A Dissertation On

"A STUDY OF IMPACT OF PERINATAL ASPHYXIA ON THYROID HORMONE LEVELS"

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THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY

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In partial fulfillment of regulations

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MAY 2020

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This is to certify that this dissertation entitled **"A STUDY OF IMPACT OF PERINATAL ASPHYXIA ON THYROID HORMONE LEVELS"** is the original and bonafide work done by **Dr. G. RACHEL PRAKANTHASHALINI** under the guidance of **Prof. Dr.V.E.VIVEKANANDAN, M.D,,DCH.,** Professor and Head of the Department of Paediatrics, Government Kilpauk Medical College & Hospital Chennai–600 010, during the tenure of her course in M.D. Paediatrics from May-2016 to May-2020 held under the rules and regulations of the Tamilnadu Dr. M.G.R Medical University, Guindy, Chennai–600 032, in partial fulfilment for the award of the degree of M.D Branch VII Paediatrics.

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CONTENTS

A STUDY OF IMPACT OF PERINATAL ASPHYXIA ON THYROID HORMONE LEVELS

INTRODUCTION

Perinatal asphyxia is one of the major causes of early neonatal mortality in India. It ranks as the second most important cause of neonatal death after infections, accounting for around 30% mortality worldwide. [1]. In India perinatal asphyxia is one of the most common cause of mortality (28.8%) and morbidity and is the commonest cause of stillbirths (45.1%). An Apgar score of <7 at 1 min and at 5 min respectively is seen in 8.4% and 2.45% cases. The overall incidence of severe birth asphyxia which accounts for poor clinical prognosis is 4.6%.[1]

Anoxia indicates the consequences of a complete lack of oxygen as a result of a number of primary causes. Hypoxia refers to decreased oxygenation to cells or organs. Ischemia refers to insufficiency of blood flow to cells or organs that is required to maintain functional normalcy. [2]

Hypoxic-ischemic encephalopathy is defined as encephalopathy with objective data to support hypoxic ischaemic mechanism as the underlying cause. Neonatal encephalopathy is a clinical term that describes an abnormal neurobehavioral state consisting of decreased level of consciousness and other signs of brain stem and / or motor dysfunction.[61]. About 20-30% of infants

with hypoxic-ischemic encephalopathy die in the neonatal period, and approximately 33-50% of survivors are left with permanent neurodevelopmental abnormalities (cerebral palsy, mental retardation).[3]

Predictive diagnostics in perinatal asphyxia has been a long standing challenge. Several methods for predicting outcomes in infants with HIE were used in the past including: neonatal clinical examination and clinical course, monitoring general movements, early electrophysiology testing, cranial ultrasound imaging, Doppler blood flow velocity measurements, magnetic resonance imaging (MRI) and MR microscopy. The role of thyroid hormones in various physiological and metabolic functions essential for sustenance is well recognized. But its changes in perinatal asphyxia is sparsely studied.

PERINATAL ASPHYXIA - DEFINITIONS:[4,5]

Perinatal asphyxia is the medical condition resulting from deprivation of oxygen to a newborn infant that lasts long enough during the birth process to cause physical harm, usually to the brain. The Greek etymology of perinatal asphyxia literally means‘stopping of pulse’. It is also the inability to establish and sustain adequate or spontaneous respiration upon delivery of the newborn. It remains a serious condition which causes significant mortality and morbidity. It is situation of dire emergency requiring swift and adequate resuscitation measures.

Perinatal oxygen deficit ranges from the 28th week of gestation to the first 7days following delivery. This insult to the fetus or newborn due to lack of oxygen and lack of perfusion to various organs is associated with lack of ventilation.

Hypoxia incurs maximum damage the infant's vital organs like heart, lungs, liver, gut, kidneys, but brain damage is of most concern due to increased neuronal sensitivity to hypoxic damage. In more pronounced cases, an infant will survive, but with permanent neurological damage such as developmental delay or intellectual disability, or physical impairment such as spasticity.

CASE DEFINITION:

The ICD-10 [International Classification of Diseases] classifies perinatal asphyxia under two categories of codes: intrauterine hypoxia as P20 and birth asphyxia as P21. Instead of severity, the categories are classified by onset characteristics whether the insult has occurred in the intrauterine period or associated with the intrapartum period. The code P20 intrauterine hypoxia has broad inclusion criteria and manifestation properties. The codes of category P21 asphyxia are defined in the ICD-10 by the 1-minute Apgar score and additionally by some of the individual elements of the 1-minute Apgar score.

The various criteria elaborated in the ICD-10 WHO classification have been given below :

P21.0 severe birth asphyxia. At least 3 of the criteria mentioned below must be fulfilled:

· 5-minute Apgar score of 5

· Severe acidosis during first hour of life: Ph of 7.00 (UV, UA, capillary or arterial blood sample)

· Base deficit of 16 mmol/L in UV or UA during first hour of life

· Moderate to severe encephalopathy (Sarnat stage II or III)

· Lactate equal to 12 mmol/L in UV or UA or during first hour of life

P21.1 moderate birth asphyxia. At least 2 of the criteria mentioned below must be fulfilled:

· 5- minute Apgar score of 7

· Moderate acidosis during first hour of life: pH <7.15 (UV, UA, capillary or arterial blood sample)

· Mild to moderate encephalopathy (Sarnat stage I or II)

P21.9 mild asphyxia without metabolic acidosis. Both of the two criteria mentioned below must be fulfilled:

· 5- minute Apgar score of 7 and

· Lowest value at 1 hour of life pH of 7.15 (UV, UA, capillary or arterial blood sample)

P20.1 metabolic acidosis without neurological impairment. Metabolic acidosis without clinical impairment (i.e. asphyxia)

· 5- minute Apgar score >7

· Moderate acidosis during first hour of life: pH <7.15 (UV, UA, capillary or arterial blood sample)

Neonatal encephalopathy is a clinical syndrome defined by disturbance of neurological function manifested by a subnormal level of consciousness or seizures, and often accompanied by difficulty in initiating and sustaining respiration and depression of tone and reflexes. The assessment measures used to ascertain this clinical syndrome needs accuracy and reliability while being done at the staff level. The contributing events to an acute hypoxic or ischemic event have temporal proximity to the and delivery process. Thus the assessment measures compile a constellation of clinical information which includes neonatal mental status, contributing events, and developmental outcome to determine their consistency with acute hypoxia–ischemia.

The American College of Obstetricians and Gynecologists (ACOG) and the American Academy of Pediatrics (AAP) released the following guidelines for diagnosis of neonatal encephalopathy in January 2003

NEONATAL SIGNS CONSISTENT WITH AN ACUTE PERIPARTUM OR INTRAPARTUM EVENT

A. Apgar Score of Less Than 5 at 5 Minutes and 10 Minutes

Low Apgar scores at 5 minutes and 10 minutes correlates with an increased relative risk of cerebral palsy. Low APGAR scores may be confounded by a number of factors that include maternal acidosis, maternal medication or sedation, the use of general anaesthetics, muscular dystrophy in the fetus, etc.

The various components of APGAR score are given below:

Sign/Score	0	1	2
Activity (muscle tone)	Absent	Some flexion	Active
Pulse	Absent	<100 bpm	>100 bpm
Grimace (reflex irritability)	Floppy	Minimal response to stimulation	Active cry and movement
Appearance	Blue, pale	Pink body, blue extremities	No cyanosis
Respirations	Absent	Slow, irregular, weak cry	Vigorous crying

B. Fetal Umbilical Artery Acidemia

Fetal umbilical artery pH less than 7.0, or base deficit greater than or equal to 12 mmol/L, or increases the impending possibility of neonatal encephalopathy.

However the presence of metabolic acidemia does not delineate the time of the onset of the hypoxic insult.

C. Neuroimaging Evidence of Acute Brain Injury Seen on Brain Magnetic Resonance Imaging or Magnetic Resonance Spectroscopy Consistent With Hypoxia– Ischemia

Magnetic resonance imaging (MRI) stands as the modality of choice to define the nature and extent of cerebral injury in neonatal encephalopathy. In spite of ease of administration cranial ultrasonography and computed tomography lack the sensitivity to detect the nature and extent of neuronal injury in the term infant with encephalopathy. Neuroimaging studies show characteristic distinct pattern of involvement in a term neonate and even act as a prognosticating tool for later neurodevelopmental impairment prediction. The predictive capacity regarding the timing of perinatal cerebral injury is high for an early MRI obtained between 1 to 4 days of life whereas an MRI done between 1 to 2 weeks of life signifies the extent of injury.

D. Presence of Multisystem Organ Failure Consistent With Hypoxic–Ischemic Encephalopathy

Multisystem organ failure include renal injury, hepatic injury, hematologic abnormalities, cardiac dysfunction, metabolic derangements, and gastrointestinal injury.

TYPE AND TIMING OF CONTRIBUTING FACTORS THAT ARE CONSISTENT WITH AN ACUTE PERIPARTUM OR INTRAPARTUM EVENT

A. A Sentinel Hypoxic or Ischemic Event in the Peri-partum period

1. A ruptured uterus
2. Severe abruption placentae
3. Umbilical cord prolapse
4. Amniotic fluid embolus with coincident severe and prolonged maternal hypotension and hypoxemia
5. Maternal cardiovascular collapse
6. Fetal exsanguination from either vasa previa or massive fetomaternal hemorrhage

B. Fetal Heart Rate Monitor Patterns Consistent With an Acute Peripartum or Intrapartum Event

Persistently minimal or absent basal variability in heart rate with absence of accelerations, even while lacking decelerations is indicative of a previously compromised or injured fetus.

The patient who presents with a Category I fetal heart rate pattern that converts to Category III is suggestive of a hypoxic–ischemic event i.e. presence of tachycardia with recurrent decelerations and persistent minimal variability with recurrent decelerations.

C. Timing and Type of Brain Injury Patterns Based on Imaging Studies Consistent With an Etiology of an Acute Peripartum or Intrapartum Event

A combination of conventional magnetic resonance imaging with diffusion studies and spectroscopy analysis—provides a valid tool to the potential timing of a cerebral insult. The various pathognomonic patterns of brain injury include deep nuclear gray matter or watershed cortical injury.

D. No Evidence of Other Proximal or Distal Factors That Could Be Contributing Factors

The presence of other significant risk factors—such as abnormal fetal growth, maternal infection, fetomaternal hemorrhage, neonatal sepsis, and chronic placental lesions indicate the presence of chronic hypoxia rather than an acute intrapartum hypoxic event.

ETIOLOGY [1,4,8]

The asphyxia can occur prior to the birth or can occur immediately following birth in a compromised patient requiring resuscitation. The majority of cases of perinatal asphyxia occur intrapartum, although 20% occur antepartum and other cases occur in the early post-natal period. Basically, understanding of the etiology of perinatal asphyxia provides the platform on

which to build on its pathophysiology. The general principles guiding the causes and the pathophysiology of perinatal asphyxia are grouped into antepartum causes and intrapartum causes. [11,12] as these are the various points in which insults can occur to the fetus.

Antepartum causes

- Inadequate oxygenation of maternal blood due to hypoventilation during anesthesia, heart diseases, pneumonia, respiratory failure
- Low maternal blood pressure due to hypotension e.g. compression of vena cava and aorta, excess anesthesia.
- Premature separation of placenta
- Placental insufficiency.
- Premature rupture of membranes

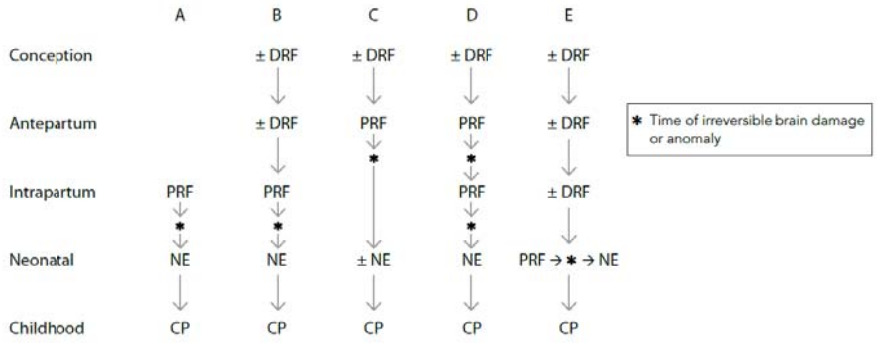
Intrapartum causes

- Inadequate relaxation of the uterus
- Prolonged latent phase or second stage of labor
- The knotting of the umbilical cord around the neck of the infant

- Abnormal presentations including breech presentation, face presentation, deflexed head, asynclitism.
- Cephalopelvic disproportion (CPD) or contracted pelvis.
- Inadequate uterine contractions, cervical dystocia and obstructed labor.
- Augmentation by oxytocin and uterine hyperstimulation.

RISK FACTORS

The risk factors affecting the development of a sentinel hypoxic event in utero are classified into two groups, the proximal and the distal risk factors. Distal risk factors are those that inflict a pathogenic effect on the developing fetal brain at a time that is remote from the onset of irreversible brain injury. Examples include genetic abnormalities, environmental and sociodemographic factors, and some placental abnormalities. Proximal risk factors are those that inflict pathogenic effects on the developing fetal brain at a time that closely correlates with the onset of irreversible brain injury. Examples include abruption placentae, chorioamnionitis, and twin–twin transfusion.



Other potential risk factors include:

- Elderly or young mothers
- Lack of antenatal care
- Low birth weight infants
- Meconium-stained amniotic fluid
- Multiple births
- Antepartum haemorrhage
- Severe eclampsia and pre-eclampsia
- Antepartum and intrapartum anaemia

STAGING OF HYPOXIC-ISCHAEMIC ENCEPHALOPATHY

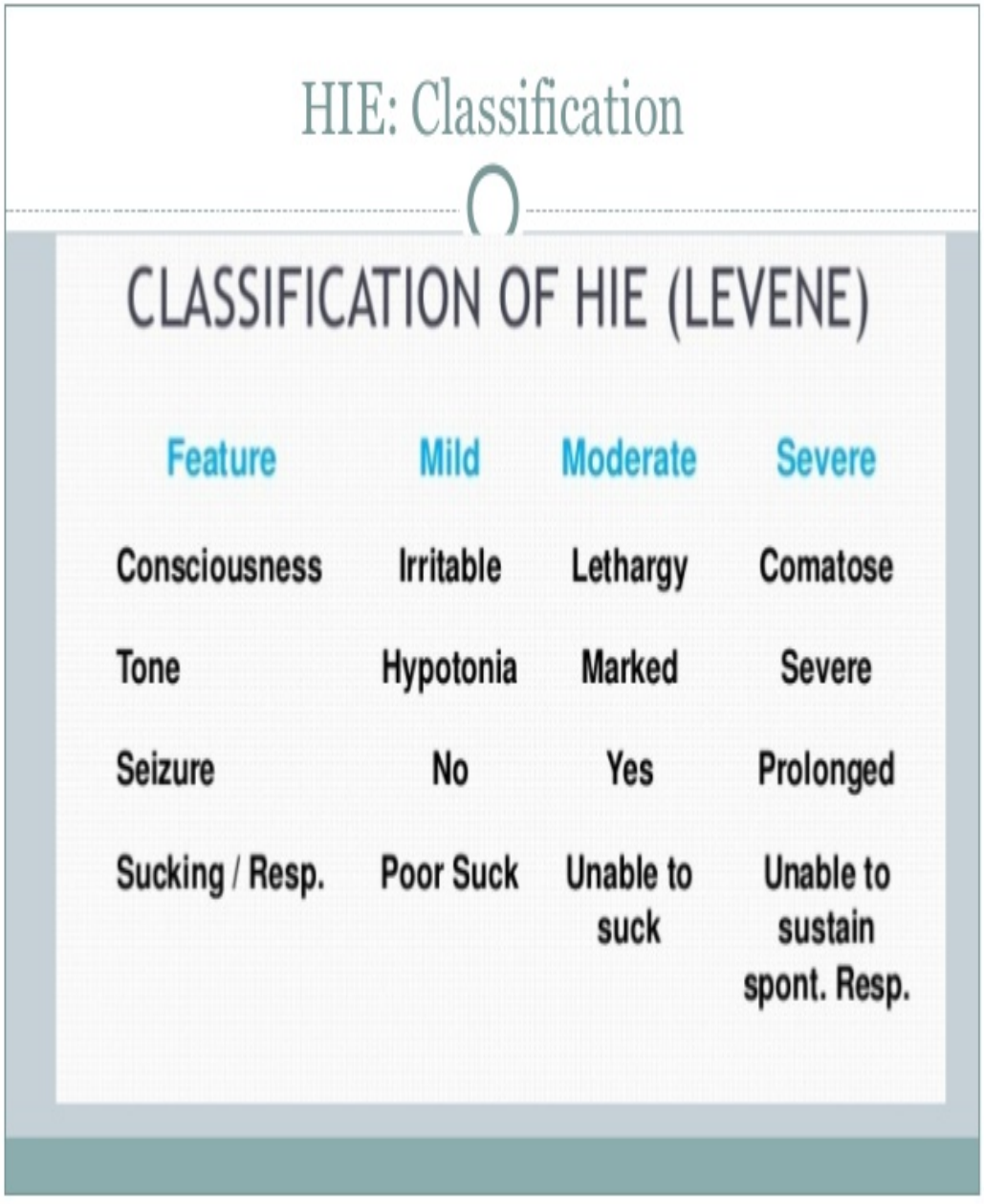
Several staging criteria have been developed for grading the severity and prognostication of hypoxic ischemic encephalopathy. Each has its own advantages and limitations like ease of administration, requirement of investigations or imaging modalities.

Hypoxic-ischaemic encephalopathy of the newborn (HIE) is a syndrome caused by a lack of adequate oxygenation around the time of birth which manifests as altered consciousness, altered muscle tone, and seizures. HIE is graded based on the infant's clinical presentation, examination findings, the presence of seizures and the duration of illness by the time tested Sarnat and Sarnat classification.

Sarnat staging is used alongside electroencephalogram findings to provide information about the prognosis for the infant. Mild HIE, according to the scale, usually has a normal outcome, whereas in severe HIE the mortality rate is 75%, and 80% of survivors have neurological sequelae. The Sarnat and Sarnat staging is given below:

	Stage 1	**Stage 2**	**Stage 3**
Level of consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong, low threshold	Weak, incomplete, high threshold	Absent
Oculo vestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Absent
Autonomic function	Generalized sympathetic	Generalized parasympathetic	Both systems depressed
Pupils	Mydriasis	Miosis	Variable, often unequal, poor light reflex
Heart rate	Tachycardia	Bradycardia	Variable
Bronchial and salivary secretions	Sparse	Profuse	Variable
Gastrointestinal motility	Normal or decreased	Increased, diarrhoea	Variable
Seizures	None	Common, focal or multifocal	Uncommon (excluding decerebration)
Electroencephalogram findings	Normal (awake)	**Early:** low-voltage continuous delta and theta **Later:** periodic pattern (awake) Seizures: focal 1-to 1-Hz spike-and-wave	**Early:** periodic pattern with Isopotential phases **Later:** totally isopotential
Duration	Less than 24 hours	2 – 14 days	Hours to weeks

The LEVENE‘S MODIFICATION is a more simplified version which is more practicable clinically. The Levene’s staging is given below:



The THOMPSON SCORE is yet another staging criteria which has also been used in a number of prognosticating studies for HIE.

Score Sign	0	1	2	3
Tone	Normal	Hyper	Hypo	Flaccid
LOC	Normal	Hyperalert, stare	Lethargic	Comatose
Fits	None	< 3/day	>2/day	
Posture	Normal	Fisting, cycling	Strong distal flexion	Decerebrate
Moro	Normal	Partial	Absent	
Grasp	Normal	Poor	Absent	
Suck	Normal	Poor	Absent ± bites	
Respiration	Normal	Hyperventilation	Brief apnea	IPPV (apnea)
Fontanelle	Normal	Full, not tense	Tense	

Thompson score
Mild (1 - 10)
Moderate (11 - 14)
Severe (15+)

ETIOPATHOGENESIS OF HYPOXIC ISCHAEMIC ENCEPHALOPATHY

As a consequence of perinatal asphyxia there is a radical shift from aerobic to inefficient anaerobic metabolism. This results in a decreased production of high energy phosphates. Decreased ATP leads to formation of phosphocreatine and accumulation of byproducts of anaerobic glycolysis such as lactate. Eventually the cellular acidosis leads to decreased phosphorylation of protein and over-production of free radicals or reactive oxygen species (ROS) that result in cell death. The spectrum of mechanisms involved in neuronal cell death after perinatal asphyxia include necrosis, apoptosis, autophagy depending primarily on the severity of the hypoxic insult and the principal maturational state of the cell.

There is a disruption in the permeability of the blood brain barrier. This leads to increased predisposition for toxic metabolites to cause damage to the brain. The factors affecting the extent of neurological deficits include the gestational age, severity of neuronal insult and the time lag between commencement of resuscitation and the restoration of normal breathing [66].

Severe asphyxia has reported to be responsible for mental retardation, cerebral palsy and epilepsy. Mild to moderate asphyxia is found to cause cognitive and behavioral defects like autism spectrum disorder, attention deficit hyperactivity and learning disability. Studies have hypothesized that

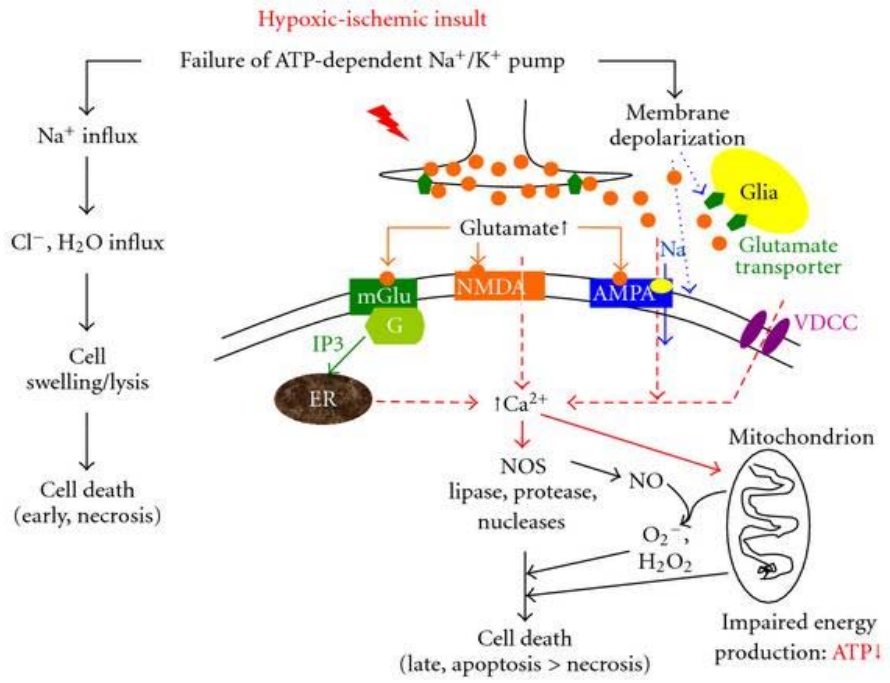
these problems may be due to downregulation of brain derived neurotrophic factors [BDNF] causing neuronal atrophy in these cases [67]. Moreover, hypoxic insult targets specific areas of the brain like perirolandic cortex, venterolateral thalamus, hippocampus, striatum and posterior putamen. This leads to targeted cognitive problems like memory impairment, lack of co-ordination and hyperactivity.

Due to deficiency of ATP production the resting membrane potential of the cell membrane is disrupted. This leads to imbalances in ionic homeostasis. Depolarisation reaction follows and extracellular rise of glutamate ensues. This results in hyperactivation of several excitatory receptors including NMDA, AMPA, KA, mGluR receptors. Consequently the metabotropic action of these receptors induces a massive influx of calcium into the cells. The cytosoliccalcium triggers a catastrophic cascade of events including degradation of cytoskeleton and extracellular matrix proteins by a number of enzymes like proteases, lipases and endonucleases.

Early neuronal death occurs by necrosis, while delayed neuronal death is mostly by apoptosis. Apoptosis by both caspase dependent and caspase independent mechanisms have been identified. The various death receptors include BCL2, BAX, BAD, cleaved caspase 3, calpain dependent fodrin breakdown products, cathepsin D, acid phosphatase, microtubule associated

protein and battery of several others which have been investigated for developing neuroprotective strategies [69].

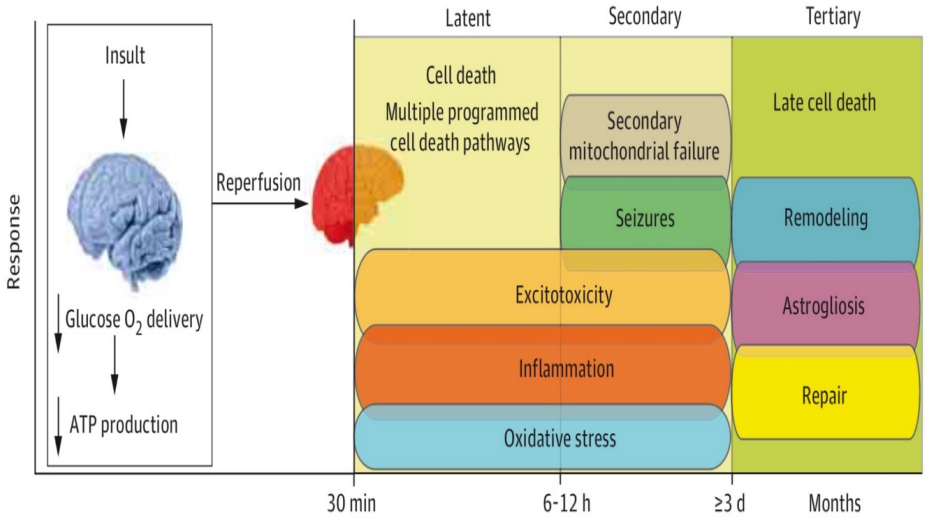
There is a crosstalk between above mentioned inflammatory processes and excitatory neurotransmitters. Hypoxic damage releases excitatory amino acids into the extracellular space. Decreased reuptake capacity of the synaptic nerve terminals affects the recycling equilibrium of glutamate and aspartate which reach excitotoxic levels. Their activity is further augmented by upregulation of NMDA receptors in perinatal period to aid neuronal plasticity. Increased TNF alpha levels due to neuro inflammation upregulated AMPA receptor leading to a vicious cycle of inflammation and excitotoxic damage. The protective mechanisms of the astrocytes is also disrupted. Monoamine neurotransmitters like dopamine also aggravate hypoxic damage especially in the striatum area[70].



There are three stages of brain injury in hypoxic-ischemic encephalopathy. Firstly, there is an immediate *Primary neuronal injury* that occurs due to the interruption of oxygen and glucose to the brain. This decreases ATP and results in failure of the ATP-dependent Na-K ATPase pump. Sodium enters the cell followed by water, causing cell swelling, widespread depolarization, and cell death. Cell death and lysis causes release of glutamate, an excitatory amino acid. Further this causes an increase in intracellular calcium and further cell death. Following the immediate injury is a *latent period* of about six hours, during which reperfusion occurs, and some cells recover. The late *secondary neuronal injury* occurs over the next 24-48 hours as reperfusion results in blood flow to and from damaged areas, spreading toxic neurotransmitters and widening the area of brain affected.[22,23,24]

Decrease in neurotrophic factors induced by hypoxic ischemic encephalopathy may lead to dendritic atrophy and disruption of synaptogenesis, In response to this energy deficit, redistribution of blood flow occurs to the vital organs like heart, brain and adrenal glands. This redistribution occurs at the expense of decreased perfusion to less vital organs like kidneys, gastrointestinal tract, muscles, skeleton and skin. Inside the brain also there is a redistribution of blood flow, favouring the brain stem at the expense of the cortex, showing a re-compartmentalisation of structures to privilege survival. This is called ***diving reflex***. Oxidative stress is associated with inactivation of a number of enzymes, including mitochondrial respiratory enzymes accompanied by low capacity of the antioxidant mechanism at this early developmental stage.

Figure 1. Schematic Overview of the Pathophysiological Features of Hypoxic-Ischemic Encephalopathy



MULTIORGAN DYSFUNCTION IN PERINATAL ASPHYXIA

The healthy fetus or newborn is equipped with a range of adaptive, strategies to reduce overall oxygen consumption and protect vital organs such as the heart and brain during asphyxia. Acute injury occurs when the severity of asphyxia exceeds the capacity of the system to maintain cellular metabolism within vulnerable regions. Birth asphyxia has detrimental effects on various organ systems, the functional derangements of which are responsible for associated complications. Of prime importance is the cardiac dysfunction which is targeted in the resuscitation of an asphyxiated infant. Some of the major physiological alterations are given below:

CARDIOVASCULAR RESPONSE:

The first and foremost response of a fetus to hypoxia is the ***primary apnea*** which is defined as the initial cessation of respiration associated with profound bradycardia with blood pressure levels being preserved within normal limits. With worsening asphyxia, the fetus progresses to the stage of ***secondary apnea*** otherwise termed as ***terminal apnea*** following a brief period of gasping. Secondary apnea is accompanied by hypotension and if not intervened progresses to cardiac arrest. Following this there is a downhill sequelae of organ injury. Fetal bradycardia is the result of diminished chemoreceptor response by the carotid and aortic body, demonstrated in fetal sheep [61]. The stress response to hypoxia induces the activation of sympathetic-adrenergic system that alters the peripheral vascular resistance causing the diving reflex.

When this increase in peripheral vascular resistance is outmatched by the hypoxic insult blood pressure begins to fall.

There are multiple factors that play a pathogenic role in the decrease of cardiac output and stroke volume in asphyxia. These include ischemic myocardial injury due to reduced coronary perfusion, myocardial dysfunction leading to insufficient cardiac contractility and acidosis. Cyanosis and decreased capillary blood flow occurs secondary to vasoconstriction. In the severely depressed infant, the necessity for very early artificial ventilation with oxygen is undisputed. Resuscitation will require artificial ventilation using positive pressure bag and mask and oxygen to establish spontaneous and effective respiration prior to endotracheal intubation. This hemodynamic instability is the basis for several other organ dysfunctions [62].

LIVER DYSFUNCTION:

Perinatal hypoxia causes ischemic hepatitis. The damaged hepatocyte membrane results in leakage of enzymes and increased plasma levels of liver enzymes like alanine transaminase and aspartate transaminase. The tight junctions lining the bile canaliculi lose their integrity and causes release of alkaline phosphatase into the circulation.Additionally, there is a sustained rise in lactate dehydrogenase levels due to ischemic hepatitis. [63]

RESPIRATORY INVOLVEMENT IN PERINATAL ASPHYXIA:

The pulmonary effects of asphyxia include increased pulmonary vascular resistance, pulmonary hemorrhage, pulmonary edema secondary to cardiac failure, and possibly secondary deficiency of surfactant production with secondary hyaline membrane disease. Meconium aspiration if present may add to the spectrum of problems [66].

GASTROINTESTINAL TRACT INVOLVEMENT IN PERINATAL ASPHYXIA:

The gastrointestinal tract has multiple watershed regions that are prone to hypoxic injury from birth asphyxia. Necrotizing enterocolitis has been reported in these infants, but is a rare complication. Gastrointestinal damage might include injury to the bowel wall, which can be mucosal or full thickness and even involve perforation. The extent of the damage influences the nutritional management, in particular when to begin feedings once recovery occur. The shunting of blood away from the intestine in a fashion similar to the diving reflex in aquatic mammals has been postulated as a potential mechanism for producing the initial gut ischemia. This reflex occurs most commonly in response to asphyxia and it forms the basis of gastrointestinal involvement in birth asphyxia. Probably the most serious gastrointestinal disorder occurring in neonates is necrotizing enterocolitis. Clinical presentations vary widely. Abdominal distention usually is one of the earliest

and most consistent clinical signs. Other symptoms include bloody stools, apnea, bradycardia, lethargy, shock and retention of gastric contents due to poor gastric emptying. Thrombocytopenia, neutropenia and metabolic acidosis may develop during bowel ischemia. Feeding intolerance and subtle alterations of intestinal motor activity and gastrointestinal peptides have also been reported in association with perinatal asphyxia.[66]

RENAL INVOLVEMENT:

Acute kidney injury is also a consequence of the adaptive mechanism. Amongst the recognized complications i.e., acute tubular necrosis, renal vein thrombosis and renal failure, ARF is the commonest and carries a poor prognosis and may even result in permanent renal damage in up to 40% of survivors.

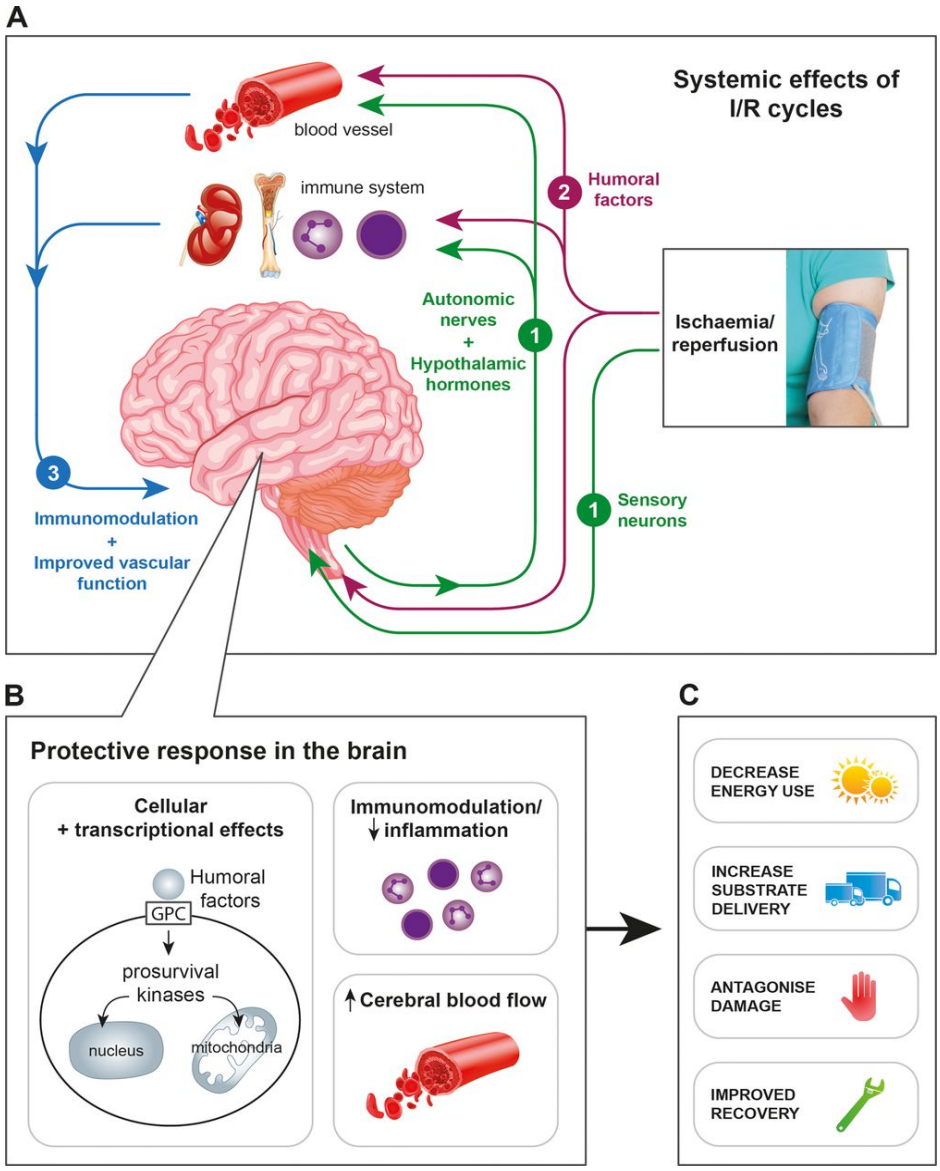
Non-oliguric renal failure is a recognized entity secondary to perinatal asphyxia. Renal parenchymal injury in non oliguric as well as oliguric renal failure is essentially similar but heterogenous response of individual nephron and variable damage to tubular epithelium results in anatomical damage in majority of nephrons leading to reduction in single nephron GFR and decreased tubular fluid flow. But if damage to tubular epithelium is less severe there occurs decrease in fractional reabsorption which exceeds the decrease in single nephron GFR leading to polyuria in non-oliguric renal failure

Obstruction of tubular lumen and back leak mechanism contributed to increase in urea and creatinine levels in asphyxiated neonates. A great correlation between severity of asphyxia and ischemic damage to the kidneys manifesting as ARF has also been noted. Hyponatremia occurs as the capacity of sodium reabsorption is limited and if the load of sodium reaching the DCT increases significantly, reabsorption does not occur proportionately and the sodium load is excreted in the urine. Other contributing factors to hyponatremia may be occurrence of SIADH secondary to perinatal asphyxia and partial resistance to aldosterone. Hyponatremia per se may lead to contraction of intravascular volume further reducing the renal functions [65]

HAEMATOLOGICAL CHANGES IN PERINATAL ASPHYXIA:

Coagulopathy in asphyxia is a consequence of diminished blood flow to the bone marrow and liver. Impaired synthesis of clotting factor and platelets leads to disseminated intravascular coagulation. Levels of factor XIII are lower in infants with birth asphyxia. Plasma levels of thrombin-antithrombin complexes, D-dimer, fibrinogen, and fibrin degradation products are higher in infants with birth asphyxia. Hypoxia is believed to have a direct effect on platelet formation for a clinical presentation termed thrombocytopenia of perinatal asphyxia. Hypoxia in adult mice causes a decrease in the size and production of the megakaryocytes in the bone marrow. Although the megakaryocytes appear to not be injured by hypoxia, the cells in the bone

marrow surrounding them are affected and decrease the release of platelet promoting factors. Thrombocytopenia was more common in infants with more chronic hypoxia (>24 hours). An increased nucleated red blood cells count is also seen in asphyxia. All these contribute to consumptive coagulopathy and disseminated intravascular coagulation in perinatal asphyxia [64].



HORMONAL IMBALANCES IN PERINATAL ASPHYXIA

Perinatal asphyxia triggers rapid alterations in the concentration of several hormones such as thyroid hormones, catecholamine, glucocorticoids, antidiuretic hormone, aldosterone, renin, atrial natriuretic peptide, and insulin. [10]Several agents intervene with the thyroid function, acting on several stages of its metabolism. The effect of hypoxia on thyroid hormones has been long recognized. In animals, hypoxia reduces thyroid function and extrathyroidal metabolism of T4.[11]

Thyroid hormones are important for energy metabolism, the metabolism of nutrients andinorganic ions, thermogenesis, and for stimulation of growth and development of varioustissues at critical periods including the central nervous system and skeleton.

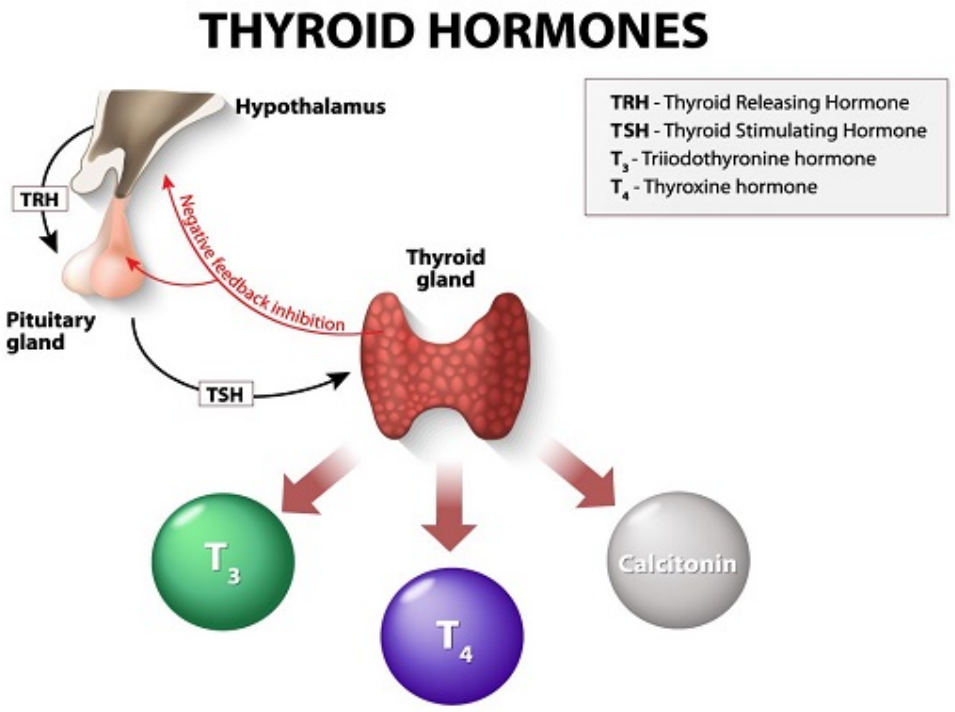
The action of these hormones on the synthesis of mitochondrial enzymes and structural elements is extremely important, in addition to participating in thermogenesis, water and electrolyte transportation, and in the growth and development of the central nervous system and skeleton. The importance of thyroid hormones to the normal development of the brain and intellectual function and their relation with patients' prognosis requires studies that correlate hormonal alterations with the occurrence of neurological sequelae.[12,13]

THYROID FUNCTIONS IN THE NEONATAL PERIOD:

During fetal life, the thyroid gland develops with secretion of thyroxine (T4) and triiodothyronine (T3) from about 12 weeks gestation. These levels increase towards term gestation. In the first trimester maternal T4 that crosses the placenta plays a crucial role in central nervous system development. From mid-gestation, hypothalamic expression of thyrotropin releasing hormone (TRH), pituitary production of thyroid stimulating hormone (TSH), and thyroidal production of T4 rise steadily until 36 weeks gestation. Even after the fetal thyroid gland gains autonomy, normal thyroid function in the mother is important for normal neurological development.

The bioactivity of thyroid hormone is regulated by enzymatic de-iodination in peripheral tissues. T4 is converted by outer ring de-iodination into T3, which has three to four times the metabolic potency of T4. Both T4 and T3 are inactivated by inner ring de-iodination to reverse T3 (rT3) and 3,3'-diiodothyronine respectively. Three iodothyronines are involved in this process. Type I deiodinase (D1) has both inner and outer ring de-iodination activity. It is located in the liver, kidney, and the thyroid and is important for T3 production. Type II deiodinase (D2) catalyses only outer ring de-iodination and is found in the brain, pituitary, and brown adipose tissue. It is important for local T3 production within these tissues. Type III deiodinase (D3) has only inner ring activity and is present in brain, skin, and intestine.

In the fetus, levels of T3 are low, and increase only at the end of gestation. In contrast, rT3 levels are high and decreases in late gestation and into the neonatal period. This is mainly for minimizing endogenous thermogenesis and promoting anabolism. High D3 activity in the placenta and in both fetal liver and the liver of preterm babies contribute to the high rT3 levels. Both D1 and D2 are present from the third trimester. T3 dependent tissues, particularly the brain rely on local T4 into T3 conversion via D2.



THYROID REGULATION:

The thyroid is regulated by TSH, a glycoprotein produced and secreted by the anterior pituitary. This hormone activates adenylate cyclase in the thyroid gland and is important in all steps of thyroid hormone biosynthesis, from the trapping of iodine to release of thyroid hormones. TSH is composed of 2 non covalently bound subunits (chains): alpha and beta. The alpha subunit is biochemically similar to luteinizing hormone, FSH and HCG: the specificity of each hormone is confirmed by the beta subunit. [22,23] TSH synthesis and release are stimulated by TSH releasing hormone (TRH) which is synthesized in the hypothalamus and secreted into the pituitary. TRH is found in the other parts of the brain apart from the hypothalamus and also in many other organs. TRH is a simple tripeptide.[24] In states of decreased production of thyroid hormone, TSH and TRH are increased. Exogenous thyroid hormones or increased thyroid hormone synthesis inhibits TSH and TRH production.

THYROID HORMONE RECEPTORS AND MECHANISM OF ACTION

Thyroid hormones receptors are intracellular DNA-binding proteins that function as hormone-responsive transcription factors, conceptually similar to steroid hormones. Thyroid hormones enter cells through membrane transporter proteins. Once inside the nucleus, the hormone binds its receptor, and the hormone-receptor complex interacts with specific sequences of DNA in the promoter regions of responsive genes. The effect of the hormone-receptor

complex binding to DNA is to modulate gene expression, either by stimulating or inhibiting transcription of specific genes. Thyroid hormone influences the relative ratio of different types of proteins. Transcription of some proteins is stimulated by thyroid hormones, while transcription of others in inhibited. The net effect is to alter the ratio toward the decided effect[25,26].

PHYSIOLOGIC EFFECTS OF THYROID HORMONES

It is likely that all cells in the body are targets for thyroid hormones. Thyroid hormones have profound effects on many physiologic processes, such as development, growth and metabolism, and deficiency in thyroid hormones is not compatible with normal health.

Metabolism: Thyroid hormones stimulate diverse metabolic activities in most tissues, leading to an increase in basal metabolic rate. One consequence of this activity is increase in thermogenesis, increased oxygen consumption and high rates of ATP hydrolysis. Specific metabolic effects of thyroid hormones include:[18,19]

- *Lipid metabolism*: Thyroid hormones stimulate mobilization of fat, leading to increased concentrations of free fatty acids in plasma. They also enhance oxidation of fatty acids in many tissues. Plasma concentrations of cholesterol and triglycerides are inversely correlated with thyroid hormone levels.

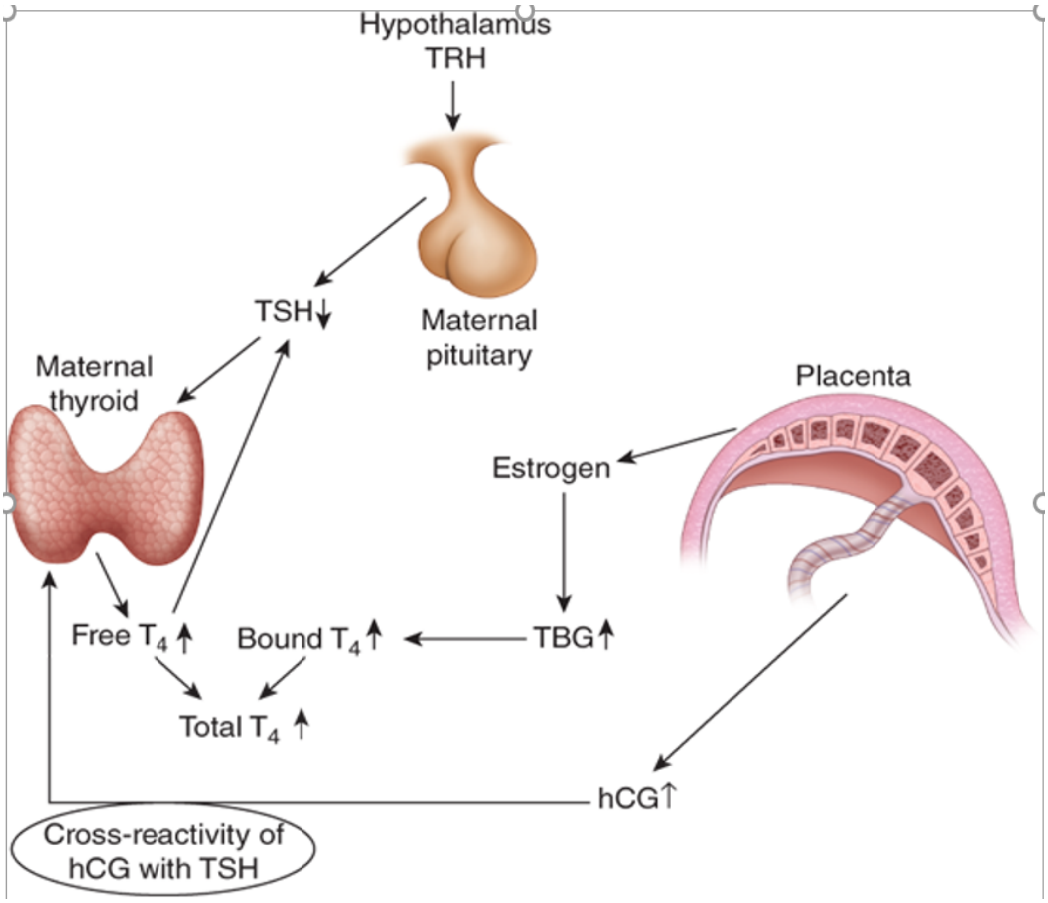
- *Carbohydrate metabolism*: Thyroid hormones stimulate almost all aspects of carbohydrate metabolism, including enhancement of insulin-dependent entry of glucose into cells and increased gluconeogenesis and glycogenolysis to generate free glucose.[20,23]

- *Growth and Development*: Thyroid hormones are clearly necessary for normal growth in children as evidenced by the growth-retardation observed in thyroid deficiency. Normal levels of thyroid hormone are essential to the development of the fetal and neonatal brain.[24,25]

- *Cardiovascular system*: Thyroid hormones increases heart rate, cardiac contractility and cardiac output. They also promote vasodilation, which leads to enhanced blood flow to many organs. [26,27]

- *Central nervous system*: Both decreased and increased concentrations of thyroid hormones lead to alterations in mental state. [28,29,30]

MATERNAL THYROID FUNCTION DURING PREGNANCY [18,19,35]



Normal pregnancy entails substantial changes in thyroid function in all animals. These phenomena have been studied most extensively in humans, but probably are similar in all mammals. Major alterations in the thyroid system during pregnancy include:

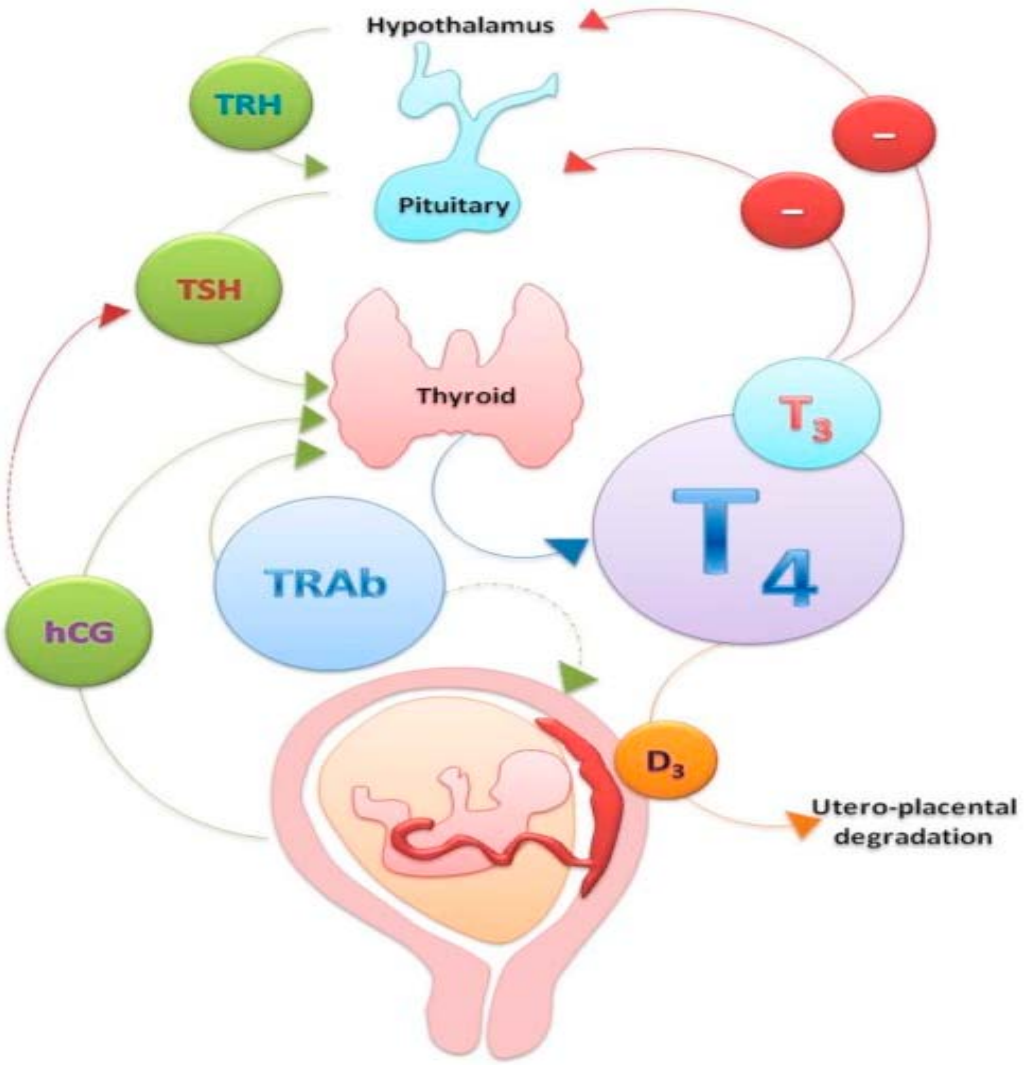
- *Increased blood concentrations of T4-binding globulin:* TBG is one of several proteins that transport thyroid hormones in blood, and has the highest affinity for T4 (thyroxine) of the group. Estrogens stimulate expression of TBG in liver, and the normal rise in estrogen during pregnancy induces roughly a doubling in serum TBG concentratrations.

- *Increased levels of TBG lead to lowered free T4 concentrations*, which results in elevated TSH secretion by the pituitary and, consequently, enhanced production and secretion of thyroid hormones. The net effect of elevated TBG synthesis is to force a new equilibrium between free and bound thyroid hormones and thus a significant increase in total T4 and T3 levels. The increased demand for thyroid hormones is reached by about 20 weeks of gestation and persists until term.

- *Increased demand for iodine:* This results from a significant pregnancy-associated increase in iodide clearance by the kidney (due to increased glomerular filtration rate), and siphoning of maternal iodide by the fetus. The World Health Organization recommends increasing iodine intake from the standard 100 to 150 ug/day to at least 200 ug/day during pregnancy.

THYROID STIMULATION BY CHORIONIC GONADOTROPIN

- The placentae of humans and other primates secrete huge amounts of a hormone called chorionic gonadotropin (in the case of humans, human chorionic gonadotropin or hCG) which is very closely related to luteinizing hormone. TSH and hCG are similar enough that hCG can bind and transduce signalling from the TSH receptor on thyroid epithelial cells. Toward the end of the first trimester of pregnancy in humans, when hCG levels are highest, a significant fraction of the thyroid-stimulating activity is from hCG. During this time, blood levels of TSH often are suppressed. [3,16]



THYROID HORMONES IN FETAL AND NEONATAL PERIOD [23,24,27]:

Thyroid hormones act by binding to nuclear receptors and modulating transcription of responsive genes. Thyroid hormone receptors are widely distributed in the fetal brain, and present prior to the time the fetus is able to synthesize thyroid hormones. It has proven surprisingly difficult to identify the molecular targets for thyroid hormone action in the developing brain, but some progress has been made. The promoter of the myelin basic protein gene is

directly responsive to thyroid hormones and contains the expected hormone response element. This fits with the observation that induced hypothyroidism in rats leads to diminished synthesis of mRNAs for several myelin-associated proteins.

The fetus has two potential sources of thyroid hormones - its own thyroid and the thyroid of it's mother. Human fetuses acquire the ability to synthesize thyroid hormones at roughly 12 weeks of gestation, and fetuses from other species at developmentally similar times. Current evidence from several species indicates that there is substantial transfer of maternal thyroid hormones across the placenta. Additionally, the placenta contains deiodinases that can convert T4 to T3.

POSTNATAL CHANGES IN THYROID HORMONE LEVELS

The extra uterine adaptability of the neonate is reflected by the changes in thyroid hormone economy in the postnatal period. After birth, there is an acute discharge of TSH provoked by the fall in ambient intra-uterine temperature. This reaches a peak at 30 min before falling towards basal levels within the first 3 days. There is an associated release of thyroid hormones and enhanced peripheral conversion of T4, which results in a pronounced increase in T3 in the first hours of life. There is a further increase in total T3 and T4 levels for about 36 hrs around the time of the postnatal peak, and T4 levels remain relatively high for the first weeks of life. [26].

Several factors affect the level of thyroid hormones in the perinatal period. But studies have shown ambiguity in their relationships. Prematurity, neonatal illness, and neonatal and maternal medications may influence neonatal TSH and thyroid hormone levels. Apart from that birth order, mode of delivery, birth weight, maternal thyroid status were found to have equivocal relationship with neonatal thyroid profile. Preterm infants show similar lesser changes in TSH and thyroid hormone concentration. In the case of infants under 30 wks of gestation, the postnatal surge does not occur and T4 levels frequently fall to a nadir around 1-2 wks of age, which is more pronounced with increasing prematurity. Thyroxine levels remain below those of full-term infants through the first few weeks of life and climb gradually to normal postnatal levels. By 1 - 2 months of age, thyroid hormone levels are comparable to the term infant.

Alterations in thyroid hormone metabolism due to nonthyroidal illnesses are known as euthyroid sick syndrome.[27] The typical pattern of the euthyroid sick syndrome includes a reduction in T3 concentration and an increase in rT3 concentration, with a suppressed response of TSH to TRH and only a minimum tendency towards a reduction in serum T4 and TBG levels. The level of involvement of the thyroid function is correlated with the severity of the disease and the prognosis gets worse with the reduction of hormone levels.[28]. Low levels of thyroid hormones in non-thyroidal illnesses are associated with poor prognosis.

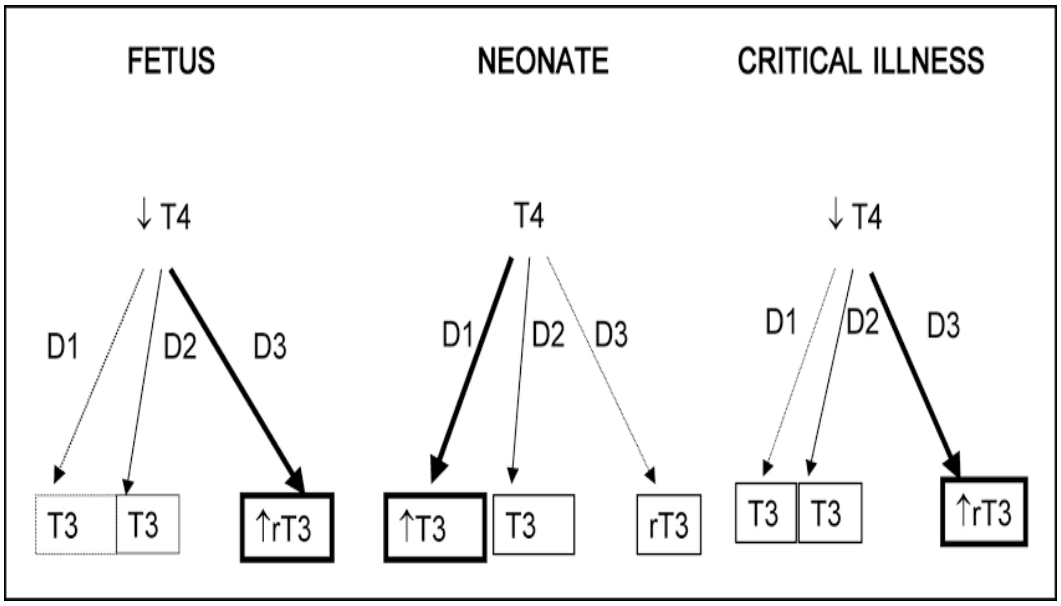
The severity of the neonatal illness is also reflected in the T4 levels, with infants who require ventilator assistance for respiratory distress syndrome having the lower T4 levels, possibly suggesting non-thyroidal illness (sick euthyroid syndrome). This may be an adaptive response to illness resulting in a depressed metabolic rate due to occurrence of central hypothyroidism which results in low levels of thyroid hormones secondary to reduced production of TSH.

Perinatal asphyxia remains a frequent cause of the chronic handicapping conditions of cerebral palsy, mental retardation, learning disability and epilepsy. Thyroxine is essential for optimal brain development and low levels are associated with adverse neurodevelopmental outcomes. [4]

In perinatal asphyxia the magnitude of this thyroid hormone surge is attenuated. Lower T4, free T4, and T3 levels are secondary to lower TSH levels in asphyxiated newborns; also, peripheral metabolism of T4 in asphyxiated infants can be altered due to low T3 and normal reverse T3 levels. Alterations in the thyroid function observed in asphyxiated new-borns may be caused by the low consumption of oxygen with low metabolic rate, suggesting that asphyxia plays an important role in thyroid metabolism. Warner S et al, they observed that hypoxia leads to activation of deiodinase type 3 in turn inactivates the peripheral conversion of T4 to T3.[16]. In hypoxic-ischemic brain injury, HIF-1, [Hypoxia Inducible Factor-1] reduces local thyroid hormone signaling through induction of D3.Thyroid hormone levels vary with

the term and those born preterms, depending upon gestational age at birth. [5] Several studies were done over asphyxiated term babies, where the Thyroid hormone levels and TSH were found to be low and different in different stages of HIE.[6] In newborns with 18-24 hours of life, lower levels of T4, T3, FT4, and TSH were observed in asphyxiated newborns, in which the basal levels (in cord blood), with exception of FT4, failed to increase.[29]

The cord serum T3 concentration was not influenced by maturity, birth-weight, or neonatal risk factors, whereas these factors did affect the concentrations of T3, T4, and TBG. [7] There is no arteriovenous T3 concentration difference across the placenta; therefore the cord T3 reflects the systemic T3 concentration in the baby at birth. As T3 in the neonate largely, if not entirely, derives from thyroxine from the fetal thyroid, measurement of the cord T3 concentration may be a good immediate screening test for neonatal hypothyroidism.[12] Few studies have shown a difference between serum concentrations of TSH, T4, T3, and FT4 in asphyxiated newborns compared to normal newborn which suggests central hypothyroidism secondary to asphyxia.[13] Moreover, asphyxiated newborns with moderate/severe hypoxic-ischemic encephalopathy present a greater involvement of the thyroid function and consequently a greater risk of death[14,15]


FETUS
NEONATE
CRITICAL ILLNESS
↓T4
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REVIEW OF LITERATURE

Perinatal asphyxia continues to be an important cause of morbidity and mortality in new-born. Organ dysfunction depends on asphyxiated neonates on the duration of asphyxia and early management. Because of diving reflex in new-born blood diverted from less vital organs to more vital organs like brain, heart, and kidney.[16]

Thyroid hormones are essential for the normal development of the brain. Thyroid disorders in the new-born form a complex group of conditions, many of which are the focus of active research at present. Well established screening programs have been implemented to detect congenital hypothyroidism, which is associated with mental and growth retardation if left undetected and untreated. [17] Thyroid status in the newborn is also influenced by maternal thyroid disease.

The importance of thyroid hormones to the normal development of the brain and intellectual function and their relation with patients' prognosis requires studies that correlate hormonal alterations with the occurrence of neurological sequelae. There are few studies evaluating the effect of perinatal asphyxia on thyroid hormones with conflicting results. Studies that evaluate the role of T4 and/or T3 restoration in patients with subnormal hormonal levels should also be considered. [27,28,30]

Kumar PS et al found an increase in the levels of rT3 in patients with acute hypoxemia, suggesting a reduction in its degradation. The study showed that patients with chronic hypoxemia showed decreased levels of T3 and increased rT3 levels, revealing alterations in extrathyroidal metabolism.[32]

Lakshminarayana SG et al found that FT4 and FT3 levels failed to increase within the first 48 hours of life in the group of asphyxiated newborns, even though their TSH levels were normal.[33]

Lee DH.et.al suggested that decreased levels of T4 and T3 at18 to 24 hours after birth in the asphyxiated group is secondary to a diminished TSH level. No difference in median rT3 levels between asphyxiated group and control group suggests a normal peripheral T4 metabolism in asphyxiated term newborn infants[34]

Léger J, et.al concluded that the means for thyroid hormones, in cord blood, were similar in both groups, except for rT3, which was higher in the group of asphyxiated newborns. Alterations in hormone production and in the peripheral metabolism of T4 may be responsible for these differences; they found low levels of T3 in contrast to normal levels of reverse T3.On the other hand, in newborns with 18-24 hours of life, lower levels of T4, T3, FT4, and

TSH were observed in asphyxiated newborns, with exception of FT4, failed to increase.[35]

Kim et al observed that serum concentrations of thyroid hormones-T4, T3, free T4 (FT4) and reverse T3 (rT3)-and thyroid-stimulating hormone (TSH) found in the umbilical cord blood of term newborns with and without asphyxia and those found in their arterial blood collected between 18 to 24 h after birth. They concluded that serum concentrations of TSH, T4, T3, and FT4 are lower in asphyxiated newborns than in normal newborns between 18 and 24 h of life; this suggests central hypothyroidism secondary to asphyxia. Asphyxiated newborns with moderate/severe hypoxic-ischemic encephalopathy present a greater involvement of the thyroid function and consequently a greater risk of death[35,36]

McElduff A et al in their study "Effect of perinatal asphyxia on level of thyroid hormones in term neonates" conducted at a tertiary care hospital in Jabalpur selected 60 asphyxiated cases based on APGAR scores and requirement of PPV and 60 healthy controls. They found out that cord blood thyroid hormones showed no significant difference while venous samples collected 18-24 hours after birth showed statistically significant levels of decrease in T3, T4 and TSH suggestive of central hypothyroidism.[37]

Meherban Singh et al studied the effect of perinatal asphyxia on thyroid hormone of neonates in a medical college hospital at Bhopal. 30 neonates with 1 and 5 minutes APGAR less than 7/10 were selected as cases and APGAR more than 7/10 where selected as controls. HIE staging was done by Sarnat and Sarnat staging. Out of 13.13% were HIE I, 50% were HIE II and 36.67% were HIE III. TFT was done at 6 hours and repeated at 18-24 hours. Asphyxiated new-borns failed to raise T3 and T4 levels at 18-24 hours due to a lack of physiological surge of TSH. The mean value of T3 and T4 were comparable between both groups while the TSH levels were significantly low in asphyxiated new-borns at 6 hours of life. At 18-24 hours of life, T3, T4, and TSH were significantly lower in the asphyxiated group.[38]

Mercado M et al conducted a study at Jaipur with 32 asphyxiated new-borns recruited as per NNF criteria for asphyxia and compared it with 32 healthy controls at 18-24 hours of life. They not only found that T3, T4, and TSH were lower in the cases but also found a significant decrease associated with advanced stages of HIE.[39]

Miyamoto N et al studied the thyroid hormone levels in 50 asphyxiated new-borns and 50 controls in Karnataka and concluded that thyroid hormones, in cord blood, were similar in both groups. In new-borns with 18-24 hours of life, lower levels of T4, T3, FT4, and TSH were observed in asphyxiated

newborns. They suggested that lower T4, free T4, and T3 levels are secondary to lower TSH levels in asphyxiated new-borns; also, peripheral metabolism of T4 in asphyxiated infants can be altered due to low T3 and normal reverse T3 levels.[40]

Nishant Prabhakar et al[13] in their study "Effect of perinatal asphyxia on level of thyroid hormones in term neonates" conducted at a tertiary care hospital in Jabalpur selected 60 asphyxiated cases based on APGAR scores and requirement of PPV and 60 healthy controls. They found out that cord blood thyroid hormones showed no significant difference while venous samples collected 18-24 hours after birth showed statistically significant levels of decrease in T3, T4 and TSH suggestive of central hypothyroidism.

Rajesh Tikkas et al[14] studied the effect of perinatal asphyxia on thyroid hormone of neonates in a medical college hospital at Bhopal. 30 neonates with 1 and 5 minutes APGAR less than 7/10 where selected as cases and APGAR more than 7/10 where selected as controls. HIE staging was done by Sarnat and Sarnat staging. Out of 13.13% were HIE I , 50% were HIE II and 36.67% were HIE III. TFT was done at 6 hours and repeated at 18-24 hours. Asphyxiated new-borns failed to raise T3 and T4 levels at 18-24 hours due to lack of physiological surge of TSH. The mean value of T3 and T4 were comparable between both groups while the TSH levels were significantly low in

asphyxiated new-borns at 6 hours of life. At 18-24 hours of life, T3, T4 and TSH was significantly lower in the asphyxiated group.

Gurjar et al[15] conducted a study at Jaipur with 32 asphyxiated new-borns recruited as per NNF criteria for asphyxia and compared it with 32 healthy controls at 18-24 hours of life. They not only found that T3, T4 and TSH were lower in the cases but also found significant decrease associated with advanced stages of HIE.

Sunil Kumar et al[12] studied the thyroid hormone levels in 50 asphyxiated new-borns and 50 controls in Karnataka and concluded that thyroid hormones, in cord blood, were similar in both groups. In new-borns with 18-24 hours of life, lower levels of T4, T3, FT4, and TSH were observed in asphyxiated new-borns. They suggested that lower T4, free T4, and T3 levels are secondary to lower TSH levels in asphyxiated new-borns; also, peripheral metabolism of T4 in asphyxiated infants can be altered due to low T3 and normal reverse T3 levels.

NEED FOR THE STUDY

The importance of thyroid hormones in neonatal homeostasis is well known but its role in perinatal asphyxia is lesser analyzed. The aim of this study is to find out the changes in thyroid hormone levels in perinatal asphyxia and also its severity and how it affects the morbidity and mortality. This study will pave way for future trials regarding need for thyroid hormone supplementation in asphyxiated babies.

AIM AND OBJECTIVE OF THE STUDY

PRIMARY OBJECTIVE

To study the effect of perinatal asphyxia on thyroid function in new-born babies and to find out the association between the thyroid hormone levels and the severity and morbidity of asphyxia.

SECONDARY OBJECTIVES

1. To compare the serum levels of thyroid hormones (Total T3 and Total T4) and TSH in term asphyxiated new-borns and healthy new-borns at 18-24 hrs of life.
2. To find the association between the severity of Hypoxic Ischaemic Encephalopathy (HIE) and thyroid hormone levels.
3. To find the association between low T3 levels and the occurrence of multi-organ dysfunction in asphyxiated new-borns.

MATERIALS AND METHODS

STUDY DESIGN: Comparative Cohort Study.

STUDY POPULATION: Newborn babies admitted to Neonatal Intensive Care Unit, Kilpauk Medical College Hospital. Total 60 full-term neonates admitted to Neonatal Intensive Care Unit, Kilpauk Medical College will be included in the study, 30 asphyxiated neonates and 30 non-asphyxiated neonates

THE ASPHYXIATED GROUP: Study population consisted of full-term newborns with perinatal asphyxia as defined below:

Two or more of the following

a) Signs of fetal distress as indicated by one or more of the following:

- Fetal bradycardia (≤ 100 beats/min)

- Thick meconium staining of liquor

- Abnormal cardiotocography recordings as a sudden and sustained fetal bradycardia or the absence of fetal heart rate variability in the presence of persistent, late, or variable decelerations,

- Arterial cord pH < 7.2 or base deficit > 15mmol/L

b) Apgar score < 7 at five minutes of life.

c) Need for > 1 minute of positive pressure ventilation before the occurrence of sustained respiration

THE NON-ASPHYXIATED GROUP: Full-term, appropriate for gestational age new-borns, without history or clinical features of perinatal asphyxia evidenced by normal CTG findings, clear liquor, good spontaneous respiratory effort at birth, normal heart rate at birth and 5 minutes APGAR score more than or equal to 7 are considered non- asphyxiated new-borns.

STUDY PERIOD: 6 months

PLACE OF STUDY: Neonatal Intensive Care Unit, Kilpauk Medical College Hospital.

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INCLUSION CRITERIA:

1. Term neonates (Gestational age > 37 weeks).
2. Birth weight appropriate for gestational age.

EXCLUSION CRITERIA:

1.Maternal history of thyroid dysfunction.

2.Maternal history of antihypertensive and steroid intake.

3.False low APGAR due to maternal sedation.

4.Prematurity.

5.Evidence of sepsis.

6.Congenital malformations and metabolic disorders.

7.Parents refusing to give consent

SAMPLE SIZE CALCULATION

Sample size was calculated by Epi Info software based on the reference study given below using mean and standard deviation of T4. The mean T4 levels for the asphyxiated newborns was kept at 9.01±1.55 and the mean T4 levels for the non-asphyxiated group was kept at 9.03±1.35.

REF: Rajesh Tikkas, Pankaj Kumar Pal, Manasi Garg. "A Study of Effect of Perinatal Asphyxia on Thyroid Hormone in Neonates". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 69, August 27; Page: 12026-12030, DOI: 10.14260/jemds/2015/1734.

- The confidence level is estimated at 95% with a z value of 1.96.
- The power of the study was estimated at 95% and significance level 0.05 a sample size of minimum 27 is required in each group.
- Keeping an attrition of 10% a sample size of 30 subjects in each group is recruited.

METHODS:

- Gestational age was evaluated according to obstetric gestational age and ascertained by physical examination using Modified Ballard's Scoring. When the difference between obstetric gestational age and clinical evaluation was higher than 2 weeks, clinical evaluation was considered.
- Detailed maternal history is taken which includes maternal morbidity like hypertension, thyroid dysfunction, maternal drug intake.

- Perinatal events including the use of sedatives, CTG findings, prolonged second stage of labor, the colour of the liquor, APGAR score and birth weight are noted.
- Informed consent is obtained from the parents.
- Asphyxiated new-borns undergo the complete physical and neurological examination.
- The severity of HIE is graded within 24 hours by Sarnat and Sarnat staging as mild (stage I), moderate (stage II) and severe HIE (stage III).[17]
- Asphyxiated new-borns are followed up in the immediate newborn period up to 72 hours for evidence of multi-organ dysfunction like cardiogenic shock, renal failure, respiratory distress, and seizures. In the presence of multi-organ dysfunction, the neonates will be managed as per unit protocol in NICU.
- Peripheral venous samples for T3, T4, and TSH are collected from both groups at 18-24 hours of life and sent for analysis by ELISA method at the laboratory, Department of Biochemistry, Kilpauk Medical College and Hospital, Chennai.
- The values between asphyxiated and non-asphyxiated babies are compared.
- The relationship between the severity of Hypoxic Ischaemic Encephalopathy and thyroid hormone levels are analyzed.

- As T3 is the active form of thyroid hormone essential for various organ functions the association between low T3 levels at 18-24 hours of life and poor outcome as evidenced by multi-organ dysfunction is analyzed.

STATISTICAL ANALYSIS

1. Data will be entered into the Microsoft Excel Spreadsheet.

2. Data were computer analyzed using SPSS/ PC (Statistical Package for the Social Science Inc. Chicago, Illinois USA, version 13.0) statistical package.

Descriptive analysis:

Descriptive analysis was carried out by mean and standard deviation for quantitative variables, frequency and proportion for categorical variables. Data was also represented using appropriate diagrams like bar diagram and pie diagram. Various demographic and obstetric parameters were considered as Neonatal explanatory variables.

Inferential statistics:

Both the study groups (Asphyxia and No Asphyxia) were compared with respect to the HIE-stage, obstetric parameters, etc. The association between categorical explanatory variables and quantitative outcome was assessed by comparing the mean values. Simple distribution of the study variables and cross-tabulation were applied. The independent- sample t-test procedure was used to compare the means of quantitative variables by dividing

cases into two qualitative groups such as the relationship between asphyxiated and non-asphyxiated neonates. The results in all the above-mentioned procedures were accepted as statistically significant when the p-value was less than 5% ($p<0.05$). A Pearson correlation has been performed to find the relationship between variables.

RESULTS

TABLE: 1 DISTRIBUTION OF NEWBORNS ACCORDING TO THEIR BIRTH WEIGHT

BIRTH WEIGHT					
			GROUP		Total
			ASPHYXIATED	NON-ASPHYXIATED	
BIRTH WEIGHT GROUP	<2500 gms	Count	5	1	6
		% within GROUP	16.7%	3.3%	10.0%
	>=2500 gms	Count	25	29	54
		% within GROUP	83.3%	96.7%	90.0%
Total		Count	30	30	60
		% within GROUP	100.0%	100.0%	100.0%

GRAPH: 1 DISTRIBUTION OF NEWBORNS ACCORDING TO THEIR BIRTH WEIGHT

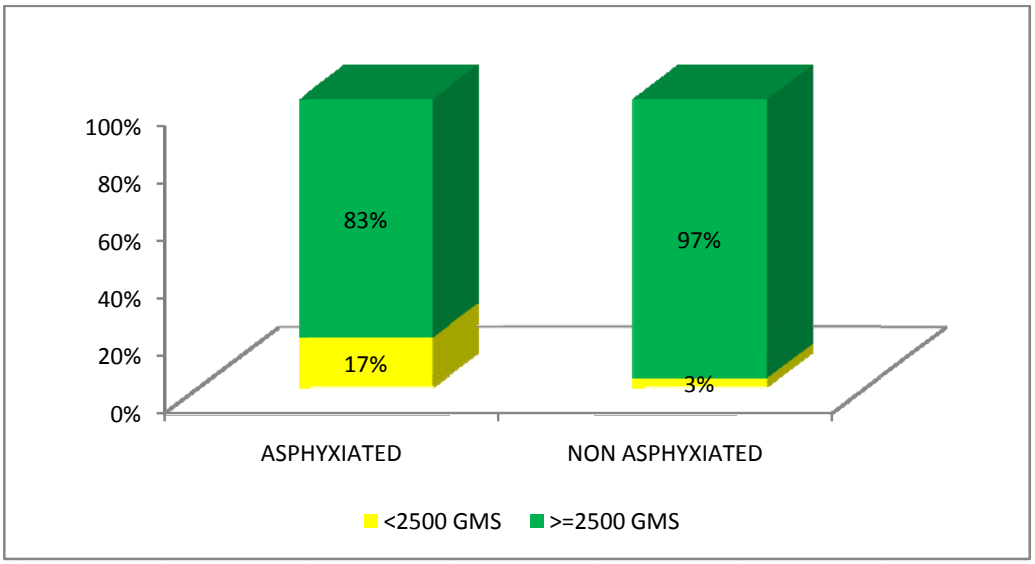


Table :1 & Graph :2 shows that in the Asphyxiated Group 5 children (16.7%) were <2500gms, whereas in the Non-Asphyxiated group it was 1 baby (3.3%).

>=2500 gms were 25 children(83.3%) in the asphyxiated group while it was 29 children in the non asphyxiated children equivalent to 96.7%. Pearson Chi-Square=2.963 P=0.085

TABLE: 2 MODE OF DELIVERY

			GROUP		Total
			ASPHYXIATED	NON-ASPHYXIATED	
MODE OF DELIVERY	AVD	Count	4	0	4
		% within GROUP	13.3%	0.0%	6.7%
	LSCS	Count	14	22	36
		% within GROUP	46.7%	73.3%	60.0%
	NVD	Count	12	8	20
		% within GROUP	40.0%	26.7%	33.3%
Total		Count	30	30	60
		% within GROUP	100.0%	100.0%	100.0%

GRAPH: 2 MODE OF DELIVERY

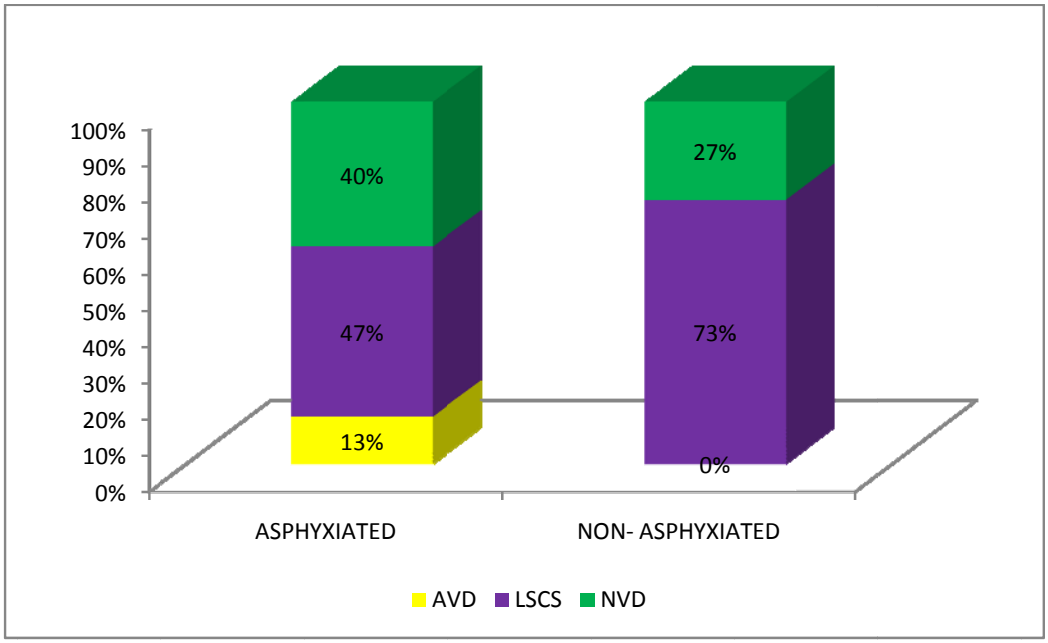


TABLE : 2 & GRAPH :2 In the asphyxiated group,4 babies (13.3%) were delivered by assisted vaginal delivery (AVD). LSCS rate in Asphyxiated group was 14 babies (46.7%) and 12 babies (40%) were delivered by normal vaginal delivery. In the Non-Asphyxiated group22 babies (73.3%) were delivered by LSCS and 8 children(26.7%) were delivered by normal vaginal delivery. There was no instrumental deliveries in the non-asphyxiated group. Pearson Chi-Square=6.578* P=0.037

TABLE :3 HIE STAGING

HIE STAGE	Frequency	Percent
STAGE 1	12	40.0
STAGE 2	13	43.3
STAGE 3	5	16.7
Total	**30**	**100.0**

GRAPH :3 HIE STAGING

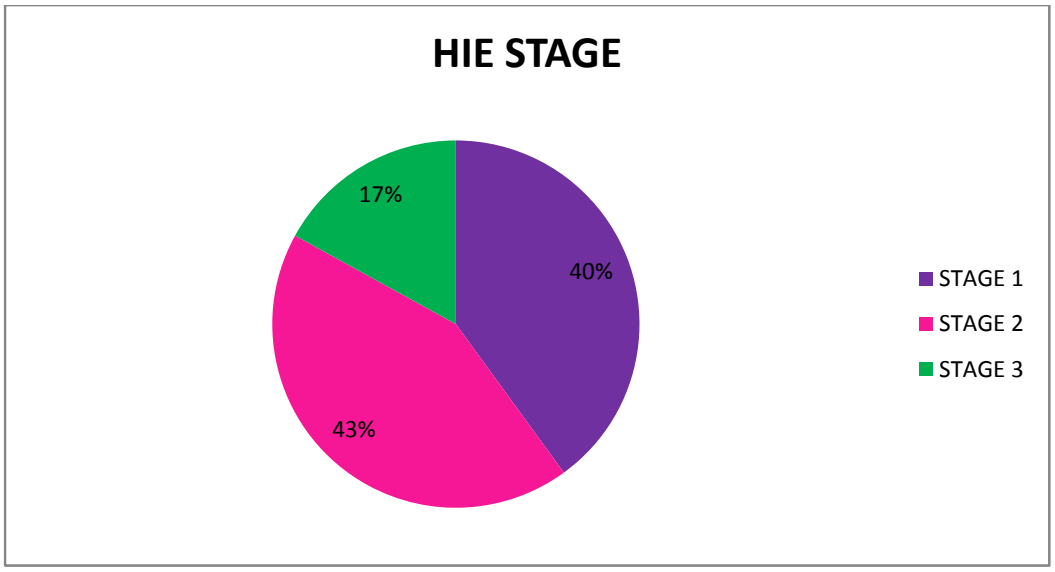


TABLE :3 & GRAPH :3 Among the 30 Asphyxiated neonates, 40 % (12 babies) belonged to Stage –I HIE, 43.3% (13 babies) were in Stage –II HIE and 17% (5 babies) were in Stage-III HIE.

TABLE: 4 EVIDENCE OF MORBIDITY

	Frequency	Percent
CARDIOGENIC SHOCK/RENAL FAILURE/ RESPIRATORY DISTRESS	5	16.7
RESPIRATORY DISTRESS	21	70.0
RESPIRATORY DISTRESS/ CARDIOGENIC SHOCK	4	13.3
Total	**30**	**100.0**

GRAPH:4 EVIDENCE OF MORBIDITY

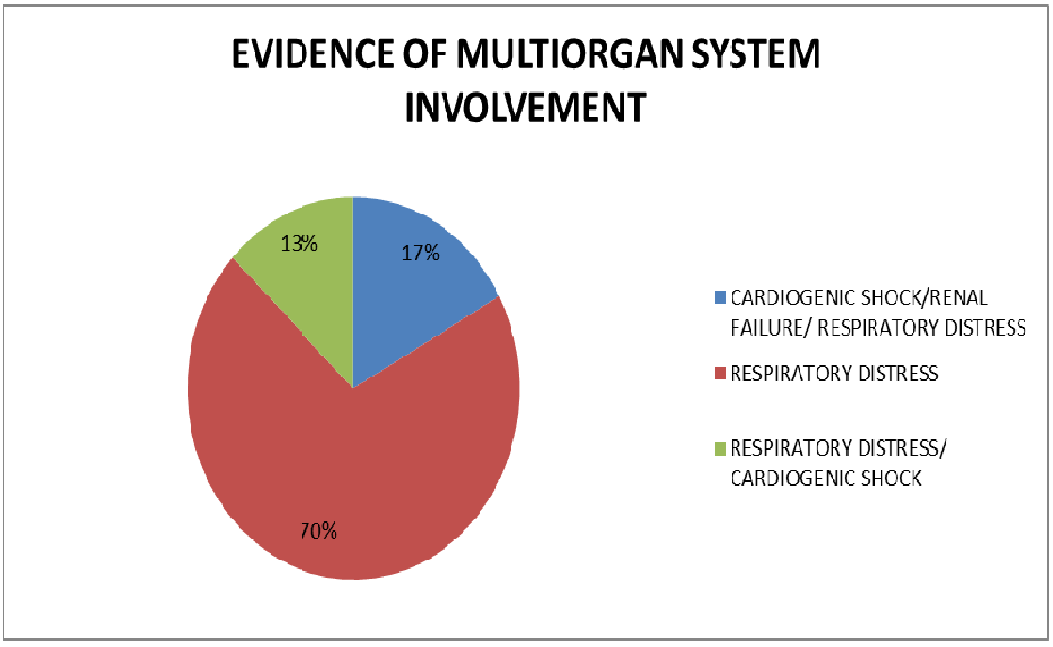


Table: 4 & Graph:4 - Respiratory Distress found to be more, around 70% in our study.

TABLE: 5 MECONIUM STAINED LIQUOR FOR ASPHYXIATED BABIES

MECONIUM STAINED LIQUOR	FREQUENCY	PERCENT
NO	15	50.0
YES	15	50.0
Total	**30**	**100.0**

GRAPH: 5 MECONIUM STAINED LIQUOR FOR ASPHYXIATED BABIES

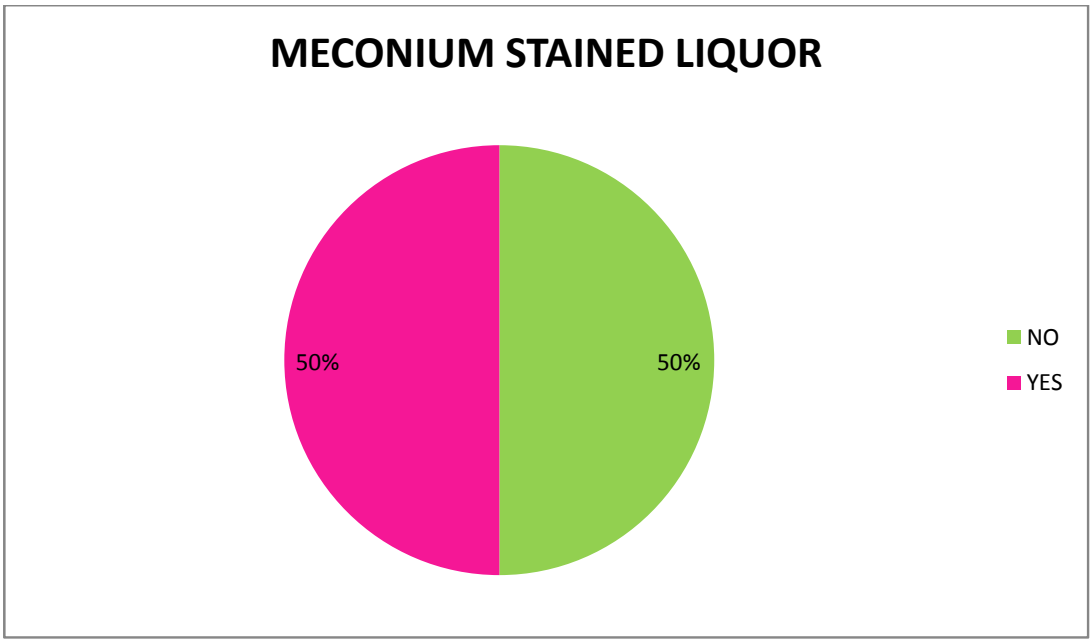


TABLE 5 & GRAPH 5 shows that in the Asphyxiated group among 30 cases 15 had shown the presence of meconium-stained liquor, 15 had clear liquor.

TABLE: 6 SHOWS APGAR AT 1 minute

APGAR AT 1 min	Frequency	Percent
<=3	6	20.0
3 TO 6	24	80.0
Total	**30**	**100.0**

GRAPH: 6 SHOWS APGAR AT 1 min

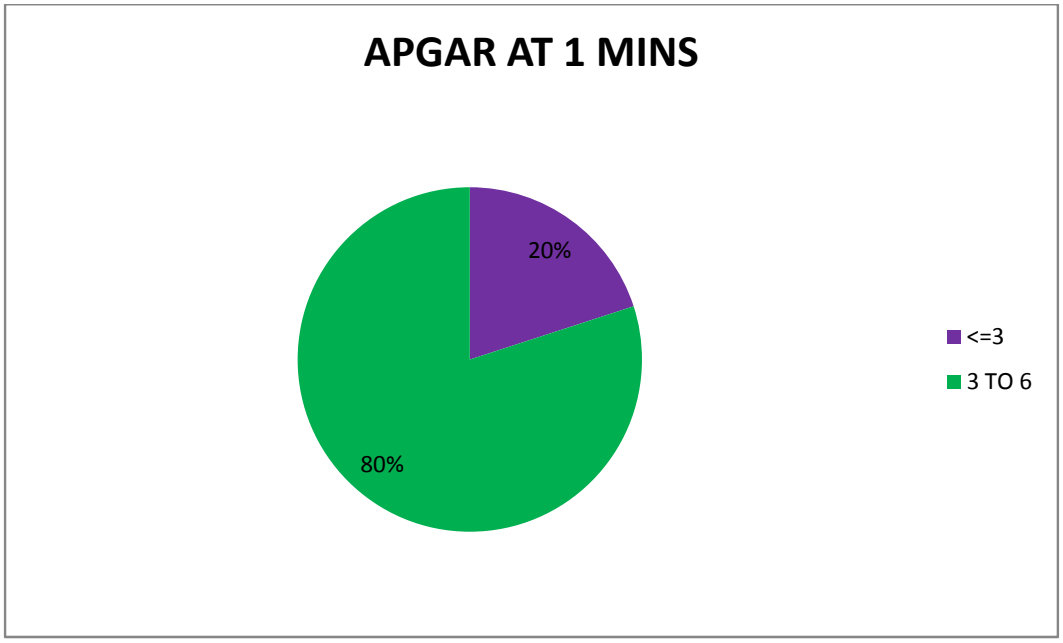


Table :6 & Graph :6 APGAR AT 1 MINS was <=3 in 6 Asphyxiated neonates which was 20%, 3to 6 were in 24 Asphyxiated neonates.

TABLE: 7 SHOWS APGAR AT 5 MINS

APGAR AT 5 MINS	Frequency	Percent
<=3	9	30.0
3 TO 6	21	70.0
Total	**30**	**100.0**

Table: 7& Graph: 7 shows the APGAR AT 5 MINS- 9 babies had <=3 which is 30% and 21 babies had 3to 6 which is 70%.

TABLE: 7 SHOWS APGAR AT 5 MINS

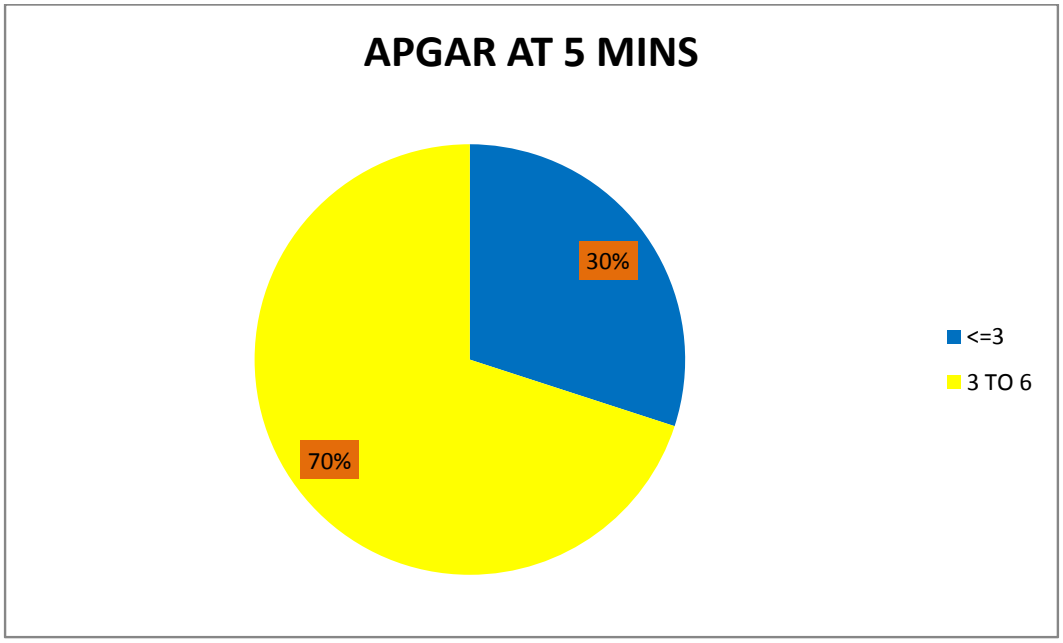
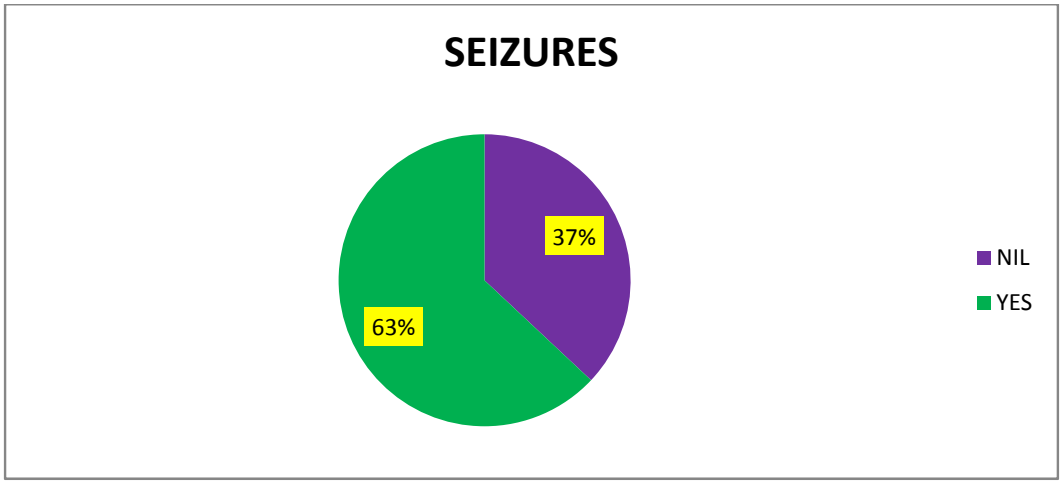


TABLE 8: SHOWS PREVELANCE OF SEIZURES

SEIZURES	Frequency	Percent
NIL	11	36.7
YES	19	63.3
Total	**30**	**100.0**

TABLE: 8 SHOWS PREVELANCE OF SEIZURES

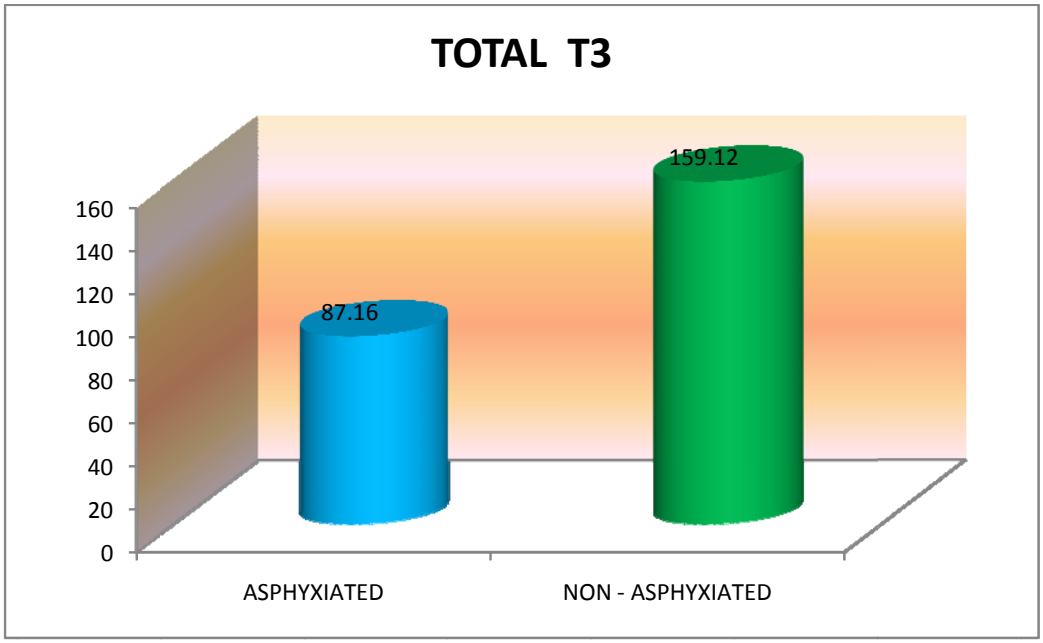


Table; 8 Shows The Prevalence Of Seizures Among Asphyxiated neonates is 19 babies accounting to 63.3%, Absent in 11 Asphyxiated neonates Which Was 36.7%

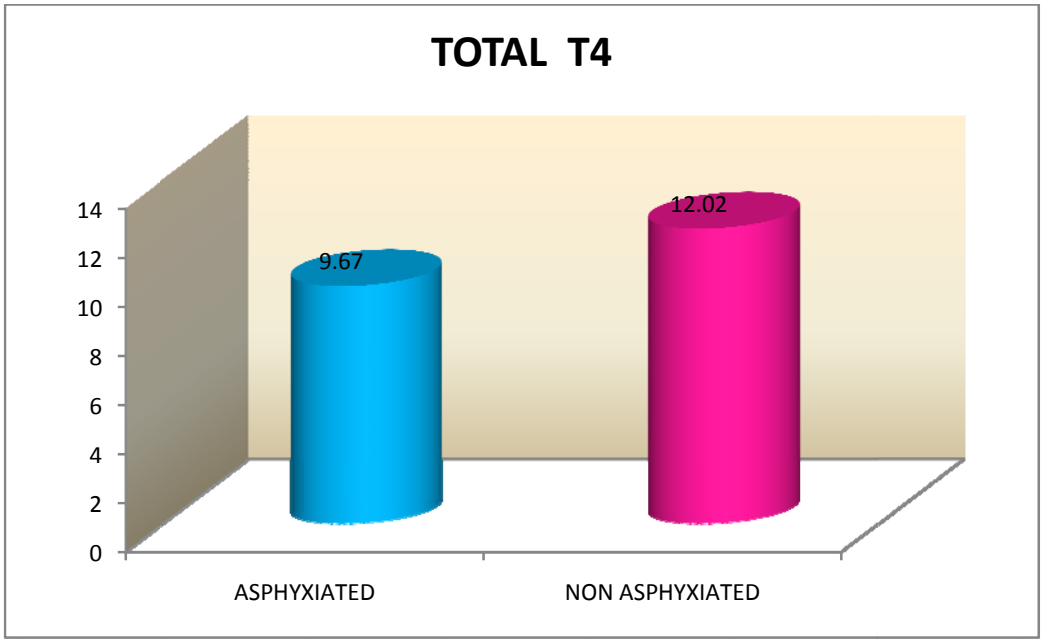
TABLE:9 THYROID PROFILE IN ASPHYXIATED AND NON-ASPHYXIATED BABIES

Group Statistics						
	GROUP	**N**	**Mean**	**Std. Deviation**	**Std. Error Mean**	**t VALUE**
TOTAL T3	ASPHYXIATED	30	87.1640	26.07250	4.76017	7.874**
	NON ASPHYXIATED	30	159.1233	42.73040	7.80147	
TOTAL T4	ASPHYXIATED	30	9.6737	3.11514	.56874	2.911**
	NON-ASPHYXIATED	30	12.0245	3.14080	.57343	
TSH	ASPHYXIATED	30	1.6742	.96896	.17691	3.159**
	NON-ASPHYXIATED	30	2.4906	1.03176	.18837	

GRAPH :9 TOTAL T3 LEVEL



GRAPH: 10 TOTAL T4 LEVEL



GRAPH -11 TSH LEVEL

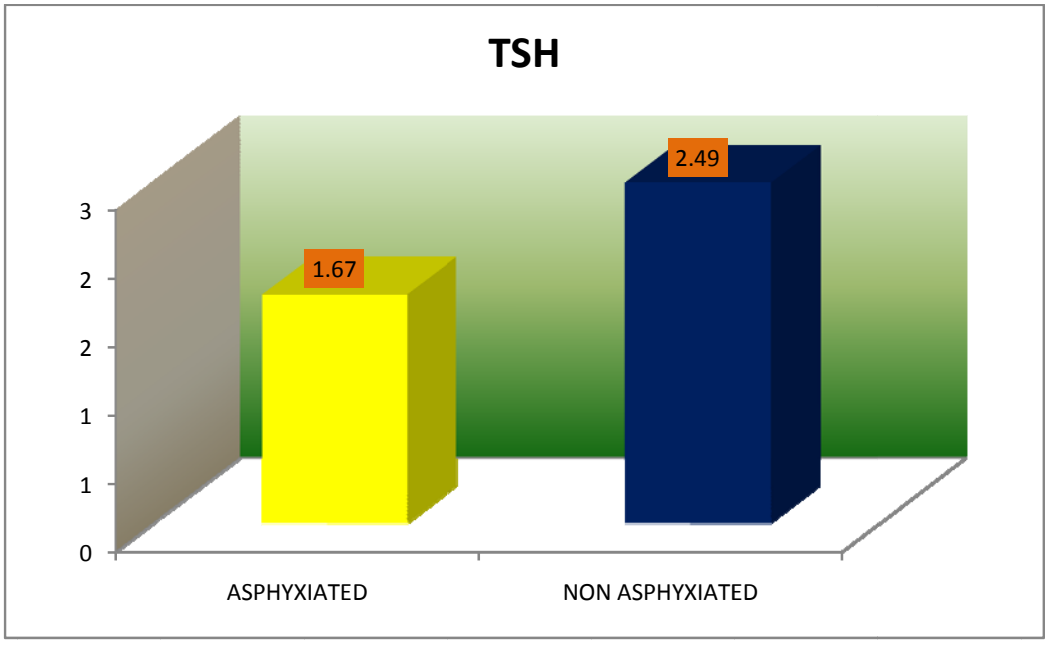


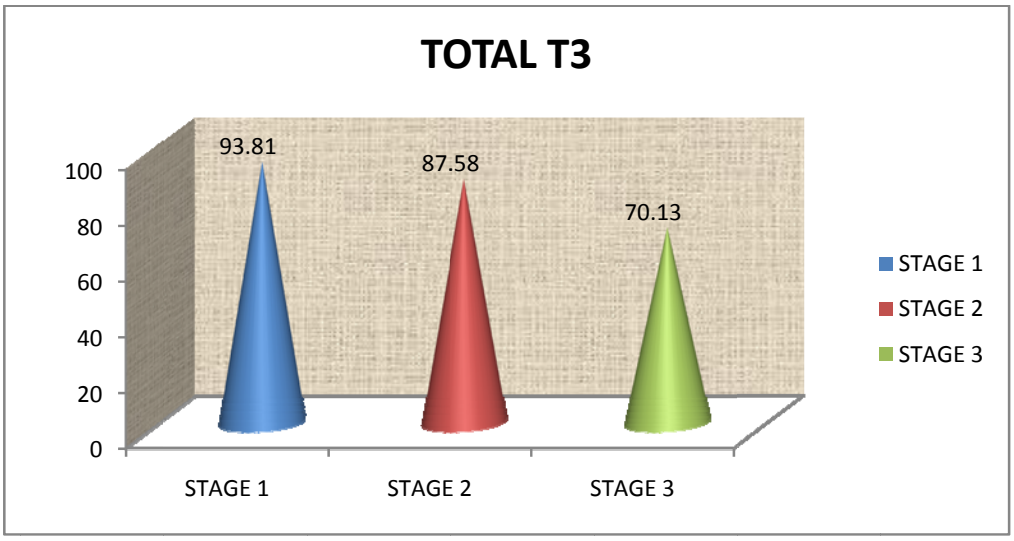
Table 9, graph 9, graph 10, graph 11 shows the thyroid profile variations in Asphyxiated neonates and Non-Asphyxiated neonates . t3- was 87.1640 ng/dl, in Asphyxiated neonates and 159.1233 ng/dl in non asphyxiated of t value- 7.874* *t4 – among Asphyxiated neonates were -9.6737 ng/dl, in Non-Asphyxiated neonates -12.0245ng/dl of t value -2.911**tsh level in Asphyxiated neonates were 1.6742ng/dl, in Non-Asphyxiated neonates were 2.4906ng/dl of t value t-value 3.159**.

**P<0.001. T3,T4,TSH Were Compared To be Less In Asphyxiated neonates When Compared To Non-Asphyxiated neonates.

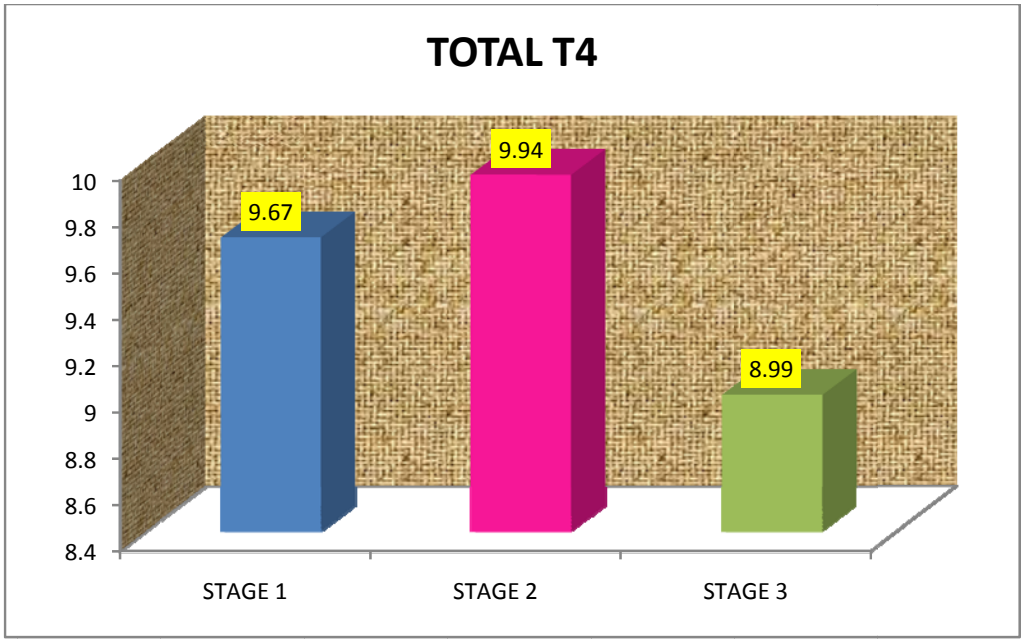
TABLE: 10 THYROID PROFILE IN DIFFERENT STAGES OF HIE

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean			
						Lower Bound	Upper Bound	f VALUE	P value
Total T3	Stage 1	12	93.81	25.06	7.23	77.89	109.74	1.510	0.239
	Stage 2	13	87.58	21.78	6.04	74.42	100.74		
	Stage 3	5	70.13	35.82	16.02	25.66	114.60		
	Total	30	87.16	26.07	4.76	77.43	96.90		
Total T4	Stage 1	12	9.67	2.11	0.61	8.33	11.01	0.160	0.853
	Stage 2	13	9.94	3.03	0.84	8.11	11.77		
	Stage 3	5	8.99	5.45	2.44	2.21	15.76		
	Total	30	9.67	3.12	0.57	8.51	10.84		
TSH	Stage 1	12	1.72	1.17	0.34	0.97	2.46	2.276	0.122
	Stage 2	13	1.93	0.76	0.21	1.47	2.40		
	Stage 3	5	0.90	0.56	0.25	0.20	1.59		
	Total	30	1.67	0.97	0.18	1.31	2.04		

GRAPH: 10 T3 IN DIFFERENT STAGES OF HIE



GRAPH: 11 T4 IN DIFFERENT STAGES OF HIE



GRAPH: 11 TSH IN DIFFERENT STAGES OF HIE

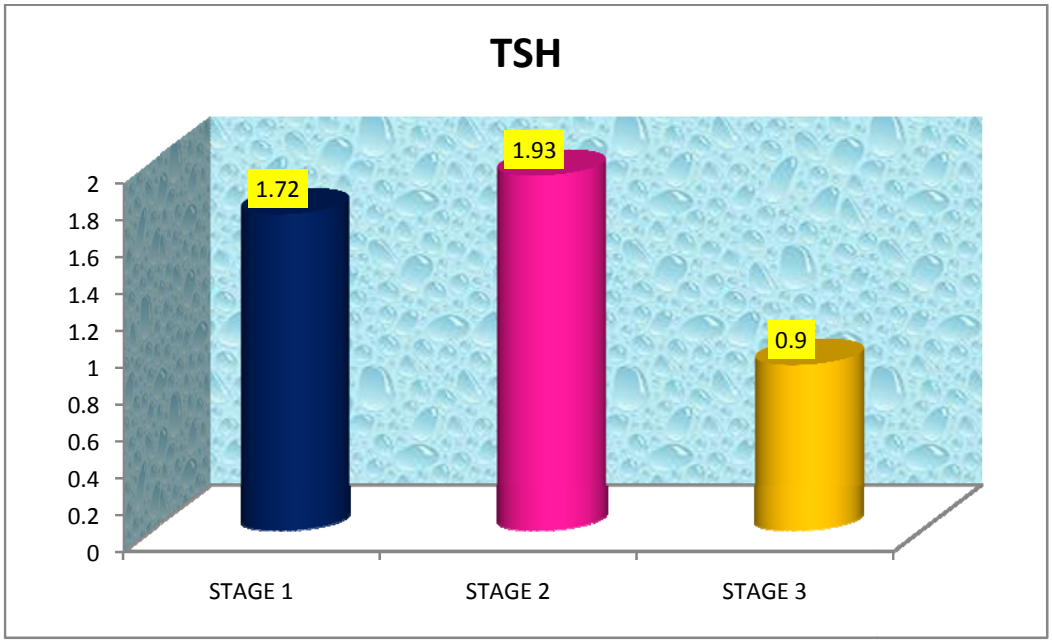


Table :10 & Graph 10 Shows that in our study on comparison of mean value of T_3 , T_4 and TSH levels of newborn between HIE-I , HIE-II and HIE-III was not statistically significant ($p<0.05$).

TABLE: 11 THYROID PROFILE CORRELATION WITH MORBIDITY

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean			
						Lower Bound	Upper Bound	F value	P value
Total_T3	Respiratory Distress	21	91.5676	24.69788	5.38952	80.3253	102.8100	4.541*	0.020
	Cardiogenic Shock / Respiratory Distress	5	94.7880	23.97215	10.72067	65.0226	124.5534		
	Cardiogenic Shock / Renal Failure/ Respiratory Distress	4	54.5150	9.19118	4.59559	39.8898	69.1402		
	Total	30	87.1640	26.07250	4.76017	77.4284	96.8996		

Total_T4	Respiratory distress	21	9.8667	3.14553	.68641	8.4348	11.2985	3.140	0.059
	Cardiogenic shock/respiratory distress	5	11.3420	2.63296	1.17749	8.0728	14.6112		
	Cardiogenic shock/renal failure/ respiratory distress	4	6.5750	.94793	.47396	5.0666	8.0834		
	Total	30	9.6737	3.11514	.56874	8.5105	10.8369		
TSH	Respiratory distress	21	1.7102	.94489	.20619	1.2801	2.1403	4.219*	0.025
	Cardiogenic shock/respiratory distress	5	2.3440	.84713	.37885	1.2921	3.3959		
	Cardiogenic shock/renal failure/ respiratory distress	4	.6480	.07715	.03858	.5252	.7708		
	Total	30	1.6742	.96896	.17691	1.3124	2.0360		

*p<0.05

Table 11- shows that there is significant relationship between low T3 and TSH levels with morbidity but T4 levels were not significant.

DISCUSSION

The incidence of perinatal asphyxia is two per 1000 births in developed countries, but the rate is up to 10 times higher in developing countries where there may be limited access to maternal and neonatal care. Of those infants affected, 15-20% die in the neonatal period, and up to 25% of survivors are left with permanent neurologic deficits.[25,38]

Perinatal asphyxia can result in systemic effects, including neurologic insult, respiratory distress, and pulmonary hypertension, and liver, myocardial, and renal dysfunction. Depending on the severity and timing of the hypoxic insult, a neonate with hypoxic-ischemic encephalopathy due to perinatal asphyxia can demonstrate a variety of neurologic findings. Using the Sarnat staging for encephalopathy can be useful. [39,40]

Maternal diseases such as overt and gestational diabetes, essential or pregnancy-induced hypertension, and hyper- or hypothyroidism did not affect.TSH levels, in agreement with many previous studies and in disagreement with one study in which the authors reported an increased TSH level in maternal diabetes and preeclampsia. In addition, the use of medications to mothers did not affect TSH levels in that study. Further all of the infants in that study were born through normal vaginal delivery. This means that any maternal diseases were well controlled with proper medications. These results suggest that a well-controlled maternal disease during pregnancy is not likely

to influence neonatal TSH levels. Therefore, acute stress during labor may have caused increases in TSH levels.[8,12,13]

The thyroid hormones, thyroxine (T4) and triiodothyronine (T3), are tyrosine-based hormones produced by the thyroid gland. An important component in the synthesis is iodine. The thyronines act on the body to increase the basal metabolic rate, affect protein synthesis and increase the body's sensitivity to catecholamines (such as adrenaline) by permissiveness.[34,35] The thyroid hormones are essential to the proper development and differentiation of all cells of the human body. These hormones also regulate protein, fat, and carbohydrate metabolism, affecting how human cells use energetic compounds. Numerous physiological and pathological stimuli influence thyroid hormone synthesis.[36,37]

The thyroid hormone, thyroxine-binding globulin, and thyroid-stimulating hormone concentrations in term and preterm infants at birth, over the neonatal period, and during early infancy is in a state of flux during the perinatal period. However, very little data available which attempt to evaluate the possible effect of perinatal asphyxia on neonatal thyroid function.[38,39]

Few studies have shown a difference between serum concentrations of TSH, T4, T3, and FT4 in asphyxiated newborns compared to normal newborn which suggests central hypothyroidism secondary to asphyxia. Moreover, asphyxiated newborns with moderate/severe hypoxic-ischemic encephalopathy present a greater involvement of the thyroid function and consequently a

greater risk of death[39,40] In our study, the greatest difference among newborns was related to asphyxiation and non-asphyxiation. [40,41]

The clinical diagnosis of perinatal asphyxia is based on several criteria, the two main ones being evidence of cardiorespiratory and neurological depression (defined as an Apgar score remaining less than 7 at 5 minutes after birth) and evidence of acute hypoxic compromise with acidaemia (defined as an arterial blood pH of less than 7 or base excess greater than 12 mmol/L).[40,41] In many settings, especially resource-poor countries, it may be impossible to assess fetal or neonatal acidaemia. In the immediate postpartum period when resuscitation is being undertaken, it may not be possible to determine whether the neurological and cardiorespiratory depression is secondary to hypoxia-ischemia, or to another condition such as feto-maternal infection, or metabolic disease.

Perinatal asphyxia continues to be an important cause of morbidity and mortality in the newborn. Organ dysfunction depends on asphyxiated neonates on duration of asphyxia and early management. Because of diving reflex in newborn, blood is diverted from less vital organs to more vital organs like brain, heart, and kidney. The present study included 60 neonates of which 30 were cases of perinatal asphyxia and 30 were neonates without asphyxia. The asphyxiated neonates were further divided into three groups on the basis of severity of hypoxic-ischemic encephalopathy (HIE).[42,43]

In the present study, the mean weight in asphyxiated newborns was 2.732kg while in the non-asphyxiated group it was 2.81kg. A study conducted by Pereira DN et al. mean birth weight was 3.6kg and 3.3kg respectively. This difference in the mean weight of newborn observed in our study and other studies is due to ethnic and geographic variation.[44]

In our study, among the asphyxiated neonates 40% were delivered by labour naturale, 13% by assisted vaginal delivery using vacuum or forceps and 47% by lower segment caesarian section. Among the non asphyxiated group 27% were delivered by labour naturale and 73% by LSCS. There is no statistical difference observed in mean thyroid values of newborns delivered by either route. These observations were contrary to those observed by Procainoy RS et al where the majority of deliveries were vaginal.[45]. The increased rate of LSCS is attributed to several obstetric indications being a tertiary care referral institute.

In our study cases were classified into three groups as per the Sarnat and Sarnat staging of hypoxic-ischemic encephalopathy (HIE), 40% were in stage I, i.e. mild, 43% were in stage II i.e. moderate and 17% were in stage III i.e. severe. On comparison of mean value of T_3, T_4 and TSH levels at the age of 18-24hrs between HIE-I and HIE-III, HIE-II and HIE-III it was not statistically significant ($p<0.05$). [46,47]

The difference in mean T_3, T_4 and TSH value between asphyxiated and non-asphyxiated group statistically was significant (p value<0.05).The mean T_3 and T_4 of asphyxiated and non-asphyxiated group newborns within the first 18-24 hours were 87.16, 9.67 and 159.12, 12.02 which was statistically significant. The mean TSH of asphyxiated and non-asphyxiated group newborns at the age of 18-24 hours was 1.67 and 2.49 respectively. The difference was found to be statistically significant (p value<0.001). We observed in our study that normal physiological TSH surge was absent in asphyxiated newborns.[41,22,8]. These findings were comparable to Rajesh Tikkas et al, who found that mean value of T_3 and T_4 were significantly lower in cord blood of asphyxiated newborns compared to healthy term babies. They observed that means of TSH were significantly lower in study group when compared to control group (p-value <0.001) within 6 hours of life but on the contrary, observed rapid increase in TSH at 5 min and 3 hours of birth.[48.60]

Rashmi et al observed significantly higher levels of TSH and lower levels of T_3, T_4 and FT_4 in cord blood of asphyxiated newborns. They had not studied mean thyroid levels within 6hrs or 18-24 hours of birth.[49] Ryckman KK reported same finding in her study. The difference in results found in our study and others maybe because of difference in timing of collection of samples.

One study reported that neonates with asphyxia (Apgar score at 1 minute<3, and 5 minutes<5) had higher TSH levels than neonates with 1 minute Apgar score ≥8 and 5 minutes Apgar score ≥9. Another study reported high TSH levels with 1 minute Apgar score <6, but no difference in TSH level according to 5 minutes Apgar score.[50] In contrast, Sak E et al. reported that infants with 5 minutes Apgar score <8 had higher TSH levels, but there were no differences in TSH level according to 1 minute Apgar score. Some studies have reported no differences in TSH levels according to Apgar score as we found. Subjects in these studies were healthy normal babies with relatively high Apgar score without birth asphyxia. Thus, they were a relatively homogeneous group in terms of Apgar score. Besides, Apgar score is related to an examiner's subjectivity.[51,57]

On the other hand, in newborns at 18-24 hours of life, lower levels of T3, T4 and TSH were observed in asphyxiated newborns. Shah P et al. found that FT4 and FT3 levels failed to increase within the first 48 hours of life in the group of asphyxiated newborns, even though their TSH levels were normal. [52,56]

In some studies, one reported by Shi LX Ma QL et al on premature infants, they found an association between low thyroid activity and respiratory distress syndrome at birth.[53] However, in another study by Tahirovic HF et al there was no significant differences in thyroid function indices and respiratory distress syndrome in premature infants at birth. Several factors, alter levels of thyroid hormones, thyroid-stimulating hormone and less is known about the

effect of perinatal asphyxia on neonatal thyroid hormone levels despite their importance.[54]

When comparing the level of morbidity in asphyxiated neonates as evidenced by respiratory distress, cardiogenic shock, renal failure and seizures, we found that infants with low T3 and TSH levels had increased predilection for morbidity with statistically significant p value less than 0.05. But the relationship between low T4 levels and morbidity was not statistically significant.

We conclude that there are differences in the plasma concentration of T3,T4, and TSH of asphyxiated newborns; however, these differences are less pronounced among the various stages within this group. Low T3 levels are also associated with significant morbidity. Alterations in hormone production and in the peripheral metabolism of T4 may be responsible for these differences[55]

CONCLUSION

1. In perinatal asphyxia, decreased levels of T3 and T4 are due to the occurrence of central hypothyroidism which results in low levels of thyroid hormones secondary to reduced production of TSH.
2. Normally at delivery at term, with the fall in ambient temperature, there is a surge in TSH within about 30 minutes. This stimulates the thyroid gland to release T4 and T3, which rise to well above normal levels.
3. Our study suggests that lower T4 and T3 levels are secondary to lower TSH levels in asphyxiated newborns; also, peripheral metabolism of T4 in asphyxiated infants can be altered leading to low T3 levels.
4. We compared the serum concentrations of thyroid hormones-T4, T3 and thyroid-stimulating hormone (TSH) found in the peripheral venous blood of term newborns with and without asphyxia collected between 18 to 24 h after birth.
5. Serum concentrations of TSH, T4, and T3 are lower in asphyxiated newborns between 18 and 24 h of life; this suggests central hypothyroidism secondary to asphyxia.
6. Asphyxiated newborns with moderate/severe hypoxic-ischemic encephalopathy present a greater involvement of the thyroid function and consequently a greater risk of morbidity.
7. In our study mean value of T_3, T_4 and TSH of asphyxiated and non-asphyxiated newborns during 18-24 hours after birth were 87.16, 9.67, 1.67 and 159.12, 12.02, 2.49 ng/dL respectively.

8. The difference in the mean value of T_3, T_4, and TSH between asphyxiated and non-asphyxiated group was found significant (p value<0.001).This study showed that asphyxiated newborns failed to increase their T_3 and T_4 levels due to a decrease in TSH surge when compared to normal newborns.

9. After evaluating all parameters of the study, it was seen that there was a decrease in the physiological TSH surge among asphyxiated neonates due to the effects of asphyxia. Following this low TSH surge, the corresponding increase in T_3 andT_4 was diminished in asphyxiated neonates.

10. This suppression of thyroid hormones needs to be followed up on a long term basis to determine its detrimental effects on growth and development of neonates.

SUMMARY

1. Birth asphyxia is one of the major causes of early neonatal mortality in India. It ranks as the second most important cause of neonatal death after infections, accounting for around 30% mortality worldwide.
2. The aim of our study is to find out the effect of perinatal asphyxia on thyroid function in new-born babies and to find out the association between the thyroid hormone levels and the severity and morbidity of asphyxia.
3. A total of 60 full-term neonates admitted to Neonatal Intensive Care Unit, Kilpauk Medical College were included in study, 30 asphyxiated neonates and 30 non-asphyxiated neonates.
4. Asphyxiated new-borns are followed up in the immediate newborn period up to 72 hours for evidence of multi-organ dysfunction like cardiogenic shock, renal failure, respiratory distress, and seizures. In the presence of multi-organ dysfunction, the neonates will be managed as per unit protocol in NICU.
5. In the Asphyxiated Group, birth weight <2500 gms were 5 children (17%) and in the non-asphyxiated group it was 1 child(3%). Birth weight >=2500 gms were 25 children (83%) and 29 children (97%) respectively in both the groups which is found to be statistically significant.
6. Mode of delivery by AVD in asphyxiated group was 4 babies (13.3%). LSCS rate in asphyxiated group was 14 babies (46.7%) and in non-

asphyxiated group was 22 babies (73.3%). NVD was 12 in asphyxiated neonates (40%) and in non-asphyxiated it was 8 children (26.7%) Pearson Chi-Square=6.578* P=0.037.

7. Among the 30 Asphyxiated neonates, Stage –I HIE Was 12 Children Which Was 40 %, Stage II Was 13 Children (43%) and Stage-III was 5 Asphyxiated neonates accounting for 17%.
8. Respiratory Distress was found to be more, around 70% in our study
9. In the asphyxiated group,15 babies had shown meconium-stained liquor, 15 showed clear liquor, which was statistically significant**.**
10. APGAR AT 1 min was <=3 in 6 asphyxiated neonates which was 20%, 3to 6 in 24 asphyxiated neonates which was 80%.
11. APGAR AT 5 mins was <=3 in 9 neonates which is 30%, 3to 6 in 21 neonates which was 70%.
12. Prevalence of Seizures among Asphyxiated neonates was63.3%.
13. Thyroid profile variations in asphyxiated neonates and non-asphyxiated neonates: Mean T3- in asphyxiated neonates 87.1640 ng/dl, in non-asphyxiated neonates -159.1233 ng/dl. MeanT4 – among asphyxiated neonates9.6737 ng/dl, in non-asphyxiated neonates12.0245ng/dl. Mean TSH level in asphyxiated neonates1.6742ng/dl, in non-asphyxiated neonates 2.4906ng/dl. P<0.001. T3, T4 and TSH Were Compared To be Less In Asphyxiated neonates When Compared To Non asphyxiated neonates.

14. In our study, difference of the mean value of T3, T4 and TSH was statistically significant at 18-24 hours between asphyxiated and non-asphyxiated group.
15. Among the three stages of HIE, the difference in thyroid hormone levels was not significant.
16. Low T3 and TSH levels were associated with statistically significant morbidity. But this was not the case with low T4 levels.
17. Normally at delivery at term, with the fall in ambient temperature, there is a surge in TSH within about 30 minutes. This stimulates the thyroid gland to release T4 and T3, which rise to well above normal levels.
18. In perinatal asphyxia, decreased levels of T3 and T4 are due to the occurrence of central hypothyroidism which results in low levels of thyroid hormones secondary to reduced production of TSH.
19. Our study suggests that lower T4 and T3 levels are secondary to lower TSH levels in asphyxiated newborns; also, peripheral metabolism of T4 in asphyxiated infants can be altered leading to low T3.
20. Asphyxiated newborns with hypoxic-ischemic encephalopathy present a greater involvement of the thyroid function and consequently a greater risk of morbidity.

LIMITATIONS OF THE STUDY

The study is limited to a small sample size and matching of cases and controls have not been done to eliminate the baseline confounding characteristics between the two study groups. Hence a study involving larger population and appropriate matching is required. One should not be too quick to arrive at any conclusion before large multicentric comparative studies involving representative samples across the country are carried out.

RECOMMENDATIONS

The scope of treating the hypothyroidism due to perinatal asphyxia to improve morbidity and mortality have not been covered in this study. This study entails the need for further randomized trials whether or not treatment is needed for the central hypothyroidism occurring due to perinatal asphyxia.

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ABBREVIATIONS

1. WHO – World Health Organisation
2. NNPD – National Neonatal Perinatal Database
3. ICD – International classification of Diseases
4. BDNF – Brain Derived Neurottropic Factor
5. NMDA – N- Methyl D- Aspartate Receptor
6. AMPA – Alpha amino methyl propionic acid
7. KA –Kinate receptor
8. BAX – Bcl-2 associated alpha protein
9. BAD – Bcl-2 associated death promotor
10. UA – Umbilical artery
11. UV – Umbilical vein
12. T3 – Tri-iodo-thyronine
13. T4 – Thyroxine
14. TSH – Thyroid stimulating hormone
15. HCG – Human Chorionic Gonadotropin
16. HIE – Hypoxic Ischaemic encephalopathy

PROFORMA

1) NAME: B/O

2) IP. NO:

3) AGE/SEX:

4) DATE:

5) ANTENATAL HISTORY:

a) MATERNAL MEDICAL MORBIDITIES

Thyroid dysfunction/ Anaemia /Diabetes Mellitus/Hypertension /PIH

b) MATERNAL MEDICATION

Antithyroid drugs/ Thyroxine/ Steroids/ Antihyertensives

6) PERINATAL EVENTS

a) Prolonged latent phase / second stage of labour
b) History of maternal sedation
c) Evidence of Risk of Sepsis – prolonged membrane rupture/ intrapartum maternal fever/ fowl smelling liquor, etc.
d) Evidence of fetal distress – CTG abnormalities
e) Liquor- clear/ meconium stained (thick/ thin)

7) NATAL HISTORY

a) Mode of delivery
b) Indication for LSCS if done
c) Cried at birth / good spontaneous respiratory efforts at birth
d) Mode of resuscitation
e) APGAR score 1min 5 min

8) GENERAL EXAMINATION

a) Gestational age by New Ballard's score
b) Gestational age by dates
c) Vitals: HR RR

9) ANTHROPOMETRY

a) Weight b) Length c) Head circumference

10) HEAD TO FOOT EXAMINATION

11) SYSTEMIC EXAMINATION

a) CVS c) P/A

b) RS d) CNS

Staging of Hypoxic Ischaemic Encephalopathy by Sarnat and Sarnat :

12) INVESTIGATIONS (venous sample at 18-24 hours of life)

a) Total T3

b) Total T4

c) TSH

13) EVIDENCE OF MULTI-ORGAN DYSFUNCTION-
Cardiogenic shock / Renal failure/ Respiratory distress /Seizures

14) IMPRESSION

Signature of Investigator Signature of Guide

PARTICIPANTS' INFORMATION SHEET

Investigator : Dr. G.Rachel Prakantha Shalini

Name of the participant :

Title: **"A STUDY OF IMPACT OF PERINATAL ASPHYXIA ON THYROID HORMONE LEVELS"**

You are being asked to involve your child in this research study. We have got approval from the IEC. You are asked to participate because you satisfy the eligibility criteria.

What is the purpose of this research?

Perinatal asphyxia is an important cause of multi-organ dysfunction and various hormonal imbalances in the newborn period. The purpose of this study is to emphasize the changes in thyroid hormone levels in perinatal asphyxia which is essential for metabolism and neurodevelopment in the newborn period.

BENEFITS:

This study will help to find out the severity of asphyxial insult and morbidity due to low thyroid hormone levels. There are no major risks involved in the study.

CONFIDENTIALITY:

Patients who participated in the study and their details will be maintained confidentially and at any cost, those details will not be let out.

RIGHT TO WITHDRAW:

Patients will not be forced to complete the study. At any cost, in such circumstances the treatment will not be compromised.

Date :

Place :

Signature of the investigator

Signature/Thumb impression of the participant

INFORMED CONSENT FORM

STUDY**: A STUDY OF IMPACT OF PERINATAL ASPHYXIA ON THYROID HORMONE LEVELS**

STUDY CENTRE: GOVT. KILPAUK MEDICAL COLLEGE HOSPITAL

PATIENT'S NAME:

PATIENT'S AGE:

I.P. NO :

Patient may check (√) these boxes

I confirm that I understood the purpose of the procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction ☐

I understand that my participation in the study is purely voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that the Ethics Committee members and the regulatory authorities will need not my permission to look at my health records, both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. ☐ ☐

I agree not to restrict the use of any data or results that arise from the study. I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or wellbeing or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including hematological, biochemical, radiological tests. ☐

Signature / thumb impression:

Patient's name and address: Place: date:

Signature of the investigator:

Study investigator's name: Place: date:

சுய ஒப்புதல் படிவம்

"A STUDY OF IMPACT OF PERINATAL ASPHYXIA ON THYROID HORMONE LEVELS"

இடம் : அரசு கீழ்பாக்கம் மருத்துவக் கல்லூரி, சென்னை

பங்கேற்கும் குழந்தையின் பெயர்:

வயது : எண் :

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. தைராய்டு செயல்பாடு பரிசோதனைக்காக என் குழந்தையின் சிரை இரத்த பரிசோதனை ஆய்வு மேற்கொள்ள சம்மதம். எந்த காரணத்தினாலோ எந்த சட்ட சிக்கலுக்கும் உட்படாமல் நான் இவ்வாய்வில் இருந்து விலகிக் கொள்ளல்லாம் என்றும் அறிந்து கொண்டேன்.

இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்கொள்ளும் போதும் இந்த ஆய்வில் பங்குபெறும் மருத்துவர் என் குழந்தையின் மருத்துவ அறிக்கைகளை பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்து கொள்கிறேன். இந்த ஆய்வின் மூலம் கிடைக்கும் தகவலையோ, முடிவையோ பயன்படுத்திக் கொள்ள மறுக்க மாட்டேன்.

இந்த ஆய்வில் என் குழந்தை பங்குகொள்ள நான் ஒப்புக் கொள்கிறேன். இந்த ஆய்வை மேற்கொள்ளும் மருத்துவமனைக்கு உண்மையுடன் இருப்பேன் என்றும் உறுதியளிக்கிறேன்.

இடம்: பெற்றோரின்கையொப்பம்

தேதி : ஆய்வாளரின்கையொப்பம்

URKUND ANALYSIS

URKUND

Urkund Analysis Result

Analysed Document:	DR SHAILNI -UPLOAD MGR.docx (D57818813)
Submitted:	28/10/2019 17:04:00
Submitted By:	rachelpshalini@gmail.com
Significance:	8 %

Sources included in the report:

paakhi 1994.docx (D52077190)
birth asphyxia2For plagiarism.docx (D42704455)
https://www.researchgate.net/publication/284175332_A_STUDY_OF_EFFECT_OF_PERINATAL_ASPHYXIA_ON_THYROID_HORMONE_IN_NEONATES
https://www.researchgate.net/publication/305645143_Effect_of_perinatal_asphyxia_on_level_of_thyroid_hormones_in_term_neonates

Instances where selected sources appear:

31

INSTITUTIONAL ETHICS COMMITTEE
GOVT. KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Protocol ID. No. 99/2018 Meeting held on 12.03.2018

The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A STUDY OF IMPACT OF PERINATAL ASPHYXIA ON THYROID HORMONE LEVELS " submitted by Dr.G.Rachel Prakantha Shalini, M.D., Post Graduate , Dept. of Paediatrics Govt. Kilpauk Medical College, Chennai-10.

The Proposal is **APPROVED.**

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

6.4.2018

DEAN
Govt. Kilpauk Medical College,
Chennai-10.

6-4-18

ME 1 Sec> Ethical Committee

KEY TO MASTERCHART

1. Name
2. IP NO
3. Mode of delivery
4. Meconium stained liquor
5. APGAR at 1 min
6. APGAR at 5 min
7. Birth weight
8. Evidence of multiorgan dysfunction upto 72 hours of life
9. Seizures
10. HIE staging
11. Total T3 (at 18-24 hrs of life)
12. Total T4 (at 18-24 hrs of life)
13. Total TSH (at 18-24 hrs of life)

SL.NO	NAME	IP NO	MODE OF DELIVERY	MECONIUM STAINED LIQUOR	APGAR 1	APGAR 5	BIRTH WEIGHT	EVIDENCE OF MULTI-ORGAN SYSTEM INVOLVEMENT	SEIZURES	HIE STAGE	TOTAL T3	TOTAL T4	TSH
								(UPTO 72 HRS C	(UPTO 72 HRS C	(WITHIN 24 HRS	(AT 18-24 HRS C	(AT 18-24 HRS C	(AT 18-24 HRS OF LIFE)
1	B/O SWATI	22804	LSCS	NO	6	7	2.78	RESPIRATO	NIL	STAGE 1	94.39	10.42	2.091
2	B/O VISHN	23990	NVD	NO	5	7	3.08	RESPIRATO	YES	STAGE 2	76.28	6.85	1.058
3	B/O DEEPA	23185	LSCS	NO	4	6	2.92	RESPIRATO	YES	STAGE 2	86.91	8.9	1.165
4	B/O DATCH	22403	NVD	YES	6	7	3.1	RESPIRATO	YES	STAGE 2	98.3	11.63	2.225
5	B/0 MAHAI	22275	NVD	NO	4	7	2.68	RESPIRATO	YES	STAGE 2	110.52	13.7	1.91
6	B/O AKILA	22178	LSCS	YES	4	6	2.82	RESPIRATO	YES	STAGE 2	104.7	12.85	2.124
7	B/O BRIND	22123	LSCS	YES	4	7	3.06	RESPIRATO	NIL	STAGE 1	72.45	7.24	1.058
8	B/O SAGAY	22153	LSCS	NO	5	6	3.23	RESPIRATO	NIL	STAGE 1	89.2	9.68	1.109
9	B/O KALAIS	21755	AVD	NO	3	5	2.98	RESPIRATO	YES	STAGE 2	79.15	6.15	1.32
10	B/O SUHAS	21771	LSCS	NO	5	8	3.21	RESPIRATO	NIL	STAGE 1	96.6	8.3	1.21
11	B/O KOUSA	21696	NVD	NO	6	8	2.79	RESPIRATO	NIL	STAGE 1	106.26	11.2	2.125
12	B/O PRIYAI	19655	LSCS	YES	6	8	2.87	RESPIRATO	NIL	STAGE 1	90.34	10.45	0.969
13	B/O SUJATI	33425	NVD	YES	6	7	3.05	RESPIRATO	NIL	STAGE 1	86.36	6.66	1.27
14	B/O PREMA	34182	LSCS	YES	1	4	2.34	CARDIOGE	YES	STAGE 3	41.71	5.34	0.66
15	B/O ADHIL	33647	AVD	NO	5	8	2.88	RESPIRATO	YES	STAGE 2	70.36	9.1	2.1
16	B/O SUGAN	33419	LSCS	YES	6	8	3.12	RESPIRATO	NIL	STAGE 1	71.29	11.19	0.861
17	B/O INDHU	35942	AVD	YES	5	8	2.95	RESPIRATO	YES	STAGE 2	66.38	6.39	2.32
18	B/O RIFAN	34185	NVD	YES	6	8	3.85	RESPIRATO	NIL	STAGE 1	94.55	7.16	1.45
19	B/O BHAVA	33625	AVD	NO	5	8	2.21	RESPIRATO	YES	STAGE 2	76.89	10.99	3.24
20	B/O UDHA	33788	LSCS	YES	2	5	2.45	RESPIRATO	YES	STAGE 2	87.99	11.14	2.98
21	B/O RAJESH	33729	NVD	NO	5	8	2.84	RESPIRATO	NIL	STAGE 1	78.75	9.61	1.69
22	B/O FARIDI	32734	NVD	NO	6	8	2.38	RESPIRATO	NIL	STAGE 1	166.3	14.13	5.2
23	B/O LINGU	32723	LSCS	NO	4	8	3.12	RESPIRATO	YES	STAGE 2	135.9	15.75	2.59
24	B/O AMUD	27812	NVD	YES	2	6	2.98	CARDIOGE	YES	STAGE 3	62.48	6.4	0.732
25	B/O NAGOI	26145	LSCS	NO	4	8	2.56	RESPIRATO	YES	STAGE 2	93.9	8.82	1.35
26	B/O MARG	28994	NVD	YES	1	4	2.76	CARDIOGE	YES	STAGE 3	54.26	7.01	0.545
27	B/O NIROSHA GURUM		NVD	YES	1	4	2.66	CARDIOGE	YES	STAGE 3	59.61	7.55	0.655
28	B/O RAJESH	33729	NVD	NO	5	8	2.84	RESPIRATO	NIL	STAGE 1	78.75	9.61	1.69
29	B/O FARIDI	32734	NVD	NO	6	8	2.38	RESPIRATO	NIL	STAGE 1	166.3	14.13	5.2
30	B/O RIFAN	34185	NVD	YES	6	8	3.85	RESPIRATO	NIL	STAGE 1	94.55	7.16	1.45
31	B/O RENUC	23145	LSCS	NO	8	9	2.95				124.26	9.108	2.105
32	B/O JAYAJC	23145	LSCS	NO	8	9	2.45				152.23	11.218	2.152
33	B/O VIJAYA	22614	LSCS	NO	8	9	3.04				110.72	8.52	1.019
34	B/O SUNITI	22152	NVD	NO	8	9	3.25				165.25	12.198	4.113
35	B/O PUSHP	21866	NVD	NO	8	9	2.875				106.98	8.762	2.032
36	B/O PAPITH	21793	LSCS	NO	8	10	3.02				138.45	10.245	1.925
37	B/O UMA F	21566	NVD	NO	8	9	2.72				196.3	13.16	5.12
38	B/O NANCY	21465	LSCS	NO	8	9	2.845				131.45	11.19	2.23
39	B/O EZHILA	31246	LSCS	NO	8	9	2.625				93.19	6.25	1.79
40	B/O BAKIYA	34784	NVD	NO	8	9	2.745				109.5	8.49	1.62
41	B/O USHA	32137	LSCS	NO	8	9	3.125				237.9	13.51	3.535
42	B/O NAGAV	36412	LSCS	NO	8	9	3.01				247.4	20.96	4.78
43	B/O SANDH	32512	LSCS	NO	8	9	2.685				109.5	16.9	1.11
44	B/O ROSHN	26427	LSCS	NO	8	9	3.26				176.42	14.7	2.98
45	B/O SHANT	27924	LSCS	NO	8	9	2.55				209.1	13.19	2.79
46	B/O LAVAN	27925	LSCS	NO	8	9	2.85				255.3	17.17	2
47	B/O ROHIN	29625	LSCS	NO	8	9	2.74				120.8	10.39	1.348
48	B/O MAHES	29684	NVD	NO	8	9	2.92				153	14.6	2.26
49	B/O ALAMI	29671	NVD	NO	8	9	2.675				166	14.26	2.87
50	B/O NANDI	29737	LSCS	NO	8	9	3.175				177	14.1	2.7
51	B/O ARCHA	28924	NVD	NO	8	9	2.82				165.2	10.2	2.39
52	B/O GOWR	22451	LSCS	NO	8	9	2.745				182	13.9	2.44
53	B/O SAIRA	31480	LSCS	NO	8	9	3.625				140.2	12.9	1.62
54	B/O KANIM	26431	NVD	NO	8	9	2.75				110.72	7.45	1
55	B/O RAJAL	27626	LSCS	NO	8	9	2.66				125.85	8.95	1.97
56	B/O BANUI	27564	LSCS	NO	8	9	2.74				179.24	10.7	2.04
57	B/O NITHY	27703	LSCS	NO	8	9	2.94				202.6	12.97	4.08
58	B/O ADHIL	27629	LSCS	NO	8	9	2.71				168.86	11.7	3.75
59	B/O KAVITH	27423	LSCS	NO	8	9	3.4				153.46	10.45	1.85
60	B/O ALAMI	29671	NVD	NO	8	9	2.675				166	14.26	2.87