMANENCE

- Help the baby hold on to the spoon while feeding, this will help him to learn to hold it and feed by himself later.
- Guide the baby's hand to a hidden toy or tap the toy on the floor to give him a clue.
- Peek-a-boo games, pulling a scarf off a hidden musical toy, etc. can be made fun.
- Encourage independent mobility at home.

HEARING**EARLY STIMULATION FOR HEARING IMPAIRMENT**

Without adequate sound stimulation in infancy and early childhood, speech and language development will be compromised. Later treatment may never fully compensate for this early deprivation. The critical period for language and speech development is the first 2 years of life.

TECHNIQUES

- Encourage him to produce new sounds by imitation or by continuous repetition of words
- Maintain face-to-face conversation while talking to him.
- The child could sing through a mouthful of cereal—‘mum-mum-mum’ and think that he is at least saying Mom. The mother could reward him with a smile and cuddles
- Make a variety of sounds in the environment—patting plastic chairs, banging a wooden table, banging the rattle across the wall, banging a cup and spoon together. The child will gradually begin to associate certain sounds with a sequence of events.
- The ding-dong of the doorbell, the sound of the bath water running, noises of family pets—such sounds will contribute to the baby’s idea of home and security
- Provide plenty of noisemakers for the baby to shake, bang, kick, hit or drop
- Have a code sound for a certain activity—e.g.using a little rattle to announce mealtime, or splashing a hand in the water before bathing.
- Speak to the baby as much as possible. All young babies need to listen to speech for many months before they can sort out and imitate the sound of words. With a hearing-impaired child this listening stage often lasts for a long time and because the child does not appear to respond, it can be very easy to forget to talk to him.
- Make the child listen to record players, the radio and the TV, etc.
- Making sound pictures—first think of a situation and then create the appropriate noises, which will conjure up that image. An easy one is ‘a walk down the street’. This includes traffic noises, scraps of conversations, footsteps of different people, a police siren, sounds from different shops, supermarkets, etc.

GENERAL ACTIVITIES

- Do not overprotect the child. Treat him like a normal child.
- The anticipatory movements should be accurate. For example, call the baby to lift his head while holding his shoulders and axilla.
- Encourage moments of experimentation in every day situations, which create sounds and sensations.

Section 13

Prenatal Strategies

- 30. Prenatal Risk Factors**
- 31. Multiple Fetal Pregnancies**
- 32. Assisted Reproductive Technique—Is It Safe?**

Prenatal Risk Factors

During the last two decades, the improved neonatal care in our country has resulted in increasing numbers of high risk neonates surviving and being discharged from neonatal intensive care units (NICU). However, the quantum of neurodevelopmental disability (NDD) noted at follow-up has not decreased; reasons for this vary from poor implementation of potentially best practices (PBPs) in neonatal care to insufficient attention to a crucial period of brain development—prenatal period.

Intra-partum and neonatal events are just a **continuation of the antenatal life** of the fetus. Several antenatal factors influence the well being of the baby and the neurodevelopmental outcome is dependent on these factors that operate during the prenatal period.

RISK FACTORS

1. Prematurity
2. Growth restriction
3. Maternal nutrition
4. Intrauterine infections
5. Maternal diseases
6. Maternal factors
7. Teratogens.

PREMATURITY

The risk of NDD in newborns is inversely proportional to their gestational age. The gestation represents a composite of all the morbidities likely to occur after birth. Babies born before 28 weeks gestation have been observed to have some degree of neurodevelopmental compromise even

when the NICU stay has been “uneventful”.² Despite description of several antenatal strategies, only one strategy has proven benefit.

ANTENATAL STEROIDS (ANS)

A single course of antenatal glucocorticoids has been shown in several elegant randomized controlled studies and meta-analysis to decrease the incidence of mortality, respiratory distress syndrome, intraventricular hemorrhage and necrotizing enterocolitis.^{11,12} It is now the standard of care and is routinely administered in suspected preterm delivery prior to 34 weeks gestation with few exceptions. Several randomized controlled studies have studied repeated weekly courses of antenatal steroids. Adverse long term neurodevelopmental outcome are feared in babies who received repeated courses.^{13,19} Decrease in head circumference, increased rate of cerebral palsy (CP), cognitive and motor deficits, delayed psychomotor development and behavioral problems are some of the adverse outcomes that were noted. Hence, the current recommendation is a single course of antenatal steroids in women at risk for preterm delivery. Repeated or multiple courses of steroids is recommended to be used only in randomized controlled studies settings. Betamethasone is preferred over dexamethasone as dexamethasone was found to be associated with increased incidence of periventricular leukomalacia.

GROWTH RESTRICTION—BABIES WHO ARE SMALL FOR GESTATION, EITHER TERM OR PRETERM

In India nearly two thirds of the newborn babies are small for gestation (SGA). A study done by Bhargawa et al revealed that among the 150 LBW infants followed up, 7.0% had developmental delay, 4% had CP and 10% had transitory dystonia.²² Many more of these babies scored much less than the controls on the developmental scales.

In many babies born SGA, growth *in utero* is impaired and such babies are higher risk of perinatal mortality and morbidity. Many others are constitutionally small and not short of their best potentials, and at no increased risk of perinatal problems.

GROWTH RESTRICTION AND NEURODEVELOPMENT—WHAT HAPPENS?²³⁻²⁵

Some of the IUGR babies have increased risk of **minor motor dysfunction (not CP)**^{30, 31} impaired speech and language development but **most have only behavioral problems and attention deficit disorders** in their later years.

The key factor is the malfunction of the placental unit resulting in inadequate supply of nutrients and oxygen. This malfunction could be due to **maternal factors** like systemic illness, teratogens or **placental circulation** being affected as in pregnancy induced hypertension, or an abnormal placental unit. Babies with bad dopplers are at increased risk of IVH.²⁵

Schreuder and colleagues³² reported no significant differences between the children who had forward flow in the umbilical artery. Those with absent EDF, those who had **reversed EDF did worse** on tests of general conceptual ability and spatial/pictorial ability. There were more children with **severe visual deficits** in the groups with reversed EDF than in the absent EDF group. Furthermore, children with reversed EDF scored higher on assessments of **hyperactivity and peer problems** than the group with forward flow. However, 50% of the children from the reversed EDF group were doing well in normal school without any additional help.

Brain—sparing hemodynamics (fetal hemodynamic adaptation—the U/C ratio, comparing umbilical artery and Middle Cerebral Artery (MCA) Pulsatility Indices.^{33,34}

At 5 years of age, 54% of children with a raised umbilical/cerebral or U/C ratio were functioning below the expected level, compared to 20% of children born with normal U/C ratios. Children born after raised U/C ratios had a 9-point lower IQ score at 5 years of age compared to those who had normal U/C ratios. ‘Brain-sparing’ may be protective against gross neurological abnormalities in early childhood, but these adaptations may **predispose the infant to later cognitive problems.**^{33,34}

IDENTIFYING PREGNANCIES AT RISK OF IUGR

A combination of maternal risk factors and screening tools are use. The purposes of early detection of IUGR are two

- **Interventions to improve fetal circulation, e.g aspirin if detected very early**
- **Timing of delivery.**

Maternal History

Previous pregnancy IUGR, advanced maternal age, maternal medical illnesses—SLE, bowel, renal, cardiac, obstetric—PIH, GDM, maternal habits—smoking, alcohol, maternal nutrition, socioeconomic status, etc.

Biochemical Screening

The OR for delivering an SGA infant for women with a low PAPP-A level at 8-14 weeks gestation was 2.8 (with 95% CI 2-4) and when levels

of alpha fetoprotein (AFP) were also elevated at 15 -21 weeks in the same pregnancy, the OR for SGA rose to 8.5. (95% CI 3.6-20).²⁹

Ultrasound Screen

Uterine artery Doppler done at 23 weeks identifies those pregnancies at high risk of adverse obstetric outcomes, with a high positive predictive value for early delivery.

DO BABIES BENEFIT BY EARLY DELIVERY IF IUGR IS SEVERE?

Babies may have to be delivered preterm if the *in utero* growth restriction is very severe. Studies have shown that babies should not be delivered before 26 weeks gestation and estimated fetal weight of 600 grams for IUGR. Best predictors of intact outcome were gestation > 29 weeks and weight > 800 grams.

MATERNAL NUTRITION AND BRAIN DEVELOPMENT

Many nutrient deficiencies, particularly macronutrients, can have profound effects on the neuroanatomy, neurochemistry, and neurophysiology of the developing brain. Affected brain structures include neurons, progenitor cells, and supporting cells such as oligodendrocytes, astrocytes, and microglia. Depending on the timing and duration of restriction, neuronal division, growth, and complexity can be affected, with attendant deficits in neuronal number, size, dendritic arbors, and synapses. Earlier restriction (prior to 24 weeks post-conception) is more likely to affect neuronal number; later fetal and postnatal restriction tends to affect size and complexity.

The **effect of malnutrition on the supporting cells of the central nervous system** should not be underestimated. Oligodendrocytes are glial cells that produce myelin and depend on macronutrient substrate for their own energy metabolism and for fatty acids to be incorporated into myelin. Astrocytes serve multiple functions, including nutrient delivery. Microglia is a macrophage derived cell that serves an important role in neuronal migration prior to 24 weeks post-conception. Therefore, restriction of macronutrients can result in **hypomyelination**, further reductions in nutrient delivery, and **migration abnormalities** during early brain development. These alterations subsequently could cause **behavioral abnormalities characterized by reduced speed of processing, reduced synaptic efficacy, and potentially a predisposition to later developmental psychopathologies** (e.g. schizophrenia, depression, or autism).

Neurochemical effects of protein-energy malnutrition include altered **synthesis of neurotransmitters**, their postsynaptic receptors, and their pre-synaptic reuptake transporters. Protein-energy malnutrition could affect neurophysiology, defined as the ability of neurons to work in an electrically optimal way, by directly altering neuronal metabolism or by indirectly altering neuronal structure or neurotransmitter homeostasis.

INTRAUTERINE INFECTIONS

Intrauterine infections that involve the fetal central nervous system result in devastating neurological sequelae. Most infections occur during the first and second trimesters with some exceptions. Etiological agents are popularly remembered by the acronyms TORCHS (toxoplasmosis, others, rubella, cytomegalovirus, herpes, syphilis) or SCRATCHES (syphilis, cytomegalovirus, rubella, AIDS or HIV infection, toxoplasmosis, chickenpox, herpes, enteroviruses).

These infections are often missed during pregnancy as maternal infections can be asymptomatic or can cause just mild mononucleosis-like symptoms. Route and timing of transmission are shown in the Table 30.1. **Severity of CNS involvement can vary with the timing of transmission.**

Table 30.1: Route and timing of transmission of intrauterine infections

	<i>Major route of transmission</i>	<i>Predominant period of transmission</i>
Cytomegalovirus	Transplacental	First and second trimesters
Toxoplasmosis	Transplacental	First and second trimesters
Rubella	Transplacental	First trimester
Syphilis	Transplacental	Second and third trimesters
Human immunodeficiency virus	Transplacental	First and second trimesters, birth
Herpes	Ascending, parturition	Birth
Varicella	Transplacental	Peripartum, first 20 weeks of gestation
Enterovirus	Contact, parturition	Postpartum, birth

The IU infections are often asymptomatic in the newborn period. Certain clinical signs and symptoms can raise suspicion of these infections. CMV and toxoplasmosis can cause intrauterine growth restriction, preterm birth, microcephaly, hepatosplenomegaly, anemia, cutaneous petechial rash, pneumonitis or hyperbilirubinemia. Chorioretinitis is a prominent feature in CMV and toxoplasmosis infections; the latter tending to involve the macular region. Rubella can cause ‘blueberry-muffin’ cutaneous lesions,

ocular or cardiac defects. Congenital varicella can present with cutaneous depressed scars in a segmental distribution, muscle or limb hypoplasia. Congenital syphilis is likely to present with symptoms and signs only after 2 weeks of age, involve the skin and reticuloendothelial and skeletal systems. Coxsackie B infection causes myocarditis and fever. Progressive neurological disease in congenital CMV infection can manifest in the months to years following birth; progression of hearing loss during childhood has been reported.

NEUROPATHOLOGY

Intrauterine central nervous infections are characterized primarily by inflammatory and destructive processes. Meningoencephalitis can involve all cellular elements of the brain parenchyma resulting in necrosis and reactive gliosis. Multicystic encephalomalacia, porencephaly and hydrancephaly can result. Microcephaly is the result of these multifocal necrotizing lesions as well as inhibition of neural proliferation. Delayed myelination may also be seen. Intracerebral calcifications are seen in 51-75% of symptomatic CMV infections and in 15% of toxoplasmosis infections; calcifications tend to be periventricular in the former as compared to the diffuse calcifications in the latter. Herpes simplex meningoencephalitis can be devastating with serious consequences. Microcephaly is seen in infections acquired during early pregnancy; other features include chorioretinitis, microphthalmia, multicystic encephalomalacia and cerebral calcifications.

Hydrocephalus is commoner in **toxoplasmosis**; it can result from occlusion of the aqueduct with periventricular inflammation and thrombosis with resultant infarction. **Migrational disorders** such as lissencephaly, polymicrogyria, pachygyria and schizencephaly have been described in **congenital CMV** infection thus giving it a teratogenic potential. The **early stage of congenital syphilis** is characterized by acute and subacute **meningitis, hydrocephalus, cranial neuropathies and cerebrovascular infarcts. Optic atrophy and auditory nerve injury**, juvenile general paresis and tabes dorsalis are seen in the **late stage of congenital syphilis**. HIV differs in that the neuropathology is more related to the immune response of the host. Cerebral atrophy and resultant microcephaly is a prominent feature resulting from loss of neurons and myelin. Enteroviruses cause primarily meningoencephalitis. Neuropathological features in congenital varicella infection include meningoencephalitis, myelitis, dorsal root ganglionitis and denervation atrophy of muscle in segmental distribution.

***Cytomegalovirus*²⁶ (CMV)**

Congenital CMV infection is a leading cause of hearing loss and neurodevelopmental disabilities, and of the common IU infections. Of those children with congenital CMV, 80-90% have a normal developmental outcome. One third of children with symptomatic congenital CMV infection are normal.

Infection in early gestations results in neuronal migrational disorders, whereas later gestations produce only myelination defect. **Microcephaly and abnormal neuroradiologic imaging** are associated with poor neurodevelopmental outcomes and the normal head circumference and normal neuro—imaging favors good prognosis. Neuroradiological findings include multifocal lesions predominantly involving deep white matter, ventriculomegaly, intracranial calcification, and brain atrophy, destructive lesions, with or without gyral abnormalities. The presence of abnormalities in the **anterior part of the temporal lobe, increases the likely hood of CMV infection**. Based on a data from MacDonald (80 infants), the outcome correlates with the presence of symptoms at birth. In the symptomatic group, with overt neurological disease with microcephaly, calcifications or chorioretinitis, almost 95% exhibited major neurological sequelae or died.

If systemic signs without neurological involvement were present, almost 50% of these infants were normal and 16% exhibited major neurological sequelae or died. Major neurological sequelae included mental retardation, seizures, deafness or motor deficits.

In the asymptomatic group, sensorineural hearing impairment was seen to progress during early childhood underlying the importance of evaluating these infants periodically (can be as late as 6 years of life). In studies, 11% developed bilateral hearing loss with moderate to severe loss noted in 6%.

Visual impairment and strabismus are common due to chorioretinitis and involvement of other eye structures. It is unusual to have eye involvement in children who were asymptomatic neonates.

Infection acquired during breastfeeding and delivery is not associated with neurodevelopmental sequelae.

IgM test is useful when it is done 3 weeks after birth. It is positive in only 70% cases. Ideal diagnosis is by demonstration of virus in urine or saliva.

Currently there is no evidence to suggest antiviral therapy for congenital CMV. In an RCT, 6 weeks of Ganciclovir at a dose of 6 mg/kg/day resulted in improved hearing compared to controls at 6 months follow up. In addition 68% in untreated group had deterioration of hearing

function at 1 year follow up as compared to 21 % of the group not treated. Viral excretion decreases in the treatment period, but, only temporarily. There are only single case reports of improvement in cholestasis and retinitis.

Preventive strategies—hand washing after contact with saliva, urine in day care centers/centers for disabled. Early studies on intravenous human immunoglobulin to pregnant mother with primary CMV have claimed decrease in transmission, but further evaluation is necessary.

Toxoplasmosis²⁷

About 20-25% of infants will be affected if maternal infection occurs during the first or second trimester. In maternal infections during the third trimester, about 65% of infants will be affected. Although the risk of transmission is higher later in pregnancy, the severity of fetal involvement is greater in early pregnancy and can involve the ocular and CNS systems. **Treating the mothers** decreases the risk of transmission and severity of the **intracranial lesions, but has no impact on eye involvement.** Reduction in maternal—fetal transmission requires treatment **within 3 weeks of infection** in mother.

Affected newborns are mostly asymptomatic. In symptomatic infants, two-thirds can have neurological signs. **Chorioretinitis mainly involving the macular region is seen in 90% of these infants.** Microcephaly is seen in 10% of cases. Infants with neurological involvement have a poor outcome, with **only 9% normal on follow up.** Major neurological sequelae include visual loss.

In systemic syndrome with predominantly signs referring to the reticuloendothelial system, approximately two-thirds will have chorioretinitis. Neurological involvement is less prominent. 50% are normal on follow up and severe visual impairment is seen in 40%. Asymptomatic cases can also develop chorioretinitis and eventually visual loss; neurological deficits and hearing loss may also result.

Early treatment of toxoplasmosis can result in better outcome. Treatment for 3 months seems to be as effective as longer courses of 6-12 months. Spiramycin was effective in reducing mother to baby transmission; there is no evidence for efficacy of sulfa, pyrimethamine.

Currently, there are no recommendations on screening of pregnant women for toxoplasma infections.

Rubella²⁸

The risk of transmission and severity of infection is greatest during early pregnancy. CNS, ocular involvement, and hearing loss are seen in infections

acquired during the first two months; these are not seen in maternal infections after the fourth month of pregnancy.

Two-thirds of infants can be asymptomatic in the newborn period. Neurological involvement is seen in 50-75% of cases. **Prolonged progressive infection** occurs during early childhood. Hearing loss can be detected later during childhood. A great number of cases will have major neurological sequelae.

Syphilis

CNS involvement occurs in a majority of cases if untreated. 65-90% of cases are asymptomatic in the newborn period. Symptoms may be seen in the first two years of age in the early stage of congenital syphilis. **Neurological signs are seen rarely although abnormal CSF findings can be seen in most of the cases in symptomatic disease.**

CNS involvement in the late stage of the disease is characterized by optic atrophy, auditory nerve injury, tabes dorsalis and general paresis presenting at 10-15 years of age.

The prognosis in congenital syphilis depends on the severity of neurological injury. Symptomatic newborns have a worse prognosis than asymptomatic cases. Neurological sequelae can be **prevented by early adequate treatment.**

Herpes Simplex

The risk of transmission during primary infection in the presence of visible lesions is almost 50% if the infant is born vaginally. Ascending infection during labor can also occur especially if the duration of rupture of membranes is more than 6 hours.

Most of the affected cases are symptomatic in the newborn period. Disseminated disease almost always involves the CNS although overt neurological signs may not be seen in one third of the cases. Left untreated, the mortality rate is as high as 80% and 50% of the survivors have severe neurological sequelae. Even with early recognition and antiviral treatment, the mortality rate is high at 60% and only 10-20% normal on follow up.

Localized disease may involve the CNS in as many as 30-60% of cases. These usually present in the second or third week of life with neurological signs. Mucocutaneous lesions may be absent. If untreated, the mortality rate is about 60-80%; almost all the survivors exhibit significant neurological sequelae. With early recognition and antiviral treatment, the mortality rate is 15% with only 30-40% normal on follow up. In muco-

cutaneous localized disease, progression to involve the CNS can occur. The mortality is almost zero with 90-100% normal on follow up in localized mucocutaneous form of disease.

Human Immunodeficiency Virus

HIV infection affects the CNS with clinical features seen months to years after birth. **Neurological signs in the newborn period are rare**; onset of these occurs in about 20% of infected infants and are usually seen between 2 months and 5 years of age. **Progressive encephalopathy** can develop with spastic motor deficits, microcephaly and extrapyramidal signs developing in a rapid or subacute fashion. The median age of survival after onset of these features is 14 months. Static encephalopathy occurs in 20-25% of cases and is characterized by cognitive problems and motor dysfunction. About 75% survive to the age 6 years; approximately 25% will have mild cognitive and motor deficits. Survival rate at 10 years is 60%; approximately 25% will need special education.

Varicella

Two syndromes are recognized: congenital varicella syndrome and prenatal varicella infection. The former occurs with transplacental transmission during the first 20 weeks of pregnancy. The risk of fetal infection is reported to be about 0.4% during the first 12 weeks and 2% during 13-20 weeks of pregnancy. **CNS involvement is significant**. Seizures, muscle weakness and bulbar signs manifesting as difficulty swallowing may be seen in 26-50% of cases. Retarded neurological development may be seen in 51-75%. Ocular abnormalities occur in 76-100% of cases and include chorioretinitis, cataracts, Horner's syndrome or optic atrophy.

Perinatal varicella results when infection is transmitted close to or at the time of delivery and is clinically apparent in the infant within 10 days of delivery. **CNS involvement is rare**.

Enterovirus

Most of these infections occur postnatally. Transmission may occur during delivery. Transplacental transmission can occur near the time of delivery if maternal viremia is present. Coxsackie B infection can result in serious involvement of the CNS along with myocarditis. CNS signs may be seen in only about 25% of cases. Prognosis with coxsackie B infection is generally good; exception being those cases with encephalitis. They may develop neurological or cognitive deficits.

Chorioamnionitis

Chorioamnionitis has emerged as an important risk factor for adverse neurodevelopmental outcome in both term and preterm infants. Chorioamnionitis can be overt or subclinical. Overt infection is manifested by well known clinical features like maternal fever associated with fetal or maternal tachycardia, uterine tenderness, or foul-smelling amniotic fluid. Eastman et al reported in the 1950s that intrapartum fever **occured 7 times more common in mothers of infants with CP.**³ Nelson et al analyzed characteristics of a population registry of infants with CP and reported that a clinical or histologic diagnosis of chorioamnionitis was associated with **an 8-fold increased risk of CP.** Several studies have noted an association between placental infection/inflammation in term infants and the development of CP in early childhood.⁷⁻¹⁰

A significant number of cases of preterm labor with premature rupture of membranes may be accompanied by sub-clinical microbial invasion of the amniotic fluid producing a condition called sub-clinical chorioamnionitis. This condition is associated with increased fetal and amniotic fluid cytokines such as interleukin-6, interleukin-8, interleukin-1-beta, and tumor necrosis factor-alpha. Interleukin-6 in particular, is a pro-inflammatory mediator produced in response to infection and can elicit various biochemical, physiologic and immunological host responses that can then result in a condition called fetal inflammatory response syndrome (FIRS). Funisitis is considered a hallmark feature of FIRS. FIRS can progress on to septic shock, multiple organ dysfunction, encephalopathy and death. IL-6 has been shown to be increased in FIRS. It can directly or indirectly (by producing systemic hypotension) produce white matter lesions in the brain that can result in periventricular leukomalacia. PVL has been linked in several studies to the later development of CP.

MATERNAL DISEASES

Main mode of causing NDD is by restricting the growth of the fetus and or resulting in preterm birth.

- **Risk of LGA, jaundice, breast trauma, respiratory distress**
- **Hypertension**
Risk of SGA in mild chronic hypertension varied from 8.0 to 15.5%
- **Previous affected pregnancy(which has resulted in SGA babies)**
20% recurrence risk, depending on persistence of risk factors
- **Smoking**
Reduction in average birth weight of 458 g in smokers of 20 cigarettes/day

- **Renal disease**

women with moderate (defined as serum creatinine concentration of 124-220 mm/L) and severe renal impairment (defined as serum creatinine concentration >220 mm/L), 37% of births were SGA (<10th centile birth weight).

- **Connective tissue disease**

Incidence of growth restricted fetus 28.5% in women with active systemic lupus erythematosus, but 7.6% in those with inactive lupus.

- **Thrombophilia**

Although there is evidence for adverse pregnancy outcome with antiphospholipid syndrome, with IUGR occurring in around 30%, the risks for other thrombophilias are less clear. A systematic review concluded that women with poor obstetric outcomes (such as IUGR) are more likely to test positive for thrombophilia, but routine screening currently not be recommended.

- **Cardiac disease**

A prospective study of over 500 women (with heterogeneity of cardiac disease) found significant maternal morbidity or mortality in up to 13% of pregnancies. In this series, the incidence of a <10th centile SGA birth weight was not significantly higher than in controls (4% versus 2% in controls). However, there was a significantly increased risk of fetal death, premature delivery and respiratory distress syndrome. Maternal condition prior to the pregnancy appears to predict to some extent the maternal and possibly fetal outcome.

- **Smoking, alcohol and caffeine use**

Many studies report a reduction in birth weight at term of around 150-330 g in smokers compared with non-smokers. Comparisons have been made of anthropometric measurements of infants born to women who continued to smoke (>1 cigarette/day) throughout pregnancy, with those that stopped after the booking visit. There is an association between continued smoking and reductions in birth weight, head circumference and crown-heel length, with more pronounced effects in heavier smokers (>10 cigarettes/day).

Alcohol at low doses (less than 1 unit/day) translate to an odds ratio (OR) of delivering an infant below the 10th centile for gestational age of 1.1 (95% confidence interval (CI) 1.00-1.13). With consumption of 1-2 units a day, the corresponding OR is 1.62 (95% CI 1.26-2.09) and with 5 units a day, the OR is 1.96 (95% CI 1.16-3.31).

Caffeine: The effects of reported *caffeine consumption* on birth weight in over 2000 women in Connecticut and Massachusetts showed small observed reductions in birth weight. At high doses (600 mg/day) caffeine reduced mean birth weight by the equivalent of smoking about 10 cigarettes a day. However, when smoking was controlled for, moderate intake seemed to have little effect on the risk of birth weight under the 10th centile.

Drugs of abuse: Most studies report a high incidence of IUGR in opiate users but multiple confounders exist. The most likely drug with a particular effect is cocaine because of its associated constrictor effects, although in a review of 200 babies born to women using drugs of abuse, 11% were found to be SGA (under 10th centile), which suggests the effects may not be as great as commonly thought.

Prescribed drugs: The fetus may be exposed to drugs during pregnancy because of pre-existing maternal problems or complications of pregnancy itself, such as hypertension, or anticipated preterm delivery. Beta-blockers (including labetalol), for example, do appear to be associated with an increased risk of a SGA infant when used to treat hypertension.

MATERNAL FACTORS

Assisted conception: In 307 in vitro fertilization (IVF) pregnancies, 16.2% of babies had a birth weight below the 10th centile compared with 7.9% of controls. A recent meta-analysis found an OR of 1.6 (95% CI 1.3-2.0) for a birth weight <10th centile for singleton pregnancies conceived by IVF compared to spontaneous conceptions.

Age: There is no association between SGA and low maternal age,²⁸ but there is with older mothers.²⁹ In the London perinatal database of 385,120 singleton pregnancies, an OR of 1.28 for a birth weight <5th centile was reported in women aged >35 and an OR of 1.49 for women aged >40.

Body mass index: Obesity is not associated with the birth of a SGA fetus, whereas maternal 'underweight', i.e. a BMI <20, increases the risk of both preterm delivery and birth weight <5th centile.

TERATOGENS

There are two important mechanisms by which drugs affect the developing CNS: teratogenic effects and passive addiction. Teratogenic effect refers to the effects of any agent that causes **a structural abnormality** following

Table 30.2: List of well known teratogens that affect the fetal CNS

<i>Drug</i>	<i>Fetal effects of intrauterine exposure</i>
Phenytoin	<ol style="list-style-type: none"> 1. Fetal hydantoin syndrome (craniofacial dysmorphism especially ocular hypertelorism, hypoplastic distal phalanges and nails, growth retardation, delayed neurological development and cardiac defects. 2. Intracranial bleed (hemorrhagic disease of newborn) 3. Cleft lip/palate, cardiac defects
Phenobarbital	<ol style="list-style-type: none"> 1. Dysmorphic features, growth retardation 2. Intracranial bleed (hemorrhagic disease of newborn) 3. Cleft lip/palate, cardiac defects 4. Passive dependence (withdrawal symptoms)
Valproic acid	<ol style="list-style-type: none"> 1. Dysmorphic features 2. Cardiac defects 3. Neural tube defects especially myelomeningocele (risk 1-2%)
Carbamazepine	<ol style="list-style-type: none"> 1. Craniofacial defects 2. Neural tube defects especially myelomeningocele (risk 1-2%) 3. Developmental delay 4. Intracranial bleed (hemorrhagic disease of newborn)
Trimethadione Paramethadione	<ol style="list-style-type: none"> 1. Impaired growth 2. Craniofacial dysmorphism (v-shaped eyebrows, malformed ears, cleft lip/palate) 3. Microcephaly, mental retardation, developmental delay
Alcohol	<ol style="list-style-type: none"> 1. Fetal alcohol syndrome (impaired growth, microcephaly, developmental delay, facial abnormalities: low nasal bridge, midface hypoplasia, long featureless philtrum, small palpebral fissures and thin upper lip; cardiac defects, hearing loss, optic nerve hypoplasia) 2. Cognitive and behavioral deficits
Isotretinoin	<ol style="list-style-type: none"> 1. Craniofacial dysmorphism (malformed ears, atretic ear canals, microtia) 2. Cleft palate 3. CNS defects (hydrocephalus, migration defects, cerebellar and brain stem abnormalities) 4. Cardiac defects
Cocaine	<ol style="list-style-type: none"> 1. CNS defects (Microcephaly, migration disorders, callosal agenesis, neural tube defects) 2. Microcephaly 3. Cerebral infarction, intracranial hemorrhage 4. Neurobehavioral abnormalities 5. Abnormal EEG and brainstem auditory evoked responses
Warfarin (coumadin)	<ol style="list-style-type: none"> 1. Facial dysmorphism (nasal hypoplasia, depressed nasal bridge) 2. Severe mental retardation, seizures, microcephaly, hydrocephalus 3. Stippled bone epiphysis 4. Growth retardation
Methotrexate	<ol style="list-style-type: none"> 1. Facial dysmorphism 2. Microcephaly 3. Growth retardation, talipes equinovarus
Radiation	Microcephaly, growth restriction, mental retardation
Lead	Spontaneous abortion, neurological abnormalities

fetal exposure during pregnancy. Passive addiction of the fetus is the **physical dependence** that occurs due to maternal exposure to the drug.

The teratogenic effect of agents depends on dose of the agent, timing and duration of exposure to the agent, genotype of the pregnant woman, genetic susceptibility of the fetus, physical characteristics of the agent including size, solubility and polarity. In general, the embryonic stage (first trimester) is more vulnerable than the fetal period (second and third trimesters) (Table 30.2). **The embryonic period, from 18 to 54-60 days after conception, the period of organogenesis is the period of maximum risk of teratogenicity.** Since teratogens are capable of affecting many organ systems, the pattern of anomalies produced depends upon which systems are differentiating at the time of teratogenic exposure. Teratogen exposure during the fetal phase, from the end of the embryonic stage to term which is the period of growth and functional maturation, will affect fetal growth (e.g., intrauterine growth retardation), the size of a specific organ, or the function of the organ.

KEY POINTS

Strategies to prevent or decrease the risk of fetal abnormalities include: use of the lowest dose possible, the avoidance of combination drug therapies (for the treatment of seizure disorders), the use of a different agent (heparin instead of coumadin for thrombophlebitis), the avoidance of first trimester exposures (preconception diabetes or PKU control), and folic acid supplementation.

TEAM APPROACH IN MANAGEMENT OF THE MOTHER AND THE BABY FOR REDUCING NDD

1. There should be a **close liaison between the obstetric and pediatric** colleagues in managing high risk and for that matter all pregnancies. Appropriate consultation with other specialists like physicians, cardiologists, nephrologists may be needed depending on the maternal/fetal condition
2. **Ultrasonography** plays a major part, not only in visualizing the growth of the fetus and the anatomy, but also in assessing the well being of the fetus by assessing the fetoplacental circulation.
3. Considering various factors like the lung maturity, facilities for Intensive care, etc. **optimum mode of delivery at the appropriate time** should be planned.
4. **In utero transfer** is the most desirable practice. Uterus is the best incubator known to mankind. High risk pregnant ladies should be

transferred to tertiary centers with adequate facilities to look after the preterm/sick baby. This minimizes the morbidity associated with the transport of an unstable neonate. The outcome is much better in babies who were transferred in utero as compared to sick unstable babies transferred after delivery. It is essential that every level 3 NICU build an efficient transport team for these purposes.

5. High risk pregnancies with compromised fetus, warrant a trained **neonatal resuscitation team**. A protocol for prompt resuscitation and transfer if needed of such babies to higher centers should have been put in place before the delivery.

If the child is damaged, the family is affected and the society suffers. Long term care of the high-risk infant is a multi specialty commitment small beginnings, great expectations.

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Multiple Fetal Pregnancies

About 3% of human pregnancies are multiple, and natural occurrence rate of dizygotic twins is about 1.7%. With the use of fertility drugs the incidence of multiple gestations could be as high as 25%.

IMPACT ON NEURODEVELOPMENT¹

Multi Fetal Pregnancies (MFP) are associated with a variety of adverse outcomes, including delayed development, impaired sensor-motor function, and cerebral palsy. The reported increase in risk of CP in MFP is similar from studies in different geographic areas of the world. Incidence of cerebral palsy in twins as compared to singleton was 7.4 versus 1 in 1,000 survivors at 1 year and 6.7 versus 1.1 in 1,000 survivors at 3 years of follow-up. The risk in triplets was even higher 28 vs. 7.3 vs. 1.6 in triple, twin and singleton pregnancies followed for 1 year.² The reasons attributing to the increased risk of CP in MFP are prematurity, low birth weight, abnormal presentation, monochorionicity, death of a fetus, and placental vascular anastomoses.

This increased risk of CP is probably related to the incidence of preterm and low birth weight deliveries in MFP being much higher than singleton pregnancies. When data for incidence of CP in singleton and MFPs is stratified by birth weight, there is a significant increase in CP in MFPs with birth weight 2500g or more; as compared with no significant increase in risk for CP for infants of low birth weight (<2500g).³ The third factor in MFP is the chorionicity with incidence of adverse neurodevelopmental outcome being associated with mono-chorionicity. A further confounder is the association of adverse outcome associated with death of one of the fetuses in a MFP. Co-twin survivor after the death of a twin *in utero* or at infancy has a much greater risk for cerebral palsy than if both twins remain alive through infancy. However, when both twins remain

alive, the overall risk for cerebral palsy in normal birth weight twins is greater than the risk for singletons, with a trend toward a higher prevalence in like than unlike twins.⁴

Is the increase in CP in MFP due to prematurity and LBW alone? Yokoyama and coworkers found that the risk of CP in multiple births was 20 times higher in births before 32 weeks' gestation than at ≥ 36 weeks' gestation. A strong correlation between the risk of CP in twins and gestational age at birth was also found by Williams and colleagues. Although, LBW and preterm are apparently the most significant risk factor for CP, the disadvantage of twin pregnancies becomes evident near term. When comparing twin with singleton births, the relative risk of CP was greatest and significant, only for twins delivered at more than 37 weeks' gestation. This probably implies that "term" occurs earlier in twins and it may be advisable to deliver them before 38 weeks.

Low birth weight is an important determinant of CP in MFP. But, the relative risk (in comparison to singletons) of CP was greatest (4.5-fold) among twins weighing >2499 g. Grether and colleagues and Pharoah and Cooke showed a comparable risk for CP among VLBW twins and singletons, whereas twins weighing ≥ 2500 g had a higher risk (3-4 times) of CP than singletons of similar weight.

FACTORS IN PREGNANCY AND LABOUR

MFPs are associated with adverse perinatal outcomes due to higher risk of premature onset of labor, IUGR, and difficult presentations. Hence, increased fetal surveillance has been advocated for twins and multiple gestations. Close antenatal fetal surveillance of MFPs to reduce or obviate these factors should be performed, *irrespective* of chorionicity.⁵

ASSISTED REPRODUCTIVE TECHNOLOGY (ART)³

There is an invariable rise in incidence of MFPs as a result of ART. The risk of CP is much higher after ART transfer of 3 embryos (16.8), transfer of 3 and reduction to 2 (10.3), than two embryos (8.7) in contrast to spontaneous twins (2.7) per 1000 births. This may in part be explained because IVF twin pregnancies are at greater risk for obstetric complications and adverse neonatal outcome in comparison with naturally conceived twin gestations.⁶ Monozygous (MZ) division occurs more frequently in ART (1.2%) than in spontaneous conceptions (0.45%). Babies born as a result of IVF (in-vitro fertilization) had same neurologic risks as those born as a result of ICSI (Intracytoplasmic sperm injection).⁷

MONOCHORIONIC TWIN PREGNANCY

Monozygotic twins comprise of one-third of spontaneous twins and 1 in 10-15 of ART twins. Two-thirds of monozygotic twins are monochorionic.

Monochorionic twins are at further risk of perinatal complications, i.e. Twin-twin transfusion syndrome (TTTS) and death of single or both fetuses. Data suggest that the risk of occurrence of co-twin sequelae is 3-fold greater in MC pregnancies complicated by twin-twin transfusion syndrome (TTTS).⁵ The risk of perinatal death / neurological sequelae is 3-4 folds greater in monochorionic pregnancies than dichorionic pregnancies. Ante-partum death of a single fetus complicates 2.5-5% of twin pregnancies and may be associated with a significant morbidity and mortality in the surviving co-twin. Perinatal outcome of a surviving twin in twin pregnancy depends upon several factors involving the placenta.^{8,9}

TWIN TO TWIN TRANSFUSION SYNDROME (TTTS)

Evidence suggests that the placental vascular anatomy plays a significant factor in influencing the neurological outcome in multiple pregnancies. Information which is helpful in determining the likelihood of sequelae in surviving twin are **placental histology** such as chorionicity, marginal or velamentous cord insertion and the type of vascular anastomosis and in the babies - growth restriction, hydrops, pallor, congestion and cardiomegaly. Recently studies have shown that TTTS is caused by the presence of a unidirectional deep arteriovenous (AV) shunt with paucity of superficial anastomoses.^{9, 10-13} The incidence and severity of TTTS increases with the intra-uterine fetal death (IUFD) of one twin. It has been suggested that it is the superficial anastomoses which are responsible for acute transfusional complications following intrauterine fetal death (IUFD) of one of the twins.¹⁴ Risk to the surviving MC co-twin may depend upon the **type and the size of the vascular shunts**.

GROWTH DISCORDANCE

There is inconclusive information on effect of relative growth restriction of one twin as compared to other. Some considered it a reassuring sign in twins and explained it a natural mechanism to reduce total uterine volume and prolong pregnancy. Others suggest that **growth discordance** possibly reflects a hostile intrauterine environment at least to the smaller twin. The outcomes are related to birth weight in the absence of monochorionicity and TTTS. Consequently, increased surveillance of discordant twins is commonly practiced.

INTRA-UTERINE DEATH OF ONE TWIN

Two theories have been suggested for the demise or neurological sequelae in twin/ **multiple pregnancies complicated with IUFD**.

- **Thrombotic theory:** Passage of thrombotic or necrotic material from the dead to healthy twin along the placental vascular shunts can lead

to vascular insults in the healthy twin resulting in **cerebral necrosis**.¹⁵ The incidence of fetal thrombosis in monochorionic-twin pregnancies was significantly higher than that of dichorionic-twin and singleton pregnancies. In monochorionic twins, fetal thrombosis was associated with co-twin fetal death, but in dichorionic twins no correlation was identified. Microscopically, fetal vessel thrombosis in twin placentas was associated with vascular cushions (fibrous hyperplasia of fetal vessel). The validity of this idea has been questioned recently because of the normal coagulation status and anemia in the survivors.¹⁶

- **Hemodynamic theory:** The vascular anastomosis can be superficial/deep, AA/VV/AV/VA anastomosis, unidirectional or bidirectional. In the presence of superficial AA anastomoses, a massive transfer of blood can occur, from the live to the dead twin. This may cause brain damage or fetal demise of the surviving twin simply because of **severe haemodynamic imbalance**. Placental anastomoses allow transfer of blood from the surviving twin to the dead co-twin, giving rise to periods of **hypoperfusion** resulting in neurological changes.¹⁷

Following the demise of one twin, a massive blood transfusion can occur from the survivor's arterial to the dead twin's venous circulation (AV). In the dead twin, this may lead to a rise in the systemic filling pressure which then in turn can initiate the flow along the VA anastomoses with the establishment of an intertwin circulation. In this cohort, it is theoretically possible that thrombotic material generated in the dead twin may reach the circulation of the viable fetus. However, the normal outcome in eight cases with no evidence of neurological handicap argues against the thromboembolic episode as the cause for co-twin sequelae.⁶ Antenatal cerebral white matter necrosis occurs relatively frequently in monochorionic twins. It is proposed that placental artery-to-artery or vein-to-vein anastomoses may predispose twin fetuses to hemodynamic instability. Fluctuations in blood pressure or blood volume may then result in cerebral necrosis, without requiring the death of one twin or transfer of a blood-borne factor from one twin to the other. The twin survivor with cerebral palsy can display a wide variety of anatomic abnormalities, especially if the co-twin's death occurs *in utero*. The defects include white matter infarction, hydrocephalus, multicystic encephalomalacia, cortical atrophy, ventriculomegaly, holoprosencephaly, polymicrogyria and periventricular heterotopia.^{17,18} Adverse neurologic effects are not limited to pregnancies in which when one co-twin dies *in utero*. Long term poor neurologic outcomes are also seen in live-born twins when one of the twins subsequently dies in infancy. This implies that monochorionic placentation is responsible

for cerebral lesions, not necessarily in-utero death of co-twin.¹⁹ In pregnancies where both twins are still viable, an alternative option such as the occlusion of the umbilical cord of the recipient twin is a distinct possibility.^{19,20}

FETAL REDUCTION AND VANISHING TWIN SYNDROME

Studies have shown serious increase in risk of CP when fetal reduction was done. Conversely there are studies that report the contrary – and hypothesize that decrease in prematurity and low birth weight should improve outcomes. In spontaneously disappearing twins, there is no clear information on expected outcomes.^{3,21}

Mode of delivery

Caesarian delivery offered no advantage in VLBW, ELBW babies even when fetal presentations and growth concordance by more than 1 kg were taken into consideration.²²

KEY POINTS—Reducing NDD due to multiple gestations^{1,3,22}

1. MFP are associated with an increased risk of CP. There is an exponential increase in risk of CP with increase in number of fetuses. Quadruplets have a poorer outcome than triplets and triplets do poorer than twins.
2. Low birth weight and prematurity are commoner in MFP.
3. The true difference in NDD between singleton and MFP becomes evident nearing term gestation. The risk of CP is higher for twins delivered after 37 weeks or later as compared to singletons.
4. As complications of pregnancy and delivery in MFP are higher, closer fetal monitoring is recommended.
5. Risk of CP is lower in spontaneous MFP as compared to product of ART with transfer of more than one embryo.
6. The surviving twin, in case of demise of other monochorionic twin, has higher risk of CP.
7. Monochorionic twins, are at higher risk of CP than dichorionic twins even when both are live born.
8. In TTTS there may be an increased risk of CP, even if both twins survive and TTTS is treated.
9. There is not clear data on vanishing twin and fetal reduction, but may increase NDD. Concerns are expressed on fetal reduction.
10. Caesarian delivery does not reduce NDD in twin term / preterm pregnancies.
11. There is no significant difference on the occurrence of CP in MFP caused by in vitro-fertilization or intra-cytoplasmic injection of sperm.

UNANSWERED QUERIES / FURTHER RESEARCH

In multiple pregnancies the development of newer techniques to **map the vascular anatomy of MC placentae** accurately *in vivo* are much awaited. The availability of such information during the antenatal period is likely to influence the clinical management and may reduce the

neurological handicap in some of the surviving co-twins. The challenge in multiple pregnancies is to understand the close interaction between placenta, multiple fetuses and the intra-uterine environment.

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Assisted Reproductive Technique—Is It Safe?

The most important outcome of any Assisted Reproductive Techniques (ART) should be the well being of the babies thus conceived. In the three decades, since the birth of Louise Brown in 1978 ART practice has changed hugely. Modifications in ART procedures such as embryo and oocyte cryopreservation, Intra Cytoplasmic Sperm Injection (ICSI), assisted hatching and extended culture techniques have been introduced **ignoring the risks to the child**. Even newer procedures Trans-epididymal Sperm Aspiration (TESA) and testicular biopsy have resulted in **a less naturally selective** form of reproduction. Newer techniques in *in-vitro* fertilization (IVF) are constantly being introduced, such as *in vitro* maturation (IVM) and vitrification.

In the early days, there was little awareness about the safety of IVF. The procedures were sporadic, so there was not enough human data to report safety. First clinical reports of increased risk of congenital anomalies in babies born of IVF appeared in the literature from Australia.¹

Sub-fertile parents who conceived by IVF in its various forms are per se a **skewed population of individuals**, whose offspring may well be at-risk of problems because of their parent's genetic nature, rather than the procedures for treatment of sub-fertility themselves. The overall impression from the literature concerning the risk of congenital anomalies suggests a **higher risk of anomalies after ICSI** and any ART, but that risk is modest.² Since the advent of ICSI even couples with severe male factor infertility are able to conceive and some of them clearly have known genetic defects (in non-obstructive oligozoospermia or obstructive azoospermia).

Other possible factors that may increase risks from ART are **culture media**.

Recently an increased risk of **genomically imprintable disorders** after ART has been described such as Beckwith-Wiedemann syndrome.

COMPLICATIONS DUE TO MULTIPLE PREGNANCIES

The short-term risk to children born after ART, are largely but not entirely due to the risk of high order births. As failure rates of IVF treatment were high, IVF clinics remained focused on efficacy than on safety. Efforts were concentrated on ways and means to increase efficacy. The most important option was by increasing the number of embryos placed. Success rate of IVF was expressed as the proportion of pregnancies per embryo transfer. As a result proportion of multiple births also increased. Wramsby in 1987 reported a **multiple birth rate of 14%** when transferring five embryos and this **was seen as a success rather than a problem**.³ As assisted reproductive techniques improved, the proportion of multiple births increased to appalling levels sometimes even exceeding 30%.⁴ These IVF children were siblings in sets of twins, triplets and even of higher order. Some 50% of twins are born at less than 2500 grams and 50% are born at less than 38 weeks gestation.⁵ The extremely high levels of multiple pregnancies led to a very high proportion of prematurity (five-fold or more) causing increased risks of morbidity and mortality among the newborns.⁶ **The relative importance of birth defects was masked by the iatrogenic problems following multiple pregnancies.**

EFFICACY VS SAFETY

Today, there is a transition towards reporting the success of ART as benefit rather than efficacy. Benefit is the balance between efficacy, safety, quality, cost and time. **Safety includes risk of birth defects, low birth weight and prematurity.** Genuine efforts are being taken today to reduce High Order Multiple Pregnancy (HOMP) by practicing elective **Single Embryo Transfer (SET)** embryo cryopreservation and Frozen Embryo Transfer (FET). In the new era of "SET as the norm" several countries (e.g. Sweden, Finland, Norway, Belgium, Denmark, Australia) the problem of prematurity (iatrogenic part) and related problems following IVF multiple pregnancies will obviously be reduced, although not completely eliminated.⁵ In India, the ICMR in its guidelines for ART clinics has restricted the number of embryos transferred to three or less.

Over 3 million IVF children have been born in the world and only a very small proportion have been followed-up for outcomes. Some countries have high quality national registration of birth defects, whereas others do not. Other problems are issues on definitions, coverage, lost to follow-up, validation and control groups. There is heterogeneity in selection of patients, drugs, laboratory and clinical procedures. Reporting of registered data on birth defects takes several years. Therefore, continuous

early screening of birth defects reporting is an indispensable part of high quality birth defect registers. Assessment of health of children born after successful pregnancies can be divided into health at birth, at one year and health of older children. We can also investigate congenital anomalies in ART babies.

MALFORMATIONS IN DIFFERENT ORGAN SYSTEMS

There is evidence from Bonduelle's work that **congenital urogenital malformations are more common in ICSI than in IVF**. This seems logical in view of the parental genetic background and the increased risk of male sub-fertility when there are genitourinary defects in the father. 5% of all IVF children had a relatively severe birth defect compared to 3% in the general population. Some diagnoses had a stronger association than others; **neural tube defects, atresias and cardiovascular defects**. No difference was noted between the risk after standard IVF and after ICSI, with the exception of hypospadias, which was more frequent after ICSI. The risk increase was the same whether the embryos were fresh or frozen.⁷

EVALUATION OF PUBLISHED STUDIES (CONGENITAL ANOMALIES)

- **IVF compared with general population**

Hansen's study showed an increased risk with an odds ratio of 2 even after adjusting for maternal age, parity and sex.² Others, felt that risk of anomalies disappeared after adjusting for confounders.⁸⁻¹⁰

- **ICSI compared with the general population.**

Retrospective Studies

In the Australian study of Hansen and colleagues concerning congenital malformation at 1 year of age the odd's ratio remained 2 after adjusting for confounders.² In two other Swedish retrospective studies by Wennerholm and Ericson and Kallen, there was an increase in congenital malformations in ICSI and IVF.^{9,11} But adjustment for maternal age and other confounders showed no increased risk.

Prospective Studies

In one prospective control study by a German group, 3372 ICSI children were compared with a control group of 8,016 children from natural conception. The major malformation rate was 8.7% (295/3372) for the ICSI group and 6.1% (488/8016) for the population based control cohort. Even after adjusting for confounding factors, the risk was still slightly higher (1.24) than that of the natural population.¹²

ICSI Compared with IVF

Bonduelle found no differences in malformations rates between ICSI and IVF children. This was the largest cohort studied with 2995 IVF versus 2889 ICSI children.¹³ But specific types of defects were more likely after ICSI. There is serious concern on risk of anomalies following ART.^{14,15}

Developmental Outcome Studies of IVF/ICSI Children

ICSI-CFO is an international collaborative study of intracytoplasmic sperm injections—**child and family outcomes**. This is the largest follow up study on IVF-ICSI children; 5 European countries participated.¹⁶ Approximately 500 ICSI singletons, 500 IVF and 500 naturally conceived children aged 5 years were each assessed with observer blinding to conception status. All children were singletons born after 32 weeks and matched for sex and social class and race. The study showed no effect of conception status on neurodevelopment. The ICSI and IVF children were not found to be physically different from normal class children with the exception of congenital anomalies.¹⁶

Bowen and colleagues in 1998 studied developmental outcomes in ICSI conceived children, conventional IVF children and naturally conceived controls. They found an increase in mild developmental delay using Bayley Scales of infant development. But the study used comparison of children, who were already enrolled in a separate study and there was no blinding of assessors. The ICSI children and controls differed in demographic data.¹⁷

Several other workers have also studied ICSI and IVF children. They have not found marked differences in developmental outcome between the two groups and also when compared to naturally conceived children. However, there was a greater use of health care services by ICSI and IVF children when compared to normal class children.

NEUROLOGICAL PROBLEMS

A Swedish study has shown that children born after IVF have an increased risk of developing neurological problems particularly cerebral palsy (CP).²⁶ There was a 4 fold increase in CP in these children compared with matched cohorts (OR 3.7). The risk in singletons was nearly 3-times (OR 2.8). After adjusting for birth weight and a gestation of more than 37 weeks the risk remained with an OR 2.5. However, Sutcliffe noted that the study used proxy measures for disability and it was unexplained why CP seemed higher in the singleton group than the IVF group, in contradiction to the entire twin literature!

RETINOPATHY OF PREMATURE

HOMP and premature births related to assisted conception has led to an increase in retinopathy, because of early birth and low birth weight. Anteby and colleagues reported that 26% of children (out of a small cohort of 47 children studied) born after IVF had major ocular malformations. The defects included congenital cataract, optic atrophy and retinoblastoma.²¹

GROWTH

Saunders and colleagues studied children conceived by ART and found that physical outcomes, weight, head circumference and malformation rates were not different between groups. The IVF group had a greater mean length centile. The twins in each group had poorer physical outcomes, with an increase in prematurity and low birth weight, and reduced height and weight at age two when compared to singletons.²⁰ The ICSI-CFO study also showed that the growth standard deviation scores (SDS) for both IVF and ICSI are higher than for naturally conceived children.¹⁶

USE OF MEDICAL SERVICES

IVF and ICSI children are more likely to need neonatal care mainly because of prematurity due to multiple pregnancies, pregnancy induced hypertension (PIH), intra-uterine growth retardation (IUGR), diabetes and pre-term delivery. ICSI-CFO has shown higher use of medical resources among IVF/ICSI children including surgery. There are other studies which suggest that IVF children did not require extra medical attention after the neonatal period.^{18,19}

CHILDHOOD CANCER

The UK Medical Research Council (MRC) working party and a Swedish national cohort study of IVF children found no increase in cancer rates in children conceived through ART. But the power of the studies was limited by too small a number.^{22,23}

Similarly an Australian study, and more recently Klip and associates found no increase in cancer risk in IVF/ICSI children.²⁴ But Doyle and colleagues estimated that 20,000 ART children would be required to observe a doubling or halving of the risk of childhood cancer.²⁵

GENOMIC IMPRINTING

In ART and imprintable disorders (ARTID)²⁷ four conditions known to be imprintable in man were surveyed—Beckwith-Wiedemann syndrome

(BWS), Prader Willi syndrome (PWS), Angelman syndrome (AS) and transient neonatal diabetes (TNDM). They confirmed an association between ART and BWS, showing that epigenetic changes caused by ART can lead to human disease. Epimutations are a rare cause of AS. ART related BWS and AS may be specially associated with maternal allele ICR methylation loss. The cause of the association between ART and loss of maternal allele ICR methylation in humans is uncertain, but two hypotheses have been proposed.²⁸ *In vitro* embryo culture may predispose to the mutations. Alternatively, there may be an increased risk of an imprinting disorder because of an association with infertility per se rather than with *in vitro* embryo culture. They did not find evidence of an association between ART, PWS and TNDM. But TNDM is a very rare disorder and this was the smallest patient group available for study.

KEY POINTS—safety in ART

1. The highest risks from ART are from prematurity (mainly from twins and higher-order births); therefore, single embryo transfer, at least in the first cycle, is recommended.
2. Term babies are healthy and not at long-term health risk as a consequence of mode of conception.
3. There is probably a higher risk of congenital anomalies after ART. In ICSI children there is specifically a higher risk of genitourinary (GU) anomalies marginal increase over general population.
4. ART neonates, however, do increase the health resource needs.

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Section 14

Unexplored Territories

- 33. Nutrition, Fluid and Electrolytes**
- 34. Follow-up Research—Some Methodological Issues**

Nutrition, Fluid and Electrolytes

Nutrition, fluid and electrolytes are very important components of daily management of a sick neonate and involve close monitoring and titrating. Currently, immediate end points are known but, there is a paucity of evidence on long-term neurodevelopmental consequences.

PRINCIPLES OF FLUID AND ELECTROLYTE MANAGEMENT

1. Maintenance of normal tonicity and intravascular volume.
2. Glucose homeostasis
3. Prevention and correction of dyselectrolyemia
4. Nutrition
 - a. enteral
 - b. parenteral.

MAINTENANCE OF NORMAL TONICITY AND INTRAVASCULAR VOLUME

PERINATAL CHANGES IN TBW

Total body water (TBW) is 75% of birth weight at term and even more in preterm infant (>75-80%). A greater proportion of this is extracellular fluid (ECF). During the first 7-10 days of life, the newborn baby must lose weight; decrease in weight is secondary to water losses from the ECF. Term babies may lose up to 7-10% and preterm up to 10-15% (as preterm infants have more ECF).¹

INSENSIBLE WATER LOSS (IWL)

Water is lost as urine, stool, used for metabolism and insensible water loss (IWL), i.e. via evaporation from the skin (2/3rd) and the respiratory tract. IWL is the most variable component, and relates inversely to gestational

age IWL increases with environmental temperature and relates inversely to relative humidity of nursing environment. A 26 week/ELBW baby under a radiant warmer on day 1 may lose over 150 ml/kg/day as against < 30 ml/kg/day in a term baby. Insensible losses decrease after first few days, as skin matures to its full layers (thickness).

In clinical practice, measurement of IWL is only based on surrogate parameters and empirical fluid plans are proposed as a starting point—Suggested fluid rates as per BW on day 1 of life.

Weight (gm)	<750	750-1000	1000-2500	>2500
Fluid (cc/kg/d)	120	100	80	60

Common Clinical Conditions Affecting IWL

- **Increased IWL:** Prematurity, high ambient temperature, low humidity, mechanical ventilation without humidification of gases, omphalocele, gastroschisis, burns, phototherapy, skin damage, myelomeningocele, encephalocele
- **Decreased TWL:** Thermo-neutral environment, incubator with humidity control, incubator vs open care, double walled vs single walled, PVC Film cling wrap, plastic shield.

FLUID REQUIREMENT

Goals

- Prevent dehydration or hypervolemia
- To allow 1-2% daily weight loss during first week (up to 7-10% in term and 10-15% in preterm infant).

The accurate assessment of hydration status in term babies is based on clinical perfusion, serum osmolarity, serum sodium, blood urea nitrogen, hematocrit, blood gases and electrolytes, urine output and urine specific gravity, daily weights (and more frequently in smallest babies), and hepatic size and edema. In preterm and more so in extreme preterm babies none of the above said tools individually remain reliable and an attempt to homeostasis is the only end point.

Maintenance fluid (1st week): Urine output + Insensible losses—2% wt loss

1. Increase total fluid intake by 20 cc/kg/d each day until day 5-6 (or as guided by perfusion and assessment of hydration). This is inresponse to improvement in GFR (Glomerular filtration rate).
2. If under a radiant warmer, add 20 ml/kg/day.

3. If under phototherapy, add 20 ml/kg/day.
4. Very preterm infants should be placed in humidified incubators in a neutral thermal environment as soon as practical after birth.

Decrease in total fluids may be necessary in renal failure, CHF, respiratory disease, PDA and SIADH, and **increase** in fever, increased losses (stool/urine, 3rd spacing).

Restriction of Fluids

Preterm babies: High fluid intake may be associated with higher incidence of NEC and symptomatic PDA,^{2,3} which may lead to prolongation of ventilation and associated neurologic morbidity. The most prudent prescription for water intake to premature infants would seem to be careful restriction of water intake so that physiological needs are met without allowing significant dehydration.⁴

Perinatal asphyxia: Although a convention, there is no evidence from randomized, controlled trials to support or refute that the practice of fluid restriction in neonates following perinatal asphyxia affects mortality and morbidity.⁵

Ventilated neonates: In ventilated, VLBW babies, fluid restriction in the perinatal period is proposed to reduce CLD. Colloid infusion, however, is associated with increased duration of oxygen dependency.⁶

Dehydration and Hypoperfusion

Suboptimal fluid intake can lead to dehydration and under perfusion of body organs. Severe dehydration can also lead to increased risk of shock, acidosis and when less severe, relative polycythemia and thrombo-embolism which can be associated with poor neurological outcome. The pathophysiology relevant to neonatal dehydration is related to hypernatremic states and to problems resulting from the intravenous fluid correction of such states.

The common adverse effects of dehydration are mild cognitive, behavioral, or motor impairment; these are unlikely to occur in the type of dehydration usually seen by primary care physicians in controlled environment.⁷ These benign outcomes apply only to cases of neonatal dehydration that is detected before catastrophic events. If dehydration persists long enough, the adverse effects are similar to those mediated by acidosis and hypovolemic shock.⁸

GLUCOSE**HYPOGLYCEMIA**

Hypoglycemia should always be prevented and is probably the easiest to prevent cause of NDD in neonates.⁹⁻¹¹

HYPERGLYCEMIA

Whole blood sugar >125 or plasma sugar >140 mg/dl.⁹

Causes

Prematurity (especially ELBW babies), high glucose infusion rates, sick neonates like sepsis (especially fungal sepsis), postoperative period, Drugs (Steroids, aminophylline).

Each 18 mg/dl increase in blood sugar raises the osmolality by 1 mOsm/dl and increases the risk of cellular dehydration. High osmolality may lead to osmotic diuresis, dehydration and even cerebral hemorrhage, which might have long-term implications.¹²

High blood glucose concentrations increase the risk of early death and grade 3 or 4 intraventricular hemorrhage and the length of hospital stay among survivors without intraventricular hemorrhage, which suggests that prevention and treatment of hyperglycemia may improve the outcomes of extremely low birth-weight infants.

Treatment

Down regulate glucose infusion rate by 1-2 mg/kg/min every 1-2 hr. If the glucose concentration still remains dangerously high (>250 mg/dl), insulin may have to be used.

Prevention

In ELBW, one may start with 5% dextrose. Start early feeds: promotes insulin secretion, early aminoacid promotes insulin secretion.

PREVENTION AND MANAGEMENT OF DYSELECTROLYTEMIA...**SODIUM DISTURBANCES**

Normal serum sodium — 130-150 mEq/L

Usual daily requirements 2-3 mEq/kg/d (may be higher in ELBW)

Begin supplementation on Day 2-3 of life as indicated if weight loss exceeds > 6% of body wt and serum sodium decreases to < 130 mEq/L.

Hyponatremia

Na < 130 mEq/L (concern if < 125 mEq/L).

Hyponatremia, when severe is associated with vomiting, lethargy, seizures, respiratory irregularities and coma. It increases the risk of hearing impairment in preterm babies and may be associated with other NDD.¹³

The correction of hyponatremia would depend on underlying pathology (fluid excess or loss of sodium). One should not exceed 10-12 mEq/L rise of sodium per day in chronic asymptomatic hyponatremia. Rapid and complete correction of hyponatremia in adults has been associated with central pontine myelinosis.¹⁴

Hypernatremia

Na >150 mEq/L.

More commonly pure water loss or water loss coupled with lesser degree of sodium deficit, e.g. diarrhea, lactation failure, increased insensible losses under warmer, osmotic diuresis, diabetes insipidus, renal immaturity. Rarely net sodium gain, e.g. excess administration of normal saline boluses or soda bicarbonate or improperly prepared formula.

Acute hypernatremia: Hypertonic ECF results in cell shrinkage, which can lead to intracerebral bleed or cerebral venous thrombosis.

Chronic hypernatremia: Cells generate osmoprotective amino acids and idiogenic osmoles to preserve neuronal cell volume.

Clinical features: Irritability, drowsiness alternating with irritability, excessive/high pitched crying, hyperpnoea, doughy skin, fever, tremulousness, seizures, focal deficit, coma.

- Signs of dehydration: weight loss, Urine Output >5 ml/kg/hr, Sp. Gr. <1005, Urine osmolarity < 200 (e.g. renal tubular immaturity, diabetes insipidus).
- Signs of over hydration, weight gain, UO normal or, Urine Na high, e.g. excess NaHCO₃/saline administration.

Treatment: Rate of decline in serum sodium should not be > 12 mEq/L per day as abrupt fall in serum osmolality may lead to movement of water into brain leading to brain edema with deleterious consequences.¹⁴

Hyper/hypokalemia

They are both associated with disturbances in systemic circulation and indirect effects on neurodevelopment. Hyperkalemia can occur even when urine output is normal and can result in sudden severe bradycardia and circulatory collapse. Routine monitoring of serum potassium is indicated

in preterm and sick neonates. Management is extrapolated from adult physiology and evidence to practices is not definite (Cochrane review).

NUTRITION

GOALS

- Calorie intake 80-100 cal/kg/day for term infant, and 110-165 cal/kg/day for preterm infant.
- Protein intake 3.5 gm/100 cal is appropriate, particularly in preterm infant.

ENTERAL FEEDING

Start enteral feeds as early as possible and increase as per tolerance.

Breast Milk

Numerous beneficial effects of breast milk have been demonstrated for term and near-term infants, including improved cognitive skills,¹⁵⁻²⁴ improved behavior ratings,²⁵⁻²⁷ Improved neurodevelopment has been related to the presence of long-chain polyunsaturated fatty acids (LC-PUFA; arachidonic and docosahexaenoic), which are found in human milk but not bovine milk. . ELBW babies in the breast milk group were more likely to have a Bayley Mental Development Index ≥ 85 , higher mean Bayley Psychomotor Development Index, and higher Bayley Behavior Rating Scale percentile scores for orientation/engagement, motor regulation, and total score. For every 10 ml/kg per day increase in breast milk ingestion, the Mental Development Index increased by 0.53 points, the Psychomotor Development Index increased by 0.63 points, the Behavior Rating Scale percentile score increased by 0.82 points. **In preterm babies breast milk should be the feed of choice and all efforts should be made to encourage mother and enhance milk production.**^{28,29}

If formula milk is used, several components have come under discussion:

- Polyunsaturated fatty acids (PUFA) are component of human milk and many formulas and have been associated with body growth vision and cognition.^{30,31}
- Adding milk fortifier to human milk improves calcium and protein accretion and greater weight gain and linear growth (short-term increase in OFC) compared with unfortified human milk.³²

Minimal Enteral Feeding and Necrotizing Enterocolitis (NEC)

Continuation of small non-nutritive amount (10 ml/kg/day) of enteral feed during initial days might be trophic for gut mucosa and intestinal enzymes and leads to better feed tolerance, once started and reduces total duration of parenteral nutrition.³³ Also, the risk of NEC is reduced. Among ELBW infants, surgical NEC is associated with significant growth delay and adverse neurodevelopmental outcomes at 18 to 22 months' corrected age compared with no NEC. Medical NEC does not seem to confer additional risk. Surgical NEC is likely to be associated with greater severity of disease.³⁴

PARENTERAL NUTRITION

Early use of parenteral nutrition may minimize protein loss and improve growth and neurological outcome in NICU graduates. There is significant negative protein balance (2% per day), if there is no amino acid supply in immediate postnatal period. Amino acid intake of 1.1 to 2.3 gm/kg/day can change protein balance to neutral to slightly positive side, even at low caloric intake.³⁵ Higher amino acid intake is required for optimal protein accretion. Early amino acid (AA) were associated with significantly better growth outcomes at 36 weeks' postmenstrual age, and fewer infants who received early AA were found to have suboptimal head growth at 18 months' CA.

SUMMARY

Maintenance of normal fluid and electrolyte status and good nutrition is essential for normal functioning of all body systems and plays vital role in improving survival and optimal neurodevelopmental outcome in sick neonates. We should try our best to use evidence based practices in the management, but unfortunately evidence may not be available for many current standard practices. So it is of utmost importance to keep our mind open and adopt evidence based changes in the management which is bound to happen in times to come.

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Follow-up Research—Some Methodological Issues

The ‘disability process’ involves a *postnatal impairment* becoming a *disability* in the early childhood, leading to a *handicap* later. Depending on the age at which outcomes are measured, we need to make sure which out of the three—impairment, disability or handicap—are we measuring. Whereas in the first two years developmental delay and tone abnormalities are important outcomes, neurodevelopmental disabilities (NDD) become the outcome measure later on. Neurodevelopmental disabilities are a diverse group of severe chronic conditions that begin at any point in development up to 22 years of age, usually lasting throughout a person’s life time.¹ NDD include the following specific conditions or syndromes: mental retardation, autistic spectrum disorders, attention deficit hyperactivity disorder, learning disorders, epilepsy, hearing impairment, vision impairment, CP and neuromuscular disorders.

Neurodevelopmental outcome studies continue to be reported from most parts of the world, but there is very little consistency in the entry criteria, measurement tools used as well as outcomes measured. These studies have been criticized for the overall poor quality and hence standards have been suggested for conducting developmental follow up studies.²⁻⁵ Major criticisms include inadequate sample size, heterogeneity of populations, short duration of follow-up, lack of control populations, lack of uniformity in assessment of outcome and definitions of handicap, and questions with regard to the representativeness of study samples and generalization of results to other populations.

The majority of studies published since the 1970s have been descriptive in nature attempting to monitor the outcomes associated with neonatal intensive care and to examine specific risk factors. Most studies are descriptions of longitudinal changes in outcome or cross-sectional in nature.⁶⁻⁸ The planning of such studies has been problematic, partly because

advances in technology and new therapies have, with few exceptions (for example, surfactant), been introduced haphazardly and without controlled trials. Thus, it is not surprising that follow-up studies have reported a patchwork of outcomes.⁴ An additional problem inherent in determining the long-term outcomes of very low birth weight infants is that, by the time meaningful assessments of outcomes such as school-age performance are obtained, neonatal treatment has also changed, and these changes may have affected later outcomes.⁹ Changes in the definitions of normal growth and cognitive outcomes over time also limit comparison between studies, as exemplified by the recently revised Bayley Scales of Infant Development-II, which is currently being used extensively in follow-up studies.

EVALUATING LONG-TERM OUTCOME STUDIES

There are several factors to be considered in evaluating long-term outcome studies.

SURVIVAL RATE

High mortality rates may indicate poor perinatal management, which may have a detrimental effect on the long-term outcome of the survivors. Increased mortality among high-risk infants may also be associated with apparently improved outcomes in the surviving low birth weight children, as those with the greatest potential for a poor outcome may have died.

REPRESENTATIVENESS OF THE STUDY SAMPLE

The majority of studies have been based on hospital samples that may not be representative of all the survivors in a specific region. Furthermore, hospital-based studies that include infants transported from community hospitals are biased by the selective referral of the sickest infants.

SAMPLE CHARACTERISTICS

Outcomes are likely to vary in relation to differences in how the samples are constituted. Sampling parameters to consider include;

- The range of birth weight and gestational age under study
- The rate of intrauterine growth failure
- Whether, children with congenital malformations or congenital infections are included
- Perinatal and neonatal therapies used and rates of complications
- Socio-demographic indicators

- Behavioral characteristics of the parents, including smoking and drug abuse
- Post-hospital-discharge medical care and complications
- Special interventions or stimulation programs.

THE NATURE OF CONTROL AND COMPARISON GROUPS

If studies are not composed of randomly assigned intervention and control groups, then differences between the groups being compared must be taken into consideration. At a minimum, study groups should be matched for factors such as race, sex, and parental socioeconomic indices (marital status, age, level of education, and occupation).¹⁰

DURATION OF FOLLOW-UP

Children must be followed to at least 18 to 24 months to assess severe neurodevelopmental problems. Follow-up to early school age is required to measure more subtle disturbances in areas such as fine motor ability, visual-motor skills, behavior, and learning.

CORRECTION FOR PRETERM BIRTH

There is, in general, a consensus that the child's age should be calculated from the mother's last menstrual period (postmenstrual age) rather than from birth (postnatal age), at least until the child has a postnatal age of three years.¹¹

OUTCOMES MEASURED

Adverse effects of low birth weight vary in accordance with how outcomes are assessed. Medical outcomes include abnormalities on physical and neurological exams, growth attainment, illness, and re-hospitalizations. Neurological outcomes, such as rates of CP or blindness, are not affected by socio-demographic factors and, thus, are good markers of biological risk. Neuropsychological measures that are sensitive to subtle degrees of dysfunction include intelligence, memory, speech and language, psychomotor abilities, academic achievement, behavior, and attention. Social competence, child temperament, and the impact of having a low birth weight or very low birth weight child on the family system are additional outcomes, but ones rarely considered in research studies.¹²⁻¹⁴ The measurement of functional abilities include ratings by the physician or caretakers¹⁵ of the child's ability to perform age-appropriate activities of daily living.

SAMPLE ATTRITION

Children lost to follow-up are more likely to come from lower socioeconomic groups who generally have poorer outcomes. If the attrition of children with poorer outcomes does not occur evenly from the study groups, then the study outcomes will be heavily biased.

The study design to be used in follow-up depends on the research question. For example;

- A randomized controlled trial for showing the effectiveness of an early intervention program
- A case control design for measuring and quantifying the risk factors
- A diagnostic test evaluation for comparing a screening test against a confirmatory test (gold standard)
- Descriptive (observational) studies to report neurodevelopmental outcomes at different ages.

BIAS IN OUTCOME RESEARCH

Every study design has bias more in some and less in others. Bias refers to any process, which tends to produce results or conclusions that are systematically different from the truth. A process which affects results or conclusion in a random way (i.e. not systematically) cannot be considered as bias. Bias can cause a study to conclude, for example, that there is no association between a risk factor and an outcome of interest, when in truth, there is an association, or vice versa. Most biases which threaten the validity of follow-up studies fall into one of three broad categories.

- Selection bias: Occurs when observations are made on a group of babies that has been assembled incorrectly.
- Measurement bias: Occurs when the methods of measurement are consistently dissimilar among groups of babies.
- Confounding bias: Occurs when two factors or processes are inter-related or ‘travel together’, and it is incorrectly concluded that one of the factors is the causal agent.

A clinical observation is valid if it corresponds to the true state of affairs. For the observation to be valid, it must be neither biased nor incorrect due to chance. It is useful to distinguish between two general kinds of validity—internal validity or strength of study and external validity or generalizability. Sampling bias occurs when observations and conclusions about one group of babies are generalized to other group, who is not similar. An impeccable study, with high internal validity, may be totally misleading when the results are generalized to certain other populations.

CONTROLLING FOR SELECTION BIAS

- **Randomization:** The only way to equalize all perinatal factors, known and unknown, is to assign the groups randomly, so that each baby has an equal chance of falling into one or the other group.
- **Restriction:** The babies, who are enrolled in a study can be restricted to only those possessing a narrow range or characteristics, forming a homogeneous study group, but this reduces the generalisability of the results.
- **Matching:** Babies can be matched as they enter the study so that for each baby in one group there are one or more babies in the comparison group with the same characteristics except for the factor of interest. Apart from age and sex matching may be done for factors like, stage or severity of HIE, rate of progression and prior treatments.
- **Stratification:** After data are collected, they can be analyzed and results presented according to sub-groups of babies or strata decided apriori.
- **Multivariate Analysis:** Is a method for simultaneously considering the effects of many variables. This is done by developing a mathematical model based on some assumptions, relating independent variables to the outcomes.

CONTROLLING FOR MEASUREMENT BIAS

- **Blinding:** In the assessment of outcome, in general, the more clear cut are the end points used, lesser the opportunity there is for bias. For example, we want to assess and compare the developmental outcome between the group receiving early stimulation and the group without early stimulation using Bayley Scale of Infant Development (BSID). The developmental therapist doing BSID should not know, which group the baby belongs to. She should not attempt to assign a score on the same day, as there would be a tendency to adjust the score based on clinical impressions.
- **Confounding:** “The term confounding refers to the effect of an extraneous variable that wholly or partially accounts for the apparent effect of an intervention (For example early stimulation) or masks an underlying true association. Thus, an apparent association between an intervention and outcome may actually be due to another variable. Alternatively, the apparent lack of an association could result from failure to control for the effect of some other factor. Methods by which potential confounding variables can be handled in a study include *random allocation*, *stratified allocation*, *matching* in analytic studies and restriction in either selection or analysis.

POLICY PERSPECTIVES

We need to appreciate that parents do have a right to know about long-term problems that might develop in their high-risk baby. Lack of consistency in information provided by different healthcare teams creates uncertainty and increases the stresses felt by parents.¹⁶

A country like India cannot yet afford to dedicate huge amount of resources for perinatal and neonatal intensive care services. Hence, the natural question that arises in the minds of planners and policy makers would be the possibility of increasing numbers of children with disability among those who survive after severe perinatal illnesses, extremely immature birth and serious neonatal complications. This necessitates availability of national data on outcome of NICU graduates and this means that:¹⁷

- Data should be collected for all infants <32 weeks' gestation and all those who get intensive care as well as recognized priority groups. These same children should have their health and developmental status ascertained at 1 and 2 years of age
- The data collection must become a core-funded aspect of clinical care
- Extra costs can be justified by the benefits that will follow in terms of what works and what does not
- We need to have capacity building programs for the pediatricians and the PHC doctors to equip them to provide follow-up services
- Mandatory national perinatal data collection should be extremely simple and feasible.

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Section 15

Counseling

- 35. Genetic Counseling—High Risk Pregnancy
- 36. Parent Counseling

Genetic Counseling— High Risk Pregnancy

Genetic counseling is a communicative process, which deals with human problems associated with the occurrence and or recurrence of a genetic disorder in a family (American Society of Human Genetics). This should include the possibility of prenatal diagnosis. Women, whose ethnic background, race, age, personal or family history places them at increased risk to have a fetus with genetic disease, should receive appropriate counseling.

High risk pregnancies (genetic risk) that require genetic counseling are as follows:

1. Advanced maternal age
2. Previous child Down syndrome/Positive triple test
3. Previous child with mental retardation
4. Previous child with single gene genetic disorder like thalassemia
5. Previous child with congenital abnormalities
6. Previous child with neural tube defect.

ADVANCED MATERNAL AGE

Maternal age is an important and independent risk predictor of adverse pregnancy outcomes. Advanced maternal age is associated with a higher risk of stillbirth throughout gestation, and the peak risk period is 37-41 weeks. Increasing maternal age is independently associated with specific adverse outcomes.¹ Advanced maternal age, after excluding confounders, correlated with very preterm birth (gestational age <32 weeks) [adjusted odds ratio (AOR) 1.51, 95% confidence intervals (CI) 1.04-2.19], low birth weight (birth weight <2500 g) (AOR 1.69, 95% CI 1.47-1.94) and perinatal death (AOR 1.68, 95% CI 1.06-2.65).²

Advanced maternal age is also associated with increased risk of cytogenetic abnormalities especially aneuploidies in the offspring

(Table 35.1). Recent reports based on large samples of oocytes or polar bodies have provided evidence for correlation between increased aneuploidy frequency and advanced maternal age.³

Table 35.1: Incidence of Down syndrome in relation to maternal age

<i>Maternal age at the time of child birth (in years)</i>	<i>Incidence of Down's syndrome</i>
20	1 in 1500
25	1 in 1350
30	1 in 900
35	1 in 380
37	1 in 240
39	1 in 150
41	1 in 85
43	1 in 50
45	1 in 28

The high risk of aneuploidies with advancing maternal age is possibly due to increased non disjunction of chromosomes. Different mechanisms have been proposed.

- **“Production line” hypothesis:** This theory proposes that oocytes mature in adult life in the same sequence as the oogonia entered meiosis in fetal life. Oogonia that enter meiosis later in life are more likely to be defective in the formation of chiasmata, and thus more likely to undergo non disjunction.
- **Defective microcirculation:** This hypothesis proposes that aneuploidy oocytes arise from a sequence of events. It begins with hormonal imbalance that causes a less-than-optimal microvasculature to develop around the maturing and mature follicles. The resulting decrease in the size of the peri-follicular capillary bed leads to hypoxia and a concomitant increase inside the follicle of carbon dioxide and anaerobic products, such as lactic acid. This in turn causes a decrease in the intracellular pH of the oocyte that diminishes the size of the spindle, with consequent displacement and nondisjunction of a chromosome. Recent molecular studies identified an abnormal mitochondrial function and redox potentials in aged oocytes.
- **Genetic Predisposition:** The possibility of the presence of a genetic predisposition to nondisjunction has also been proposed. There is some evidence of an autosomal recessive gene that facilitates meiotic nondysjunction.

The postulation hypothesized¹—95% of Down syndrome children inherit their extra chromosome from the mother, and in 80% or more of these,

the nondisjunction occurs in the first meiotic division, which is completed in the ovary.² The ovarian follicle containing the primary oocyte has no internal circulation. The compromised microcirculation hypothesis explains the occurrence of aneuploidy in primary and secondary oocytes, sperm precursor cells, tumor and embryonic cells. It also explains why women of all reproductive ages may have a Down syndrome child.⁵

The definitive method of excluding a cytogenetic abnormality in the offspring is a diagnostic study—amniocentesis to study the karyotype of the fetus. Invasive diagnostic tests are associated with a procedure related fetal loss of 0.5 to 1%.

Among high-risk mothers (advanced maternal age, abnormal triple screen, or both), many choose invasive testing as a first option, while others use the information derived from genetic sonography to obtain an adjusted risk for Down syndrome to guide their decision on genetic amniocentesis.⁴ Genetic sonogram will help to modify the risk so that an invasive test can be optimized.

Pre-implantation genetic aneuploidy screening (PGS) in the last decade has allowed embryo selection in patients with an increased incidence of embryonic numerical chromosome abnormalities (advanced maternal age, recurrent miscarriage and recurrent implantation failure). PGS for aneuploidy screening (PGD-AS), performed by polar body or blastomere analysis, is used in infertile patients treated with assisted reproduction technologies, especially in those with a poor prognosis, e.g. repeated IVF failure, advanced maternal age, or recurrent spontaneous abortion.^{6,7} Rapid prenatal diagnostic techniques like FISH and QF-PCR are newer developments that allow quick decisions. These may totally replace conventional cytogenetics in near future.⁸

PREVIOUS CHILD WITH DOWN SYNDROME

Recurrence risk of Down's syndrome will vary depending on the type of Down syndrome (whether nondisjunction or translocation) and maternal age.

THE CHANCE OF RECURRENCE OF TRISOMY 21 IN MOTHERS WHO HAVE ONE AFFECTED CHILD⁹

For counseling purposes the chance of recurrences of Down syndrome can be rounded off to 1% greater than the maternal age specific risk. Trisomy 21 spontaneous or induced abortion has the same recurrence risk consequences as the live birth of an affected infant.

PREVIOUS CHILD WITH ROBERTSONIAN TRANSLOCATION DOWN SYNDROME (TRANSLOCATION BETWEEN 21 AND 13/14/15/22 CHROMOSOMES)

The distinction between de novo and familial forms of translocation Down syndrome is crucial: this distinction is made by chromosomal studies of the parents (Table 35.2). For the de novo translocation, a recurrence risk figure of 1% is applicable (similar to nondisjunction Trisomy). In the case of familial Robertsonian translocation Down syndrome, the genetic risk for the female carrier is substantial. The risk to have a live born child with translocation Down syndrome is 10-15%. For the male carrier, the risk to have a child with translocation Down syndrome is small, about 1%. In case of 21/21 translocation carrier, the risk to have a Down syndrome with translocation is 100%.

Table 35.2: Recurrence risk of Down's syndrome

Affected child	Chromosome constitution		Risk to offspring
	Father	Mother	
De novo inherited	N	N	1
13/21, 21/ 22	N	C	10-15
13/21, 21/ 22	C	N	5
21/21	C/N	N/C	100

N—Normal, C—Affected Chromosome
Trisomy 21 and mosaicism—1 % risk of recurrence, parents karyotype not needed

PREVIOUS CHILD WITH MENTAL RETARDATION

Mental retardation now more commonly referred to as global developmental delay is characterized by **intellectual functioning below normal, and limitations in two or more of the adaptive skills.**

Several clinical series suggest that **a diagnosis or cause of the MC can be identified in 40-60%** of all patients undergoing evaluation.¹⁰ A careful clinical examination of mentally retarded child may provide some clue for the diagnosis of chromosomal disorder or genetic syndromes. Intracranial imaging offers valuable information in many patients with MR and should be considered particularly in patients with microcephaly, macrocephaly or neurological signs. In recent years **fragile X syndrome** has been recognized as the commonest cause of inherited mental retardation. All mentally retarded children should be investigated with a cytogenetic analysis (karyotype) at 500 band level and fragile X analysis should be done in all male MR children without any obvious cause. Fragile X analysis requires chromosomal analysis under special conditions and

molecular studies. Targeted FISH and molecular cytogenetic studies should be done when clinically indicated.¹¹

It is worth while to do screening investigations for metabolic disorders in all MC children. Specialized metabolic investigations may be done if the clinical features suggest a metabolic disorder. Regression of milestones is suggestive of a metabolic disorder. If mental retardation is associated with neurological manifestations, organomegaly and/or seizures storage disorders should be excluded.

Counseling of a couple with a MC child depends on the cause in the proband.

- **Chromosomal disorders:** Aneuploidies like Trisomy 21/18/13 due to non disjunction have a recurrence risk of 1% over and above the maternal age related risk. In case of other chromosomal abnormalities, the parents (both mother and father) should be evaluated for balanced chromosomal rearrangements. If the parent's karyotypes are normal the recurrence risk is negligible—to the tune of 1%. However, fetal karyotype by amniocentesis can be done to exclude chromosomal abnormalities. If one of the parents has the chromosomal abnormality (balanced rearrangements) the recurrence risk will depends on various factors like length of translocated segment, involved chromosomes, type of chromosomal rearrangements etc. Fragile X syndrome is a X linked condition with recurrence risk of 50% in male siblings, half of the heterozygote daughters may also be clinically affected.
- **Metabolic Disorders:** Since metabolic disorders are single gene disorders, counseling similar to single gene disorders.
- **Central nervous system malformations:** see malformations
- **Perinatal asphyxia:** Recurrence risk in future pregnancies is negligible. The couple should be advised optimal obstetric care and neonatal management. A targeted anomaly scan is advised at 16-18 weeks.
- **No definite etiology identified:** If no definitive etiology is identified, then the empiric recurrence risk of mental retardation in sibling is approximately 5%.

PREVIOUS CHILD WITH SINGLE GENE DISORDERS

Single gene disorders follow Mendelian laws of inheritance making it possible to predict the risk of recurrence.

In autosomal dominant disorders the risk to an affected offspring is 50%. However, incomplete penetrance and variable expressivity will modify the risk. New mutations are frequent causes of the appearance of a genetic disease in an individual with no previous family history of disorder (example

Achondroplasia child to normal parents). Risk of recurrence in the sibling depends on the genetic make up of the parents. If one of the parents is affected, there is 50% chance of recurrence in siblings. If both parents are normal, probably the disorder is due to a new mutation and recurrence risk in sibling is negligibly low.

In autosomal recessive disease, both parents are carriers of mutant gene and recurrence risk in sibling is 25% (1 in 4). Parents of children with rare autosomal recessive disease are often consanguineous.

In case of X linked recessive disorders (e.g. Hemophilia), mother may be a carrier for the disease. In such situations, risk of recurrence in the male offspring is 50%. In case of a female offspring, 50% of them will be carriers of the disease. In case with mother is not a carrier (sporadic mutation in the affected child) recurrence risk is negligibly low. Only in cases with gonadal mosaicism, there will be an increased recurrence risk.

PREVIOUS CHILD WITH MALFORMATIONS

In predicting risk of malformations, first step is trying to identify whether the malformation is isolated or part of a syndrome. If a syndrome is identified, recurrence risk will depend on the inheritance pattern of that syndrome. If a definitive syndrome is not recognizable or the malformation is isolated, recurrence risk is as for multifactorial disorders.

<i>Causes of ventriculomegaly</i>	<i>Recurrence risk</i>
• Meningomyelocele	5%
• Dandy Walker malformation	5%
• Lissencephaly	0 to 25%
• Holoprosencephaly	10%
• Hydrolethrus syndrome	25%
• Chromosomal	1 to 10%

NEURAL TUBE DEFECT (NTD)

Neural tube defects are the most common congenital malformations. These include anencephaly, iniencephaly, encephalocele, meningomyelocele and spina bifida. The reported prevalence varies geographically (6.3 to 10.92 per 1,000 births in Ireland and Wales to 1 per 1,000 in US). The prevalence of NTD in various parts of India is reported from 0.5 to 11 per 1,000 births.

The risk of recurrence of an NTD after birth of one affected child is 3-5%, which is **10 times higher than that of general population**. It increases to 10% after two affected children and 25% after three affected

children. Affected child should be examined, try to identify a syndromic cause, if present. These syndromes carry a very different risk of recurrence depending upon the mode of inheritance and may not be amenable to prevention by folic acid. Some NTDs are associated with a polymorphism in MTHFR gene (677 C-T).

The Medical Research Council on Vitamin Study Research Group (1991) identified that if a woman, who previously delivered a baby with NTD, took folic acid supplement before conception and through out first trimester, the risk of recurrence is reduced by 72%. Efficacy of periconceptual folate has been demonstrated in the Indian population (ICMR multicentric trial). It is recommended that 4 mg of folic acid be given to the mothers with previous child with NTD in periconceptual period. Unfortunately, 90-95% cases of NTD are sporadic, and occur without any family history, and hence, not amenable to prevention.

As a primary prevention a lower 0.4 mg of folic acid is recommended to all women in the reproductive age group. It has been proposed to fortify breakfast cereals or bread to provide the recommended dietary allowances. However, the efficacy and safety of this public health intervention is yet to be validated.

AMNIOCENTESIS

Advances in techniques in prenatal diagnosis have added new dimensions to the genetic counseling. It is now possible to determine, in advance, whether the fetus is affected or not with a specific genetic disorder. Amniocentesis is the commonly used technique.

Amniocentesis is the aspiration of amniotic fluid for various biochemical and genetic tests. The test is best performed at 16-17 weeks of gestation. At this time, there is sufficient number of viable amniocytes. At this gestation medical termination of pregnancy is considered safe for the woman, should an abnormality be found.

- Amniocentesis is routinely performed in an outpatient facility under aseptic precautions. An ultrasound examination is done before the procedure to evaluate fetal number and viability, perform fetal biometric measurements, establish placental location and estimate amniotic fluid volume. It is preferable to screen the fetus for any congenital malformations.
- The needle insertion site is chosen in the abdomen so that an optimal pocket of amniotic fluid is present. If possible, it is preferable to avoid the placenta; if not possible select the thinnest portion of placenta possible through which the needle can be inserted. The umbilical cord

insertion site should be identified and avoided. The maternal bowel and bladder also should be located, as these should likewise to be avoided.

- A local anesthetic may be used (2 to 3 ml of 1% xylocaine), but not necessary always. The maternal skin should be cleaned with an antiseptic solution (iodine based and spirit based) and sterile drapes are placed around the insertion site. A 20 or 22 G spinal needle is inserted under ultrasound guidance to the amniotic sac. Ultra sonographic monitoring with continuous visualization of the needle should be performed throughout the procedure.
- At this gestation 20 to 30 ml of amniotic fluid is usually aspirated. The first several milliliters (2 ml) of amniotic fluid is aspirated to a 2-5 cc syringe. These first few milliliters are theoretically most likely to contain maternal cells and should not be used for cytogenetic or molecular studies. However, this can be used for biochemical estimations like AFP.
- Amniotic fluid and urine are often indistinguishable in appearance. The crystalline arborization pattern characteristic of amniotic fluid is observed if the fluid is allowed to dry on an acid cleaned slide and examined under low power (*Ellias et al 1979*). However, only rarely are any test is necessary.
- Bloody amniotic fluid is aspirated in 1% to 2% cases. If the needle is inserted transplacentally, there is more chance of bleeding. The blood, which is almost maternal in origin, usually does not adversely affect the amniotic cell growth. Bloody tap does not have an adverse pregnancy outcome. By contrast, brown or dark red amniotic fluid, which is suggestive of prior intra-amniotic bleeding, is associated with poor fetal outcome. Pregnancy loss eventually occurs in about one third of cases (*Milunsky 1986*).
- The administration of Rh immunoglobulin (Rh Ig) to prevent Rh isoimmunisation in unsensitized women with Rh positive fetuses remains controversial, but almost all now advocate its routine use. The dose to be administered remains controversial. The ACOG recommends that 300 μg of RhIg should be administered for an exposure of 30 ml of fetal blood (*ACOG 1999*) whereas, in UK it is 50 μg before 20 weeks and 100 μg thereafter (*Turnbull and Mackenzie 1983*).
- After the amniocentesis the fetal heart rate is monitored. It is preferable to show the fetal heart motion on ultrasound scan to the patient to reduce the anxiety. Observation for 3-4 hours after the procedure is required and is instructed to report if there is vaginal bleeding, cramps or fever. Routine normal activities can be resumed following

the procedure; However, strenuous activities, long distance travel and coitus are to be avoided for a couple of days.

- In case of multiple gestations, amniocentesis can usually be performed on all fetuses separately, provided there is enough amniotic fluid. The two sacs should be aspirated sequentially under ultrasonographic visualization and the samples should be labeled properly to avoid wrong result interpretation. Dye installation technique can be used for the identification of different sacs, but not used nowadays in most of the centers.
- The safety of the traditional amniocentesis has been addressed by several large collaborative studies. In general there is a procedure related fetal loss of 0.5%.

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Parent Counseling

Birth of a baby fulfills one of the most fundamental needs of human life and is a moment of great joy and celebration for the whole family. Parents must have the necessary skills to provide a healthy start to their babies who are a source of joy in the present and the greatest asset and hope for the future.

HEALTH AND NUTRITION OF MOTHER

Women are the creators of progeny. Health and well being of a baby is intimately linked with the health and nutrition of her mother. Healthy mothers produce healthy babies and healthy and well informed mothers are in a better position to look after the health and well being of their babies. The growth of a baby in the womb depends upon the quality of the seed (genetic endowment) and adequacy of soil (maternal health and nutrition before and during pregnancy). Adolescent children (especially girls) must receive family life education and optimal nutrition (especially supplements of iron, folic acid and calcium) so that they are nutritionally well prepared to meet the challenge of parenthood. During peri-conceptual period (just before conception and during first 8 weeks of pregnancy) mother should have adequate intake of folic acid (500 microgram /day) to prevent occurrence of neural tube defects and cleft lip.

Health and well being of the fetus depends upon the health and nutrition of the mother (not the father!) because she is both the seed as well as the soil in which baby is nurtured for 9 months.

—Meharban Singh

After initial 3-4 months of pregnancy (especially after mid-pregnancy), mother must take additional 250-500 calories and 30 g protein every day to ensure her good health and provide nutrition to her growing baby. She should consume a high fiber diet comprising of whole grain

cereals, like wheat and brown rice, pulses, legumes, fresh green leafy vegetables, seasonal fruits, milk and milk products. The non-vegetarian women can take chicken, lean meat, fish and eggs. Adequate intake of omega-3 fatty acids and docosahexaenoic acid (DHA) is also crucial to enhance brain growth of the baby in the womb. Apart from wholesome balanced diet, pregnant lady should also take nutritional supplements including iron, folic acid, vitamin A, vitamin D, iodine, calcium, zinc and DHA.

WHAT TO AVOID DURING PREGNANCY?

During first 3 months of pregnancy various organs of the baby are taking shape and if anything goes wrong in the environment of the baby at this stage, there is a risk of development of congenital malformation (s). Mother should strictly avoid any self-medications at this stage and seek the help of her doctor for taking medicines even for common problems like fever, headache and vomiting.

Practical Tip

During early pregnancy every drug is potentially harmful to the growing fetus unless proved otherwise. A drug which is entirely safe for the pregnant woman, may be unsafe or even dangerous for her baby in the womb. But during nursing, a drug that is safe for the lactating mother is generally safe for her suckling infant.

She should not get herself exposed to any X-rays. Smoking, chewing tobacco, consumption of alcohol or drugs of abuse must be avoided as they can adversely affect the growth of the baby and may cause serious developmental defects. Excessive intake of tea, coffee and cola drinks should be avoided due to risk of adverse effects of caffeine. Whenever, a woman visits any doctor for a health problem, she must inform her doctor if she is pregnant so that the doctor prescribes those medicines which are safe both for the mother as well as her growing baby.

THREE MANTRAS OF NEWBORN CARE

After the initial expert care by the midwife or obstetrician to ensure safe delivery and assist the baby to adapt from a dependent in utero abode to an independent extrauterine existence, the care of a newborn baby is guided by three principles. These principles include early and exclusive breastfeeding, ensuring that the baby is kept warm and effectively clothed and preventing development of any infection from visitors and environment.

BREASTFEEDING

Breastfeeding is the birth right of every baby and like mother's love there is no substitute for mother's milk. Breast milk is an ideal drink for all

babies whether big or small and healthy or sick. The milk of a mother is best suited to serve the biological needs of her baby and no baby should be denied the milk of her mother.

Breast milk has unique biological and chemical composition, is easily digestible and is loaded with anti-

infective substances. Breastfed babies have reduced risk of infections (diarrhea, cough and cold, pneumonia), non-infective disorders (allergy, bronchial asthma, eczema) and certain adult-onset diseases like obesity, diabetes mellitus, high blood pressure, coronary artery disease and stroke. And breast milk fed babies are smarter with higher IQ (compared to formula-fed babies) because of high content of DHA and lactose in the human milk. Breastfeeding is a boon for the suckling mother too because it is convenient, provides partial contraception, reduces the risk of post-delivery bleeding and provides protection against cancer of breast and ovaries later in life. Breastfeeding also helps the mother to regain her figure and pre-pregnancy body weight earlier because energy stores laid down during pregnancy are consumed faster during nursing.

The baby should be placed on the tummy of the mother immediately after delivery to promote bonding and breastfeeding. Baby should be put to the breast within half to one hour of delivery or as soon as the mother has recovered from the stress and fatigue of labor. Even when baby has been born by cesarean section, she should

be put to the breast as soon as the mother has recovered from the effects of anesthesia. The practice of giving glucose water, honey, tea or *ghutti* as first feed is condemned. The initial watery yellow milk which is secreted during first 1-3 days (colostrum) must never be denied to the baby. It is rich in proteins and protective antibodies and works like a “vaccine shot” to protect the delicate baby. The baby should be fed on a demand schedule (and not by clock) and most babies would like to take feeds every 2-3 hours. Cry is the commonest signal of hunger and if a baby is not crying due to a wet or soiled diaper, she should be put to the breast. The baby should be given exclusive breastfeeding during first 6 months (even water should not be offered in hot summer

Nectar of life

Nature is supreme. When a baby is born, a readymade biologically unique drink is available under the influence of various hormones produced during pregnancy. Mother craves to put her baby on the breast while baby is keen to suckle. Breastfeeding is complete nourishment for them both, not only for their body but as well for their soul.

Practical Tip

During the period of exclusive breastfeeding, there is no need to give any supplements of vitamins and minerals to healthy full term babies. The quality of breast milk can be enhanced by taking a balanced nutritious diet and supplements of micronutrients by the nursing mother

months) of life. When your child is thirsty in summer, she is likely to drink more milk and will have better weight gain.

When your baby is small or sick and cannot suck from the breast, she can be given expressed breast milk (EBM) with a spoon or *paladay*. Milk can be expressed manually or by a mechanical or electrical breast pump. Before expressing the milk, baby should be encouraged to suckle on the breast to promote lactation. Avoid bottle feeding due to risk of infection and nipple confusion.

HOW TO KNOW THAT BABY IS GETTING ENOUGH MILK?

When baby is adequately fed, she is happy and playful for 2-3 hours after the feed. The baby should pass dilute water-like urine at least 6-8 times during the day and while breastfeeding the milk should drip from the other breast. The best criterion that the baby is receiving adequate milk is the satisfactory weight gain at a rate of 30 g, 20 g and 10 g per day respectively during the three 4-monthly blocks during first year of life. Excessive crying alone should not be taken as an evidence of unsatisfactory lactation because babies cry due to a variety of causes like discomfort of wet napkins, intestinal colic or wind, exposure to cold or excessive clothing, insect or mosquito bites, boredom, etc.

HOW TO ENSURE ADEQUATE LACTATION?

A large number of traditional foods are credited to enhance lactation but there is no scientific evidence for their efficacy. Mother should take additional 550 calories/day to meet the energy cost of lactation and take balanced nutritious diet with plenty of liquids. The diet of nursing mother should be supplemented with commercially available micronutrients and DHA to enhance the nutritional quality of her milk. The best strategies to enhance milk yield include willingness or keenness on the part of the mother to breastfeed, freedom from pain and anxiety, relaxed state of mind and a vigorously sucking infant.

PROVISION OF WARMTH

The newborn babies lack the coping mechanisms to keep themselves warm due to their poor capability to generate body heat. After birth the baby should be promptly dried and effectively covered to prevent fall in body temperature. Bath should be delayed to next day or till the body temperature of the baby has stabilized. The cultural practice of keeping the baby next to the mother in her bed is useful to provide warmth to the baby and promote breastfeeding. During winter special

care should be taken to keep the room warm with a radiator or hot air blower. A basin full of water should be placed in front of the heater to increase humidity in the room. The windows should be kept closed so that there is no draughts of cold air in the room. It is a good idea to keep the baby in a room wherein sunlight peeps through a window or a door. The baby should be effectively clothed with woolens from top to bottom with a cap, mittens and socks. *When effectively covered, her trunk should feel warm to touch and her hands and feet should be reasonably warm and pink.* The baby can be kept warm by providing direct skin-to-skin contact by placing the naked baby in direct contact with your bosom.

Practical Tip

The room temperature that feels slightly uncomfortable or warm to an adult is usually satisfactory to serve the biological needs of the baby.

PREVENTION OF INFECTIONS

There is no need to apply any dressing or bandage over the navel. Skin should be kept clean by daily bath or sponge depending upon the weather. Natural orifices of the body like eyes, nostrils, mouth, nose, ears, bottom etc should be cleaned with a wet cotton or damp cloth. Avoid instillation of any *surma* or *kajal* in the eyes due to risk of irritation, cross infection or even lead intoxication. Never instill any oil into the nostrils and ears because of risk of aspiration pneumonia and fungal infection. In newborn babies instillation of few drops of colostrum into the eyes has been shown to reduce the risk of development of sticky eyes.

USEFUL TRADITIONAL HEALTH CARE PRACTICES

A number of traditional practices for the care of newborn babies are useful and should be promoted (Table 36.1).

Table 36.1: Useful traditional practices in the care of newborn babies

- Delivery at mother's place
- Isolation of mother-baby dyad for 40 days
- Oil massage
- Universal and prolonged breastfeeding
- Instillation of colostrum in the eyes to prevent conjunctivitis
- Use of cup and spoon or *paladay* for top feeding
- Baby sleeping on mother's bed

Body massage is popular and credited to improve circulation and muscle tone, relieves fatigue and provide relaxation and sense of relief. Touch is believed to send stimulatory messages to the brain to enhance neuro-

motor development of the baby. Any non-medicated non-irritating vegetable oil like coconut oil or olive oil can be used for massage. Massage should be done gently by the mother (not by an *ayah*) and she should interact and talk with her baby while doing massage and performing other chores like feeding, bathing, changing clothes, toilet care, etc.

IDENTIFICATION OF A SICK BABY

A large number of problems in newborn babies are either physiological or minor developmental variations and are of no consequence and do not need any treatment. Most babies born at term are healthy and do not develop any health problems or difficulties when you protect them against cold, promote exclusive breastfeeding, ensure asepsis and cleanliness and provide your tender loving care. At times, the baby may develop a serious health problem and vigilant parents should be able to identify it, so that there is no delay in taking the child to a specialist or hospital (Table 36.2).

Table 36.2: Common clues of sickness in a baby

- Inactive baby with refusal to take feeds or choking during feeds
- Excessive irritability or inconsolable crying
- Cold and pale extremities or fever
- Watery diarrhea
- Persistent or green-colored vomiting, abdominal distension and constipation
- Rapid breathing, chest indrawing, groaning and cough
- Jaundice extending up to palms and soles
- Bleeding from any site
- Seizures, up rolling of eyes or vacant stare
- Superficial infections like conjunctivitis, umbilical sepsis, boils, oral thrush, etc.

PARENTAL ROLE IN THE NICU

An increasing number of preterm, small and sick newborn babies are being provided technology-based intensive care in the neonatal intensive care unit (NICU). The prolonged stay of the baby in NICU is associated with anxiety, uncertainty, emotional trauma, and lack of bonding between the baby and her parents and elder siblings. The family dynamics are greatly disturbed due to physical stress, emotional turmoil and financial implications due to high cost of neonatal intensive care.

Most neonatologists tackle these issues by encouraging parents (especially mother) to visit their babies in the NICU and by handling aforementioned issues with equanimity, compassion and caring attitude. The frightening scene

of NICU is demystified by the health team by constantly informing and involving the family in the care of their baby. The mother is encouraged to touch and talk with her baby and provides routine care under the guidance of nurses. She should provide intermittent skin-to-skin contact (Kangaroo-mother care) which is credited to provide warmth and stability to the baby, enhance mother-baby bonding and promote breastfeeding. Parents should provide visual and auditory stimuli to their baby and try to establish eye-to-eye contact. Family should remain in close contact with the health team to receive necessary emotional support and professional guidance.

FATHER'S ROLE

Baby care is a full time job and quite a tiring task if left to mother alone. It is important that both parents should share the joys and jolts of bringing up the children. Father can help in many ways by doing certain tasks for the baby or by helping the spouse in various household chores. Most mothers provide low key stimulation to the baby like gentle rocking, cuddling, caressing, singing and soothing activities. On the other hand fathers tend to handle the baby more roughly, making lot of noise while rocking and bouncing the baby. When father actively participates in baby care, it leads to better inter-parental harmony and peace at home. It is important that both parents should accompany the baby when they visit the doctor for vaccinations and health check-up.

The chapter is based on excerpts from a popular parenting manual by the author, *The Art and Science of Baby and Child Care*, Sagar Publications, New Delhi, 3rd edition 2007.

PARENTING THE HIGH-RISK NEWBORN

1. Parenting is an art with a strong scientific basis.
2. In the community there are many positive along with few negative harmful practices.
3. Ultimately parents and not the doctors/nurses is the custodian of the newborn.
4. Teach them the science behind the art of parenting in a non-technical way.
5. High risk baby is perceived as different, taking away the natural parenting instincts.
6. Doctors/Nurses as parents of high risk newborns are no different from lay parents.
7. Participation and partnership in baby care takes away the undue emotional burden.
8. Breast feeding, bedding in and early stimulation help to sustain parental bonding.
9. Try to involve the father in all baby care activities and mother in decision making.
10. The family, especially the grand parents forms the best support system for mother.

Index

A

- Adverse effects of postnatal corticosteroids 195
- Apnea 101
 - doxapram 111
 - management 105
 - monitoring and evaluation 104
 - neurodevelopment 102
 - pathophysiology 101
 - prevention and treatment 105
 - antenatal steroids 106
 - blood transfusion 106
 - carnitine supplementation 108
 - CO₂ inhalation 107
 - immunization 108
 - kangaroo mother care 106
 - kinesthetic stimulation 108
 - methylxanthines 109
 - noxious stimuli 106
 - oxygen supplementation 107
 - pharmacological treatment 109
 - position 108
 - prevention of prematurity 105
 - sensory stimulation 107
 - temperature 107
 - role of home monitoring 105
 - tocolysis 106
- ventilation 111
 - continuous positive airway pressure 111
 - high-flow nasal cannulae 112
 - intubation and assisted ventilation 112
 - nasal intermittent positive pressure ventilation 112
- Asphyxia causes neurological brain deficits 45
 - neuropathology 47
 - basal ganglia and brainstem 48
 - cerebral edema 47
 - focal cerebral infarction 48
 - parasagittal injury 48
 - selective neuronal necrosis 47
 - white matter injury 48
 - primary neuronal injury 46
 - secondary neuronal injury 46
 - apoptosis 47
 - excitotoxic amino acid injury 46
 - free radical injury 46
 - nitric oxide 47
- Assisted reproductive technique 319
 - complications due to multiple pregnancies 320

- efficacy vs safety 320
- genomic imprinting 323
- malformations in different organ systems 321
 - childhood cancer 32
 - evaluation of published studies 321
 - growth 323
 - neurological problems 322
 - retinopathy of prematurity 323
 - use of medical services 323

B

- Benefits of postnatal corticosteroids 195
- Brain injury 33
- Brain-oriented management of perinatal asphyxia 52
 - antioxidants (Allopurinol) 54
 - calcium channel blockers 54
 - hyperbaric oxygen treatment 54
 - magnesium sulphate 54
 - predictors of outcome 55
 - acidosis 56
 - APGAR score 56
 - cerebral edema and increased ICP (>10 mm Hg) 57
 - fetal distress 55
 - intra-uterine passage of meconium 56
 - MRI findings 57
 - neonatal seizures 56
 - outcome in relation to severity of HIE 56
 - prolonged depression (lower extended APGAR score) 56
 - resuscitation in room air versus 100% oxygen 53
 - selective head cooling 53
 - systemic hypothermia 53

C

- Cardio-respiratory and neurological depression 41
- Cerebral autoregulation 13
- Clinical examination protocol 209
 - neurobehavior 211
 - neurobehavioral assessment 211
 - neuroimaging 214
 - CT scan 214
 - EEG 215

- magnetic resonance imaging (MRI) 214
- neurosonogram 214
- Physiological brain imaging 215
- neurological examination 213
- physical examination 209
- Cornblath's 'operational threshold' 76

D

- Developmental evaluation 243
 - assessment of vision in early infancy 251
 - assessment of hearing loss in early infancy 253
 - assessment of retinopathy of prematurity (ROP) 252
 - audiometry and BERA 255
 - brainstem evoked response audiometry (BERA) 256
 - visual development 251
- developmental assessment — below 2 years 244
 - ten commandments in assessment 244
- tools and techniques in developmental assessment 245
 - CDC grading for major motor milestones 249
 - developmental assessment scale for Indian infants (DASII) 246
 - Trivandrum developmental screening chart (TDSC) 245
- Discharge protocol 225
 - assessment of the child's home environment 228
 - home environment 228
 - tools 229
 - discharge planning 225
 - checklist before discharging a high risk neonate 225
 - checklist of NDD with definitive therapy 227
 - role of developmental therapist 225
 - role of primary care physician 225
 - role of treating pediatrician/neonatologist 225

E

- Early stimulation after discharge 264
 - babies need 'walls' around them 264
 - babies need peace and quiet 264
 - hearing 266
 - playing music 266
 - talking and imitation 266
 - newborn stimulation at home 265
 - bold patterns with strong contrast 265

- making faces 265
- moving objects 266
- vision 265
- touch 267
 - baby massage 267
 - rocking, walking and swinging 268
 - setting 267
 - technique 267
- touch therapy 268
 - touch-effect on infants 269
- understand her 'cues' 264
- waiting guest 264
- Early stimulation in NICU 259
 - aims 259
 - early intervention and parents 261
 - importance 260
 - newborn stimulation in NICU 263
 - over stimulation 262
 - precautions 262
- Early stimulation protocol 270
 - 8-10 months period
 - activities 274
 - 12-15 months period 275
 - 4-6 months period 272
 - auditory stimulation 272
 - general activities 272
 - 6-8 months period 273
 - general activities 273
 - 10-12 months period 274
 - activities 274
 - 0-2 months period 270
 - activities 271
 - auditory 270
 - tactile 271
 - vestibulo/kinesthetic 271
 - visual 270
 - 2-4 months period 271
 - auditory 271
 - general stimulation 272
 - tactile stimulation 271
 - visual 271
- Etiology and risk factors for perinatal asphyxia 48

F

- Follow-up protocol 230
 - behavioral problems/learning disorders 234
 - developmental assessment 234
 - recommended schedule 234
 - function assessment 235
 - general care/medical issues 231
 - growth, nutrition and medical assessment 230

- neurological examination 232
 - abnormal neurological signs on newborn 233
 - active tone 233
 - assessment of passive tone 232
 - cranial nerve examination 233
 - postural reflexes at 9 months 233
 - primitive reflexes at 3 months 233
 - red flags 233
- nutrition 231
- Follow-up research—some methodological issues 338
- bias in outcome research 341
 - controlling for measurement bias 342
 - controlling for selection bias 342
 - policy perspectives 343
- evaluating long-term outcome studies 339
 - correction for preterm birth 340
 - duration of follow-up 340
 - nature of control and comparison groups 340
 - outcomes measured 340
 - representativeness of the study sample 339
 - sample attrition 341
 - sample characteristics 339
 - survival rate 339

G

- Genetic counselling high risk pregnancy 347
 - advanced maternal age 347
 - amniocentesis 353
 - neural tube defect (NTD) 352
 - previous child with Down syndrome 349
 - previous child with malformations 352
 - previous child with mental retardation 350
 - previous child with single gene disorders 351
- Granulocyte transfusions 167

H

- Hearing stimulation in early pregnancy 291
 - early stimulation for hearing impairment 291
 - general activities 292
 - techniques 292
- High risk newborn 3
 - at-risk concept 3
 - environmental factors 7
 - follow-up and early intervention 4
 - intrauterine infections 6
 - low birth weight 5
 - newborn encephalopathy 5
 - policy implication 7
- Hypoglycemia 73

- best screening tools 77
- clinical diagnosis 77
- epidemiology 75
- impact on neurodevelopment 74
- pathophysiology 73
- prevention 78

I

- Impact of perinatal asphyxia on neurodevelopmental outcome 42
 - attention deficit hyperactivity disorder and behavioral problems 45
- autism and pervasive development disorders 45
- cerebral palsy 42
 - ataxic CP 43
 - athetoid (dyskinetic) CP 42
 - hemiplegic CP 43
 - spastic tetraplegic CP 43
- epilepsy 44
- hearing impairment 44
- learning disability 44
- visual impairment 44
- Impairment of placenta or pulmonary gas exchange 41
- Inborn errors of metabolism (IEM) 88
 - common neurological presentations associated with IEM 89
 - acute encephalopathy 90
 - ataxia 90
 - chronic encephalopathy with non-neural involvement 90
 - chronic encephalopathy without non-neural involvement 90
 - movement disorders 90
 - myopathy 90
 - seizures 90
 - stroke 90
 - current understanding of pathophysiology 88
 - accumulation of a normally minor metabolite 89
 - accumulation of a substrate 88
 - deficiency of a product 89
 - secondary metabolic phenomena 89
 - impact on neurodevelopment 89
 - investigations 91
 - management and prevention 91
 - treatment 92
 - immediate therapy 92
 - long-term treatment 92

L

- Late neurological disability associated with hypoxia-ischemia 57
- Lesch-Nyhan disease 90

M

- Meconium aspiration syndrome (MAS) 117
 - epidemiology 118
 - guidelines for management 120
 - antibiotics 122
 - extracorporeal membrane oxygenation (ECMO) 122
 - nitric oxide 122
 - sildenafil 122
 - steroids 121
 - surfactant therapy 121
 - ventilation 120
 - guidelines for the prevention 119
 - amnioinfusion 119
 - intrapartum monitoring 119
 - intrapartum suctioning 119
 - post delivery intubation and endotracheal suctioning 120
 - prevention of post term pregnancy 119
 - pathophysiology and impact on neurodevelopment 117
- Monitoring tools for perinatal asphyxia and their clinical value 49
 - clinical assessment after birth 50
 - multi-organ dysfunction 50
 - severity of encephalopathy 50
 - intra-partum fetal monitoring 49
 - electronic fetal monitoring (EFM) and fetal scalp pH monitoring 49
 - fetal ECG analysis 49
 - postnatal investigations 50
 - cerebral blood flow velocities 51
 - cranial ultrasound 50
 - CT scan 51
 - EEG and amplitude integrated EEG (aEEG) cerebral function monitoring 52
 - magnetic resonance imaging (MRI) 51
 - magnetic resonance spectroscopy 52
- Motor stimulation in early infancy 279
 - creeping 281
 - intervention for head control 279
 - intervention to promote crawling 281
 - intervention to promote rolling 280
 - intervention to promote sitting 282
 - intervention to promote standing 283
 - interventions for development of hand function 284
- Multiple fetal pregnancies 312
 - impact on neurodevelopment 312
 - assisted reproductive technology (ART) 313
 - factors in pregnancy and labour 313
 - fetal reduction and vanishing twin syndrome 316
 - growth discordance 314
 - intra-uterine death of one twin 314

- monochorionic twin pregnancy 313
- twin to twin transfusion syndrome (TTTS) 314

N

- Neonatal jaundice 82
 - bilirubin causes brain damage 82
 - expected long-term sequelae of severe jaundice 83
 - BERA 83
 - MRI 83
- Neonatal seizures 62
 - duration of seizure 64
 - EEG 65
 - etiology 63
 - gestational age 65
 - management of neonatal seizures 66
 - management of seizure 66
 - neuroimaging 65
 - neurological examination 66
 - origin of seizure 64
 - prevention 66
 - risk of seizures and clinical circumstances 62
 - screening and diagnosis 66
 - serious risk factor 62
 - timing of insult 65
 - type of seizure 63
 - clonic 64
 - myoclonic 64
 - subtle 63
- Neonatal sepsis 157
 - diagnosis 159
 - epidemiology 158
 - investigations 159
 - management practices in a neonate with suspected sepsis 163
 - prevention of neonatal sepsis 163
 - pathophysiology and impact on neurodevelopment 157
 - treatment 161
- Neonatal shock 143
 - cerebral blood flow (CBF) 145
 - etiology 145
 - hypotension and CNS morbidity/ neurodevelopmental outcome 147
 - low CBF and long term outcome 149
 - low cerebral blood flow and CNS morbidity/neurodevelopmental outcome 148
 - phases of neonatal shock 144
 - physiology 144
 - reliability of clinical parameters in assessment of cerebral blood flow in preterm babies 145
 - treatment of low SVC flow and neurodevelopment outcome 152

- treatment of shock and
 - neurodevelopmental outcome 150
 - corticosteroids 152
 - inotropes (dopamine versus
 - dobutamine) 151
 - volume expansion 150
 - volume expansion versus inotropes 150
 - Neonatal transport 186
 - acute complications—pneumothorax 202
 - CLD/BPD 202
 - adjuncts—surfactant 202
 - asynchronous breathing 201
 - duration of ventilation 201
 - factors in mechanical ventilation 198
 - PaCO₂ 198
 - PaO₂ 200
 - pH 199
 - impact of neonatal transport on outcomes 186
 - in-utero transport 186
 - mean airway pressure and optimal lung volume 200
 - communication 189
 - documentation 189
 - early recognition 187
 - ethics 189
 - logistic issues in transfer of neonates—
 - duration of transport 188
 - monitoring during transfer 188
 - networking 188
 - patient selection 187
 - responsibilities of referring center 188
 - reverse transfer 189
 - stabilization before transfer 188
 - standard protocols for neonatal transport 189
 - nursing issues 201
 - organization of a neonatal transport service 189
 - drugs 190
 - equipment 189
 - neonatal transport team 189
 - transport ambulance 189
 - ventilation strategies 202
 - Neurodevelopmental outcomes of preterm/LBW 30
 - cerebral palsy (CP) 31
 - growth 33
 - health outcomes 34
 - hearing impairment 31
 - intelligence quotient (IQ) 32
 - learning difficulties 32
 - quality of life 34
 - social development, behavior and psychological problems 33
 - visual impairment 31
 - Nutrition, fluid and electrolytes 329
- O**
- Organization of neurodevelopmental follow-up 236
 - for babies at high risk of NDD 237
 - for babies at low risk of NDD 236
 - for babies at moderate risk of NDD 236
- P**
- Pain and analgesia 175
 - assessment of pain in neonates 177
 - common painful procedures in neonatal period 176
 - diagnostic 176
 - surgical 176
 - therapeutic 176
 - pathophysiology 175
 - prevention and management 177
 - treatment modalities for pain 178
 - Parent counseling 356
 - breastfeeding 357
 - father's role 362
 - health and nutrition of mother 356
 - identification of a sick baby 361
 - parental role in the NICU 361
 - prevention of infections 360
 - provision of warmth 359
 - three mantras of newborn care 357
 - useful traditional health care practices 360
 - Perinatal asphyxia 41
 - Perinatal steroids 194
 - Persistent pulmonary hypertension of newborn (PPHN) 126
 - diagnosis 130
 - epidemiology 128
 - pathophysiology 126
 - PPHN and neurodevelopmental outcome 127
 - prevention of risk factor 130
 - treatment 131
 - correction of acidosis 131
 - correction of hypovolemia/hypotension 132
 - mechanical ventilation 132
 - minimal handling 131
 - sedation and paralysis 132
 - treatment of associated conditions 132
 - surfactant therapy 133
 - inhaled nitric oxide (iNO) 133
 - extracorporeal membrane oxygenation (ECMO) 134
 - alternative vasodilator therapy 135
 - Prenatal risk factors 295
 - risk factors 295

- growth restriction 296
- intrauterine infections 299
- maternal diseases 305
- maternal factors 307
- maternal nutrition and brain development 298
- prematurity 295
- teratogens 307
- Preterm brain injury 13
 - cerebral palsy 16
 - interventions to prevent preterm brain injury 16
 - clinical presentation of PVH-IVH 15
 - impact on neurodevelopment 16
 - management of preterm baby 21
 - administrative strategies in NICU 23
 - cerebral perfusion 21
 - correct coagulopathy 23
 - optimize respiratory management 22
 - unproven therapies 23
 - optimize peri-partum management 20
 - delay cord clamping 20
 - resuscitation 20
 - pathophysiology 13
 - prenatal 17
 - antenatal steroids (ANS) 18
 - antibiotics in prelabour rupture of membranes (pROM) 19
 - mode of delivery of preterm 20
 - prevention of prematurity 17
 - screening and diagnosis of preterm brain injury 24
 - clinical examination 24
 - neurosonographic screening for IVH-PVH and WMD 24
 - treatment of IVH 25
 - treatment of acute IVH supportive measures 25
 - treatment of posthemorrhagic hydrocephalus 25
 - withdrawal of care decision in severe IVH 27
- Preterm/low birth weight 29

R

- Recent advances in measuring blood glucose 77
- Risk stratification for neurodevelopmental disability 207
 - need for risk stratification 207
 - anticipatory guidance to parents 207
 - assigning level of follow-up 207
- Role of IVIg in neonatal sepsis 166
- Role of pentoxifylline in neonatal sepsis 166

S

- Screening protocol 216
 - retinopathy of prematurity (ROP) screening 216
 - screening for congenital hypothyroidism 220
 - screening for hearing impairment 219
 - screening for metabolic disorders 222
- Surveillance sonography 15

T

- Tandem mass spectrometry (TMS) 96

V

- Vision stimulation in early pregnancy 287
 - body image 291
 - early detection of visual abnormalities in young children 288
 - encouraging exploration 291
 - object permanence 291
 - stimulation techniques for visually impaired children 289
 - intervention to promote eye focus and following 289
 - senses as leaning tool 290
 - techniques 289
 - visual stimulation 288