DISSERTATION ON

STUDY OF URINARY URIC ACID AND CREATININE RATIO AS A MARKER OF NEONATAL ASPHYXIA, GOVERNMENT RAJAH MIRASDAR HOSPITAL, THANJAVUR

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

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THANJAVUR - 613 004

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This is to certify that this dissertation entitled **STUDY OF URINARY URIC ACID AND CREATININE RATIO AS A MARKER OF NEONATAL ASPHYXIA, GOVERNMENT RAJAH MIRASDAR HOSPITAL, THANJAVUR** is the bonafide original work of **Dr.SARANYA S.R** in partial fulfillment of the requirements for the Degree of Doctor of Medicine in Paediatrics ,Branch VII examination of The Tamilnadu Dr. M.G.R. Medical University to be held in April 2017. The period of study was from 2016 January to 2016 July.

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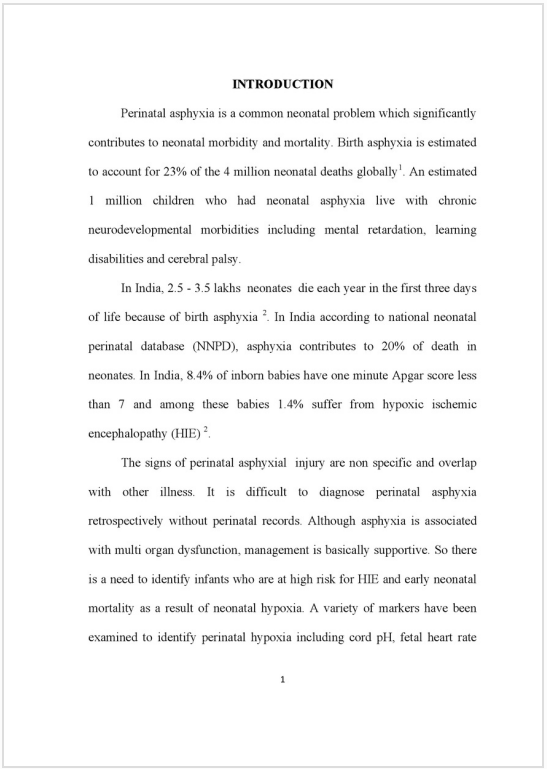

INTRODUCTION

Perinatal asphyxia is a common neonatal problem which significantly contributes to neonatal morbidity and mortality. Birth asphyxia is estimated to account for 23% of the 4 million neonatal deaths globally[1]. An estimated 1 million children who had neonatal asphyxia live with chronic neurodevelopmental morbidities including mental retardation, learning disabilities and cerebral palsy.

In India, 2.5 - 3.5 lakhs neonates die each year in the first three days of life because of birth asphyxia [2]. In India according to national neonatal perinatal database (NNPD), asphyxia contributes to 20% of death in neonates. In India, 8.4% of inborn babies have one minute Apgar score less than 7 and among these babies 1.4% suffer from hypoxic ischemic encephalopathy (HIE) [2].

The signs of perinatal asphyxial injury are non specific and overlap with other illness. It is difficult to diagnose perinatal asphyxia retrospectively without perinatal records. Although asphyxia is associated with multi organ dysfunction, management is basically supportive. So there is a need to identify infants who are at high risk for HIE and early neonatal mortality as a result of neonatal hypoxia. A variety of markers have been examined to identify perinatal hypoxia including cord pH, fetal heart rate

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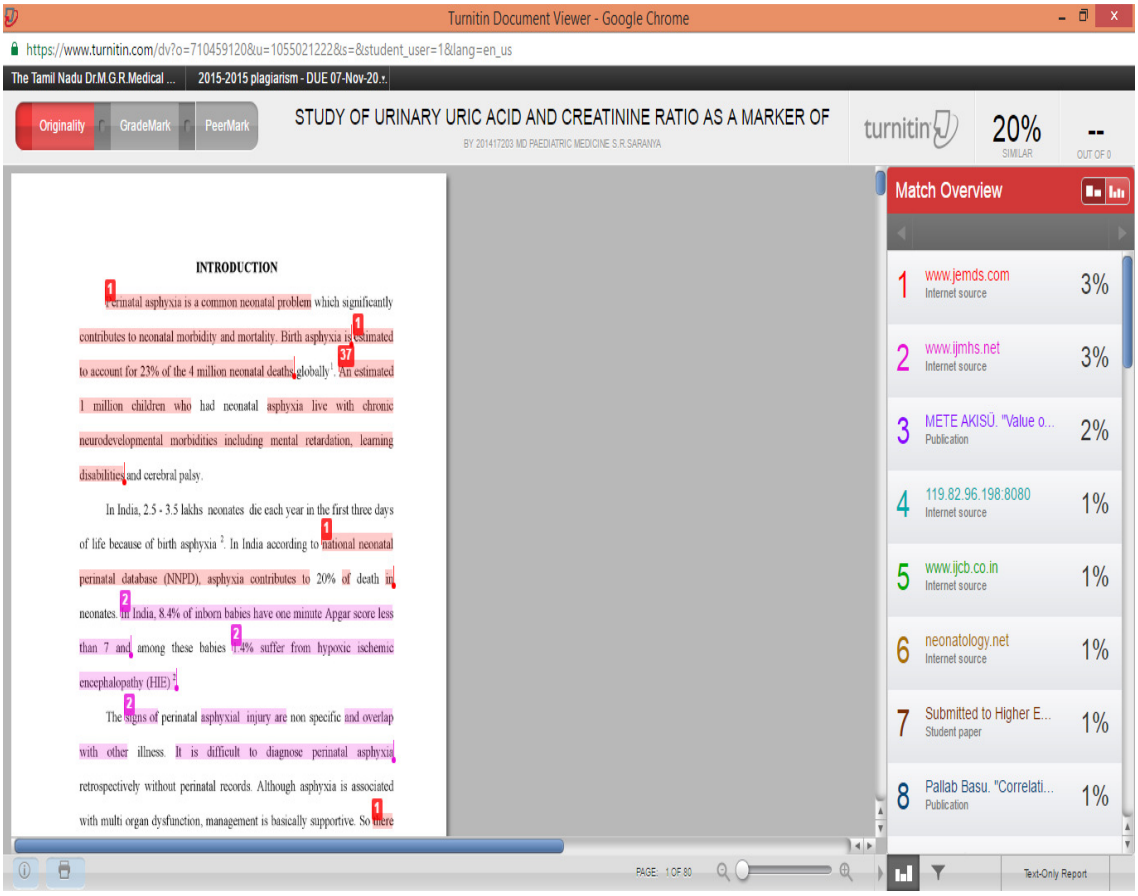
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DECLARATION

I hereby solemnly declare that the dissertation titled "**STUDY OF URINARY URIC ACID AND CREATININE RATIO AS A MARKER OF NEONATAL ASPHYXIA, GOVERNMENT RAJAH MIRASDAR HOSPITAL, THANJAVUR**" has been prepared by me under the guidance of **Dr.P.SELVAKUMAR, MD, ASSOCIATE PROFESSOR, DEPARTMENT OF PAEDIATRICS**, **THANJAVUR MEDICAL COLLEGE**, **THANJAVUR**. This is submitted to THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY, CHENNAI, in partial fulfillment of the requirement for the degree of DOCTOR OF MEDICINE (PAEDIATRICS) (BRANCH VII).

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ABSTRACT

BACKGROUND AND OBJECTIVES

Perinatal asphyxia is a common neonatal problem at times devastating because of its potential for causing permanent damage and even death of the fetus or newborn infant. Only a third of deliveries in India are institutional and many asphyxiated babies are brought late to hospitals. In the absence of perinatal records, it is difficult to retrospectively diagnose perinatal asphyxia. There is a need to identify neonates with asphyxia who will be at high risk for hypoxic ischemic encephalopathy and multi-organ dysfunction.

The value of the present biochemical parameters used for diagnosing asphyxia is inadequate and controversial. The main objective of this study was to evaluate prospectively the value of measuring uric acid to creatinine (UA/Cr) ratio in early spot urine samples in diagnosing perinatal asphyxia, and to assess the relationship between the urinary uric acid to creatinine ratio and the severity of HIE.

METHODS

The study was performed from January 2016 to July 2016 in the Neonatal Intensive Care Unit of Rajah Mirasdar Hospital, Thanjavur. The

case group consisted of 50 asphyxiated full term neonates who fulfilled the inclusion and exclusion criteria. The control group consisted of 50 full term neonates with no signs of asphyxia after an uncomplicated pregnancy. The spot urine samples were collected within 6-24 hours of birth and sent for uric acid and creatinine analysis. Urinary uric acid to creatinine (UA/Cr) ratio value of >1.22 was taken as the cut-off level. Sensitivity, specificity, Positive predictive value (PPV), Negative predictive value (NPV) were calculated.

RESULTS

The Urinary UA/Cr ratios were found to be higher in asphyxiated infants (2.59±1.04) when compared with those in the controls (0.72±0.16, P<0.001). UA/Cr ratios were significantly higher in infants with severe HIE (Stage 3) (4.29±0.46) when compared with infants with moderate HIE (Stage 2) (2.79±0.74) and those with mild HIE (Stage 1) (2.66±0.70). A significant correlation was also detected between the UA/Cr ratio and the severity of HIE in the asphyxiated group**.** The cut-off value of UUA/Cr of >1.22 has a sensitivity of 86%, specificity of 92%, positive predictive value of 91.49%, negative predictive value of 86.49% and an accuracy of 89% in diagnosing asphyxia among term neonates.

INTERPRETATION AND CONCLUSION

The urinary uric acid/creatinine ratio was found to be a quick, inexpensive, non invasive, reliable, early biochemical marker of perinatal asphyxia.

KEY WORDS

Perinatal asphyxia, urinary uric acid/creatinine ratio, hypoxic ischemic encephalopathy (HIE).

LIST OF ABBREVIATION

ABG	:	Arterial Blood Gas
ADP	:	Adenosine-5-phosphate
AMP	:	Adenosine mono phosphate
ATP	:	Adenosine-5-triphosphate
Bpm	:	Beats/minute
CK-BB	:	Creatine kinase –Brain Bound
CNS	:	Central Nervous system
CP	:	Cerebral palsy
Cr	:	Creatinine
CSF	:	Cerebro spinal fluid
CT	:	Computed Tomography
CTG	:	Cardiotocograph
DWI	:	Diffusion weighted imaging
EEG	:	Electroencephalogram
FHR	:	Fetal Heart Rate
HI	:	Hypoxia-Ischemia
HIE	:	Hypoxic Ischemic Encephalopathy

ICD	:	International Classification of Diseases
ICP	:	Intracranial Pressure
LDH	:	Lactate Dehydrogenase
MRI	:	Magnetic Resonance Imaging
MSAF	:	Meconium Stained Amniotic Fluid
NaCl	:	Sodium Chloride
NICU	:	Neonatal Intensive Care Unit
NNPD	:	National Neonatal Perinatal Database
NPV	:	Negative Predictive Value
NST	:	Non Stress Test
PA	:	Perinatal Asphyxia
PPV	:	Positive Predictive Value
UA	:	Uric Acid
UUA	:	Urinary Uric Acid
UUA/Cr	:	Urinary Uric Acid and Creatinine Ratio

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INTRODUCTION

Perinatal asphyxia is a common neonatal problem which significantly contributes to neonatal morbidity and mortality. Birth asphyxia is estimated to account for 23% of the 4 million neonatal deaths globally[1]. An estimated 1 million children who had neonatal asphyxia live with chronic neurodevelopmental morbidities including mental retardation, learning disabilities and cerebral palsy.

In India, 2.5 - 3.5 lakhs neonates die each year in the first three days of life because of birth asphyxia [2]. In India according to national neonatal perinatal database (NNPD), asphyxia contributes to 20% of death in neonates. In India, 8.4% of inborn babies have one minute Apgar score less than 7 and among these babies 1.4% suffer from hypoxic ischemic encephalopathy (HIE) [2].

The signs of perinatal asphyxial injury are non specific and overlap with other illness. It is difficult to diagnose perinatal asphyxia retrospectively without perinatal records. Although asphyxia is associated with multi organ dysfunction, management is basically supportive. So there is a need to identify infants who are at high risk for HIE and early neonatal mortality as a result of neonatal hypoxia. A variety of markers have been examined to identify perinatal hypoxia including cord pH, fetal heart rate

monitoring, EEG, neuroimaging like CT and magnetic resonance image scans and Doppler studies.

In a term neonate, perinatal asphyxia affects major systems resulting in renal, neurologic, cardiac and lung dysfunction in 50%, 28%, 25% and 23% cases respectively. The extent of multi organ dysfunction determines the outcome, either the neonate succumbing as a consequence of organ damage or recovering.

HIE is the foremost concern in asphyxiated neonates because it has the potential to produce serious long term neuromotor sequelae among survivors. Neonatal asphyxia is one of the leading causes of neonatal mortality in developing countries. 3% to 13% of infants with cerebral palsy show evidence of intrapartum asphyxia[3]. Cellular metabolism needs adequate oxygen supply. Brief hypoxia affects cerebral oxidative metabolism leading to an anaerobic glycolysis to generate ATP. In anaerobic conditions one molecule of glucose produces two molecules of ATP as opposed to 30 molecules of ATP produced in aerobic condition. Anaerobic metabolism results in production of large quantities of metabolic degradation products like lactic acid [4,5,6,7,8]. If there is prolonged hypoxia, cardiac output will fall and cerebral blood flow is compromised. A combined hypoxia ischemic insult produces further failure in oxidative

phosphorylation and ATP production, sufficient enough to cause cellular damage. Lack of ATP and increase in excitotoxic cellular damage leads to accumulation of adenine diphosphate (ADP) and adenosine monophosphate (AMP), which is catabolised to adenosine, inosine and hypoxanthine [4,5,6,7,8]. If continuous tissue hypoxia persists, increased hyoxanthine is oxidised to xanthine and uric acid in the presence of xanthine oxidase and the level of uric acid level is increased in blood and excreted in urine [4,5,6,7,8] .

This study is to evaluate the utility of urinary uric acid to creatinine ratio (UA/Cr ratio) as a cost effective, non invasive and at the same time early biochemical marker for predicting the severity of asphyxia.

AIMS AND OBJECTIVES OF THE STUDY

1) To estimate the urinary uric acid and creatinine among the asphyxiated and non-asphyxiated term neonates.
2) To validate the urinary uric acid to creatinine ratio (UA/Cr ratio) as non-invasive, easy, cheap method to diagnose asphyxia among neonates.
3) To determine the relationship between the urinary UA/Cr ratio and the severity of HIE.

REVIEW OF LITERATURE

Historical data

The term birth asphyxia has several intriguing issues in historical perspective. First, there is no satisfactory definition. Clinicians, pathologists and biochemists are using the phrase, but there is no universal definition. Dr. Eastman of Hopkins termed asphyxia "an infelicity of etymology" since Greek derivation gives the definition "without pulse". In pathology, asphyxial lesion is defined without any clinical or biochemical evidence of hypoxia whereas, in physiology asphyxia is defined as hypoxia plus hypercarbia.

Dr. N. J. Eastman was the pioneer in the study of birth asphyxia. He defined birth asphyxia as "an inability of the child to breath and apnea associated with deficiency of oxygen during labour". His initial work was related to the initiation of respiration after birth.[9]

Eastman first studied the concentration and delivery of oxygen in maternal and umbilical blood samples using 16 patients. He then used them as controls in his next study for identifying the deviations from normal. In his next study, he determined the lactate levels in cord blood in 24 neonates of which, 7 had birth asphyxia. Three of these neonates died. He explained the maternal-fetal lactate relationships and he correlated the relationship between the absence of hyperlactatemia and fetal oxygen adequacy[10]. Then

he measured the carbon dioxide and pH in normal and abnormal fetal and maternal blood. Lastly, he demonstrated that neonatal acidosis accompanies asphyxia [11].

There is no review of birth asphyxia without including the Apgar score. Dr. Apgar, in her research paper published in 1953, was obviously disturbed by the lack of specificity in resuscitation [12]. She described the lack of proper systemic evaluation of newborns and further therapeutic intervention based on the initial evaluation. She chose her criteria in such a way that it could be delineated without interfering and compromising with the ongoing resuscitation efforts. She then correlated her score with other variables like perinatal mortality and type of anesthesia. She showed that there existed an inverse relationship between the score and the need for active resuscitation. She designed her scores in such a way that the focus of attention is on the baby and its immediate needs, as well as to objectify and systematize the process for observer communications.

Since the primary goal is prevention, a variety of markers are examined for identifying perinatal hypoxia. This includes electronic fetal heart monitoring, Apgar scores, intrapartum fetal scalp blood pH, cord pH, EEG, CT, MRI and Doppler studies. The current problem, from a historical perspective, is lack of ability to differentiate the false positively diagnosed neonates from the neonates who truly had asphyxia.

Basu *et al* had done a study in which estimated urinary uric acid and creatinine ratio within 24 hours was higher in asphyxiated than the non asphyxiated neonates [13].

Ciler Erdag and Vitrinel showed that the mean uric acid and creatinine ratio in the first 24 hours of birth was more in asphyxiated neonates than non asphyxiated neonates [14].

Chen *et al* showed that urinary UA/Cr ratio may be used as an early marker of perinatal asphyxia. In both term and preterm infants, a higher urinary uric acid to creatinine ratio was found in asphyxiated neonates than in non asphyxiated neonates [15].

Akisu *et al* reported that urinary UA/Cr ratio was found to be higher in neonates with asphyxia than in neonates without asphyxia and it was effective in assessing severity of asphyxia [16.]

Bader *et al* showed that urinary uric acid and creatinine ratio may be used as a marker of neonatal asphyxia in term and preterm neonates and it was significantly higher in asphyxiated group than in non asphyxiated group. They concluded that the ratio might be used as an indicator of severity of neonatal asphyxia [17].

Banupriya *et al* reported that urinary uric acid excretion rate is higher in asphyxiated neonates than non asphyxiated neonates and it may be used

as biochemical marker for severity, evaluation and death prediction in neonatal asphyxia [18].

Dong Wen Bin and coworkers concluded that urinary uric acid to creatinine ratio is more in asphyxiated neonates than non asphyxiated neonates. It might be used as an indicator for early assessment for severity of asphyxia and post asphyxia renal injury in neonates [19].

Reem Mahmoud and Dina El Abd found significant correlation between the urinary uric acid to creatinine ratio and the severity of HIE in asphyxiated neonates ($r= 0.94$, $p<0.001$) and the ratio was found to be a good and simple screening test for the early assessment of perinatal asphyxia [20].

Tekgul *et al* [21] found the measurement of interleukin in CSF with a cut off value25.9 pg/ml had the highest predictive value among all other biochemical markers of perinatal asphyxia. He suggested that interleukin 6 measurements in CSF is superior to urinary UA/Cr ratio as a tool to diagnose neonatal asphyxia, but the test is sophisticated, expensive and invasive compared to urinary UA/Cr ratio which is simple, cheap and safe and hence may be used as a screening test.

Jensen *et al*[22] and Hasday and Grum[23] found increased uric acid in urine of asphyxiated neonates.

Neonatal asphyxia (perinatal asphyxia)

Birth asphyxia is the most important and common cause of cerebral injury occurring in neonates. The term is used to imply an abnormal process and if untreated may cause permanent injury. Hypoxia and hypo perfusion both contribute to asphyxia impairing tissue gas exchange resulting in tissue acidosis. Since there is simultaneous occurrence of hypoxia and ischemia, the term hypoxia ischemic insult is preferred now. Undoubtedly hypoxia-ischemia leads to brain injury but the major concern in these neonates is the development of long term neurodisability such as cerebral palsy. In these children there is often a false assumption that they were injured during events of labour and delivery, with the result that obstetricians and midwives are targeted as the person responsible for those neurologic injuries[24].

Birth asphyxia is defined as "the failure to initiate and sustain breathing at birth" by World Health Organization [25].

An Apgar score at 1 minute of 0-3 defines severe birth asphyxia and 4-7 defines moderate asphyxia according to International classification of Disease (ICD 10) [26].

The following terms are used in evaluating a term infant at risk for brain injury in the perinatal period. [27]

A. Neonatal depression

It is a clinical, descriptive term that relates to the condition of the neonate on physical examination in the immediate postnatal period (in the first hour of birth). In this condition infants have depressed mental state, hypotonia and possibly difficulties in spontaneous respiration and functions of cardiovascular system.

B. Neonatal encephalopathy

It is a clinical term used to describe an abnormal neuro behavioural state that includes decreased level of consciousness with abnormal neuro motor tone. It is associated with seizure-like activity, hypo ventilation or apnea, depressed primitive reflexes. It does not signify a specific etiology, nor does it imply irreversible neurologic injury as it can be caused by reversible conditions like hypoglycemia or maternal medications.

C. Hypoxic-ischemic encephalopathy (HIE)

It is an abnormal neurobehavioural state having impaired cerebral blood flow.

D. Hypoxic-ischemic brain injury

It is attributed to hypoxia and/or ischemia as evidenced by biochemical [such as serum creatine kinase brain bound (CK-BB)], Electrophysiological (EEG), neuroimaging (cranial ultrasonography, CT, MRI).

Incidence

The frequency in developed countries with advanced neonatal/obstetric care is approximately 1 to 1.5% of live births and it is inversely related to birth weight and gestational age. It occurs in 0.5% of live born newborns >36 weeks of gestation and accounts for 20% of perinatal deaths. Infants of diabetic mothers, breech presentation, infants having intrauterine growth retardation are in higher risk for perinatal asphyxia[27]. In India, 8.4% of inborn babies have a Apgar score of less than 7 at 1 minute, but only 1.4% suffer from HIE.

Etiology

In term infants, asphyxia events take place in the antepartum or intrapartum period due to impaired gas exchange across the placenta which cause insufficient oxygen supply and impaired removal of carbondioxide

(CO_2) and hydrogen from the fetus. Asphyxia due to pulmonary, neurological or cardiovascular problems can occur in the post partum period [27].

A. Factors which predispose to neonatal asphyxia include:

Impairment of oxygenation in mother.

Impaired blood flow from mother to placenta.

Impaired blood flow from placenta to fetus.

Decreased gas exchange across the placenta or at the fetal tissue level.

Increased fetal O_2 requirement.

B. Etiology of neonatal hypoxia-ischemia include:

- Maternal factors: hypertension (acute or chronic), infection, diabetes, hypotension, and hypoxia due to pulmonary, cardiac or neurologic disease, drug use and vascular disease.
- Placental factors: infarction, hydrops, abruption
- Uterine rupture.
- Umbilical cord factors: prolapse, compression, entanglement of umbilical cord, vascular abnormalities
- Fetal factors: anemia, infection, hydrops, cardiomyopathy.
- Neonatal factors: neonatal hypoxia occurs in cyanotic congenital heart disease, persistent pulmonary hypertension, cardio myopathy.

Assessment of fetal well being

The well being of the fetus is predicted using many assessments during and after delivery such as elective fetal heart rate monitoring by cardiotocograph (CTG), Apgar scores, meconium staining of amniotic fluid and cord blood arterial p^H.

Meconium staining of amniotic fluid

Heavy or thick meconium staining is considered as a marker of severe asphyxia. The incidence of meconium stained amniotic fluid complicating deliveries is 8-25% of the live births. Meconium aspiration syndrome develop in 5% of these neonates who are born through meconium stained amniotic fluid and 0.4% of these neonates developed cerebral palsy subsequently. Furthermore if we take cerebral palsy as an endpoint of severe asphyxial injury in perinatal period, then 99.6% of infants of normal birth weight with meconium staining had no evidence of this condition [28].

Electronic fetal monitoring

Continuous use of electronic fetal monitoring has not shown to reduce perinatal mortality or asphyxia when compared with auscultation by trained personnel, but has increased the incidence of operative delivery [27]. When used these monitors simultaneously record fetal heart rate and uterine

activity for ongoing evaluation. The following are the parameters of fetal monitoring

1. Baseline heart rate is between 110 and 160 beats per minute normally. The baseline heart rate must be apparent for a minimum of 2 minutes in any 10 minutes segment and must not show episodic changes, periods of marked fetal heart rate variability or segments of baseline heart rate that differ by more than 25bpm. Basal fetal bradycardia is defined as FHR <110 bpm due to congenital heart block associated with congenital heart malformation or maternal systemic lupus erythematosus. Baseline tachycardia is defined as FHR>160 bpm, due to fetal dysrhythmia, hyperthyroidism, maternal fever or chorioamnionitis.
2. Beat-to-beat variability is recorded with the help of RR interval. In awake term neonates beat to beat variability is 5 to 25 beats/minute. Fetal CNS depression due to fetal immaturity, sleep, maternal medications like sedatives, intravenous magnesium sulphate, narcotics cause reduced beat to beat variability.
3. In Non stress test, FHR are reassuring, if there is accelerations present.
4. Decelerations of the FHR are benign and indicates fetal compromise depending on their characteristic, shape and timing in relation to uterine contractions.

a) Early decelerations are symmetric in shape. They are benign and have good beat-to-beat variability. These decelerations are commonly seen in active labour when the fetal head is compressed against the maternal pelvis, resulting in a parasympathetic effect.

b) Late decelerations are apparent decrease in the FHR associated with uterine contractions. The onset, nadir and recovery of the deceleration occur after the beginning, peak and end of the contraction, respectively. It is significant when there is a fall in the heart rate of only 10 to 20 beats/minute below baseline (even if still within the range of 110-160). Late decelerations are because of uteroplacental insufficiency and possible fetal hypoxia. As the uteroplacental insufficiency worsens, (i) beat-to-beat variability will be lost, (ii) decelerations will be lasting longer, (iii) they will begin sooner following the onset of a contraction, (iv) they will take longer to return to baseline, and (v) the rate to which the fetal heart slows will be lower. Repetitive late decelerations need action.

c) Variable decelerations vary in their shape and in their timing relative to contractions. They are due to fetal umbilical cord compression. Variable decelerations assume significance if they

are severe (down to a rate of 60 beats/minute or lasting for 60 seconds or longer, or both), associated with poor beat-to-beat variability or mixed with late decelerations.

Apgar score

Apgar score is a method of describing the condition of an infant at birth described by Virginia Apgar [29]. Using heart rate, respiratory efforts, tone, reflex activity and colour, a score is determined at 1 minute then at 5 minute intervals as necessary (maximum score 10) [30] (Table 1). The ICD-10 definition for birth asphyxia is based on the 1 minute Apgar score. Asphyxia with Apgar score of 0-3 at 1 minute defines severe asphyxia according to ICD-10, 4-7 defines moderate asphyxia according to ICD-10 [31]. Regarding prognosis, Apgar scores in individual cases do not appear to correlate with outcome and hence are frequently interpreted incorrectly for long term prognostication[32]. Despite the controversy, this definition of severe birth asphyxia appears useful in identifying a high risk group which requires further follow up of their neurological status.

Table 1: Apgar Scoring system

Indicator		0 Points	1 Point	2 Points
A	Activity (muscle tone)	Absent	Flexed arms and legs	Active
P	Pulse	Absent	Below 100 bpm	Over 100 bpm
G	Grimace (reflex irritability)	Floppy	Minimal response to stimulation	Prompt response to stimulation
A	Appearance (skin color)	Blue; pale	Pink body, Blue extremities	Pink
R	Respiration	Absent	Slow and irregular	Vigorous cry

The 1 minute Apgar score is an index of intrapartum depression this correlates with the umbilical cord blood pH measurements. 1 minute Apgar scores do not correlate with outcomes. Apgar scores beyond 1 minute reflect the changing condition of the infant. It also reflects the adequacy of the resuscitative measures undertaken. Persistent low Apgar scores correlates with the baby's underlying condition. It also indicates the need for further therapeutic efforts (Table 1) [3].

Table 2: Clinical criteria necessary to establish that acute Neurological injury in the newborn was related to "Asphyxia" proximate to delivery[34,35]

Profound metabolic or mixed academia (pH<7.0) determined by an umbilical cord arterial sample, if obtained
Apgar score of 0–3 for longer than 5 min
Neonatal neurological manifestations - e.g., seizures, coma, or hypotonia
Multi system organ dysfunction - e.g., cardiovascular, gastrointestinal, hematological, pulmonary or renal system

Acidosis

Acidosis is a marker of CO_2 accumulation (respiratory acidosis) and/ or metabolic acidosis as the result of anaerobic metabolism. Severe fetal cord blood acidosis is a marker of impaired gas exchange. Metabolic acidosis is an index of anaerobic metabolism and used as retrospective evidence of tissue hypoxia and fetal distress. However, umbilical arterial acidemia at delivery, considered on its own, will not be associated with poor outcome [36]. It has been associated with poor outcome in combination with abnormal fetal heart rate patterns, depressed Apgar score and significant HIE [37].

There is poor correlation between cord blood acidosis and depression of Apgar scores. Severe fetal acidosis (pH <7.00) occurs in 2.5per 1000 term infants, representing intrapartum compromise possibly severe enough to be associated with organ dysfunction, but only a minority of infants had neurological complications [38] . So there is only a very loose association between fetal acidosis and severe fetal distress [39].

The umbilical cord blood arterial pH is more representative of the fetal metabolic status and arterial acidemia may occur with normal venous pH. Hence sampling of venous blood alone is not recommended. Umbilical cord blood pH estimation excludes birth asphyxia as the diagnosis in 80% of neonates who are depressed at birth[40].

The incidence of seizures and neonatal mortality is increased in infants with an umbilical artery pH <7.0 after birth. But even below this low level, the specificity is low with normal outcome reported in as many as 80% of neonates with an umbilical artery pH <7.0[41].

Non reassuring fetal heart rate patterns, prolonged labour, meconium stained amniotic fluid, a low 1 min Apgar score and mild to moderate acidosis have no predictive value for long term neurological injury without signs of encephalopathy and seizures [42]. So it is essential that entire pregnancy, labour, delivery and the period well beyond birth are examined

to understand fully the pathophysiological mechanisms that are responsible for any brain injury and its long term impact [24].

Fetal response to hypoxia-ischemia:

The healthy neonate has variety of adoptive responses in order to overcome the hypoxic insult. These includes [43]

- Reduction of body and breathing movements and rapid eye movement sleep which in turn reduces the energy consumption and demand of oxygen.
- Increased oxygen extraction from blood ; The maternofetal circulation represents a high output oxygen supply in which almost twice the amount of oxygen can be extracted by fetal haemoglobin before cardiac output needs to be increased. Erythropoietin concentration is increased, which stimulates fetal erythrocyte production.
- Redistribution of blood supply to central nervous system, myocardium and adrenals at the expense of kidneys, gastrointestinal tract, muscle and liver.
- Within the brain, blood flow is diverted to brainstem, cerebellum and midbrain.
- Sympathetic response: Hypoxia increases catecholamine levels which leads to increased peripheral vascular resistance and

myocardial contractility to maintain perfusion. It accelerates anaerobic glycolysis, which mobilizes glycogen stores from liver to maintain the CNS and myocardial energy substrate.

- The immature CNS utilize the pyruvate, ketones and lactate produced by anaerobic glycolysis easily as an alternative to glucose. Babies with hyperinsulinemia (eg. those born to mothers with diabetes) are not able to generate these alternative sources effectively and therefore are at risk for hypoxic-ischaemic injury.

Clinical features after birth:

Hypoxic –ischaemic encephalopathy (HIE)

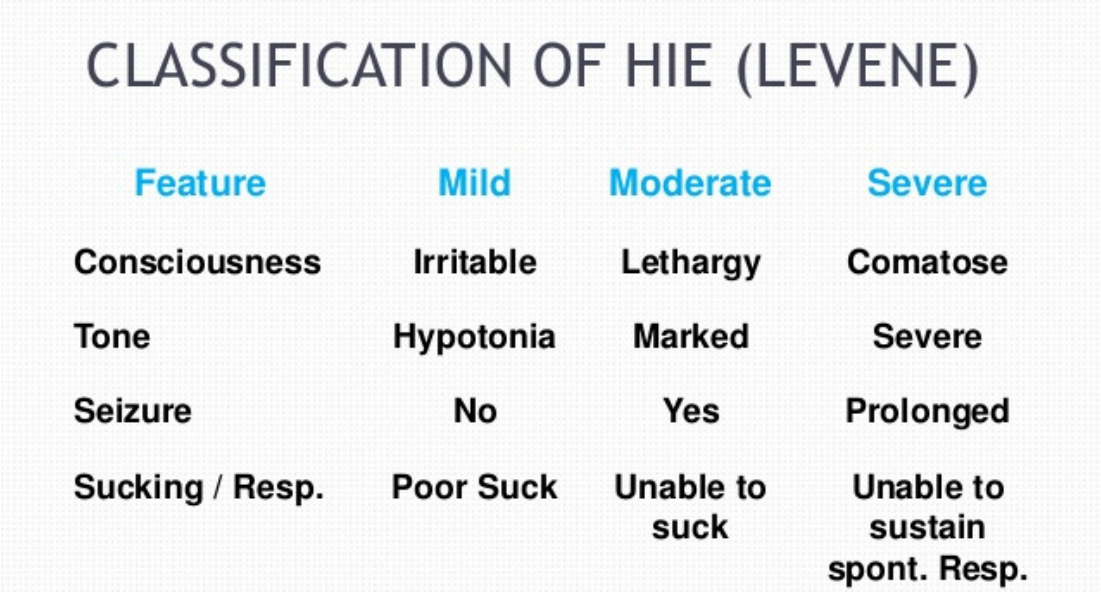
Neonatal encephalopathy refers to abnormal neurological behaviour in the neonatal period and it is due to wide range of causes. If a neonate has been affected by hypoxic-ischemic event at delivery, the infant will have disturbance in neurological behaviour that is referred as HIE. Infants have sequence of altered behavioral changes lasting for days depending on the severity and duration of the asphyxia. Grading systems are used to define degree of encephalopathy. Sarnat and Sarnat [44] introduced grading system for HIE (Table 3) and it was modified later by Levene MI [45] (Table 4).

Table 3: Sarnat and Sarnat Stages of Hypoxic-Ischemic Encephalopathy

Feature	Stage 1	Stage 2	Stage 3
Stages consciousness	Hyperalert	Lethargic or obtunded	Stuporous
Neuromuscular control			
Muscle tone	Normal	Mild hypotonia	Flaccid
Posture	Mild distal flexion	Strong distal flexion	Intermittent decerebration
Stretch reflexes	Overactive	Overactive	Decreased or absent
Segmental myoclonus	Present	Present	Absent
Complex reflexes			
Suck	Weak	Weak or absent	Absent
Moro	Strong; low threshold	Weak, incomplete, high threshold	Absent
Oculovestibular	Normal	Overactive	Weak or absent
Tonic neck	Slight	Strong	Weak or absent
Autonomic Nervous System	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; diarrhea	Variable
Seizures	None	Common; focal or multifocal	Uncommon (excluding decerebration)
ECG	Normal (awake)	Early: low-voltage continuous delta and theta. Later: periodic pattern (awake); seizures: focal 1–1.5 Hz spike and wave	Early: periodic pattern with isopotential phases. Later: totally isopotential
Duration	Less than 24 hours	2–14 days	Hours to weeks

Based on the work of Samat and Sarnat.
(Sarnat HB, Samat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. Arch Neurol 1976;33:696.)

Table 4: A clinical grading system for hypoxic-ischaemic encephalopathy by Levene MI. [45]



Mild (Grade-1) encephalopathy

This is characterized by hyper alertness, staring (decreased frequency of blinking), normal or decreased spontaneous motor activity and a lower threshold for all stimuli including the easily elicited Moro reflex. Seizures are not a feature of Grade I encephalopathy.

Moderate (Grade II) encephalopathy

Seizures occur commonly. There is lethargy, hypotonia with reduced spontaneous movements, a higher threshold for primitive reflexes, and mainly parasympathetic responses. A consistent feature is differential tone between the upper and lower limbs, with the arms being relatively hypotonic compared to the legs.

Severe (Grade III) encephalopathy

These neonates are comatose, with hypotonia and no spontaneous movements. Primitive reflexes and the suck reflex are often absent. Seizures may be frequent and prolonged, although in the most severe cases there may be no seizure activity and an isoelectric EEG.

Asphyxia is not the only cause of neonatal encephalopathy and alternative causes such as hypoglycemia and meningitis must be considered and excluded before attributing asphyxial insult as the cause of HIE [46]. In particular, neonatal convulsions alone with clinical inter seizure normality are not a feature of HIE, nor is the baby who shows an unchanging pattern of neurological abnormalities in the neonatal period. It has been suggested that in the majority of cases, 'neonatal encephalopathy' in full-term babies may not be due to intrapartum events, but may originate in the antepartum period[47]. The severity of HIE is the best clinical method currently available to predict subsequent outcome following asphyxia, but it has a number of disadvantages. Firstly, the severity of HIE can only be determined retrospectively, as the clinical neurological features of asphyxia take some time to evolve. Secondly, other organs such as the kidneys and heart may be compromised due to asphyxia but the fetus preserves blood flow to its brain thereby sparing cerebral function. The lack of

encephalopathy does not necessarily indicate that the infant has not suffered from significant intrapartum asphyxia [48].

Other neurologic considerations [49]:

Increased intracranial pressure is due to cerebral edema in HIE. Cerebral edema peaks at 36 to 72 hr after insult. It often reflects extensive prior cerebral necrosis rather than swelling of intact cells, making this finding consistent with a uniformly poor prognosis. Effects to reduce ICP and cerebral edema do not affect outcome.

Seizures develop in 20% to 50% of infants with HIE and usually occur between 6 and 24 hours of hypoxic insult. They are mostly seen in Sarnat stage 2 HIE, rarely in Sarnat stage 3 and almost never seen in Sarnat stage 1 HIE.

Seizures in HIE are subtle, tonic or multifocal clonic in nature. Generalised seizures are uncommon due to comparatively immature myelination and synaptogenesis of the neonatal brain.

Seizures may be associated with increased cerebral metabolic rate, which further leads to cerebral injury.

Seizures compromise ventilation and oxygenation, especially in neonates who are not on mechanical ventilation. In neonates who are paralysed for mechanical ventilation, seizures may be manifested by abrupt changes in blood pressure, heart rate and oxygenation.

Seizures associated with HIE may require more than one anti-convulsant for control.

Prognosis after HIE

In meta-analysis studying neonatal outcome with HIE stages showed, Stage I (mild HIE) no increased risk of disability or death[50]. Significant reduction in intelligence quotient at 8 years has been reported in stage II (Moderate HIE), compared to neonates in grade I HIE [51].

Specific outcomes depend on the severity of encephalopathy, presence or absence of seizures, EEG results and neuroimaging findings

1. Sarnat clinical stage I or mild HIE

   98-100% will have normal neurologic outcome with less than 1% mortality [52].

2. Sarnat clinical stage II or moderate HIE

   20% - 37% have abnormal neurological outcome or die. Infants in stage 2 for >7 days have poorer outcomes. Prognosis can be predicted with the use of EEG to diagnose seizure activity and MRI to assess the severity of encephalopathy and the location of hypoxic ischemic brain injury.

3. Sarnat clinical stage III or severe HIE

50-89% die and all have major neuro developmental impairment.

Prognosis is considered to be good if neonates do not progress to stage 3 and remains in stage 2 for <5 days.

The presence of seizures increases the risk of CP to 50 to 70 fold. Mortality risk is highest for seizures that begin within 12 hours of birth (53%). Neonates whose seizure duration was 1 day had 7% risk of CP and 11% had epilepsy on follow up. If seizures lasted for >3 days, the rate of CP and epilepsy were 46% and 40% respectively.

93% of neonates with extreme burst suppression activity in EEG have poor outcomes [52.]

Normal findings on diffusion weighted imaging (DWI) MRI between 2 and 18 days are associated with normal neuromotor outcome at 12 to 18 months. Deep grey matter abnormalities detected early have the worse motor and cognitive outcomes. Neonates with abnormal DWI of basal ganglia within 10 days of a hypoxic insult was associated with a 93% risk of abnormal neuro developmental outcome on follow-up when assessed between 9 months to 5 years [52].

Multi organ dysfunction

The fetus copes with an asphyxia event by a number of protective reflexes to preserve function to vital organs. Less well-perfused tissues may be particularly vulnerable to hypoxic-ischemic injury. In term neonates with perinatal asphyxia, renal, neurologic, cardiac and lung dysfunction occurs in 50%, 28%, 25% and 23% respectively[53]. The kidney appears to be most

vulnerable, followed by the brain and then the heart. Gastrointestinal complications of asphyxia are uncommon (Table 5).

Table 5.Multiorgan systemic effects of asphyxia [54]

MULTIORGAN SYSTEMIC EFFECTS OF ASPHYXIA

SYSTEM	EFFECT
Central nervous system	Hypoxic-ischemic encephalopathy, infarction, intracranial hemorrhage, seizures, cerebral edema, hypotonia, hypertonia
Cardiovascular	Myocardial ischemia, poor contractility, cardiac stun, tricuspid insufficiency, hypotension
Pulmonary	Pulmonary hypertension, pulmonary hemorrhage, respiratory distress syndrome
Renal	Acute tubular or cortical necrosis
Adrenal	Adrenal hemorrhage
Gastrointestinal	Perforation, ulceration with hemorrhage, necrosis
Metabolic	Inappropriate secretion of antidiuretic hormone, hyponatremia, hypoglycemia, hypocalcemia, myoglobinuria
Integument	Subcutaneous fat necrosis
Hematology	Disseminated intravascular coagulation

General aspects of pathophysiology of hypoxia-ischemia

Cell damage

When a cell is exposed to hypoxia, the degree and duration determines the severity of injury. If hypoxia is brief, there is reversible cellular injury and if severe, the cell will be irreversibly damaged. Cell death can occur either due to necrosis or apoptosis. Necrosis occurs after loss of blood supply to the cell, but also seen when the cell is exposed to different toxins. Apoptosis is seen in both normal and pathological states [55].

The pathophysiological mechanisms of cell death are presented in Figure 1 and 2.

Fig. 1. The principle cellular and biochemical sites of damage in cell injury. Mitochondrial damage may lead to reversible injury and death by necrosis or apoptosis. [Adapted from Robbins Basic Pathology]

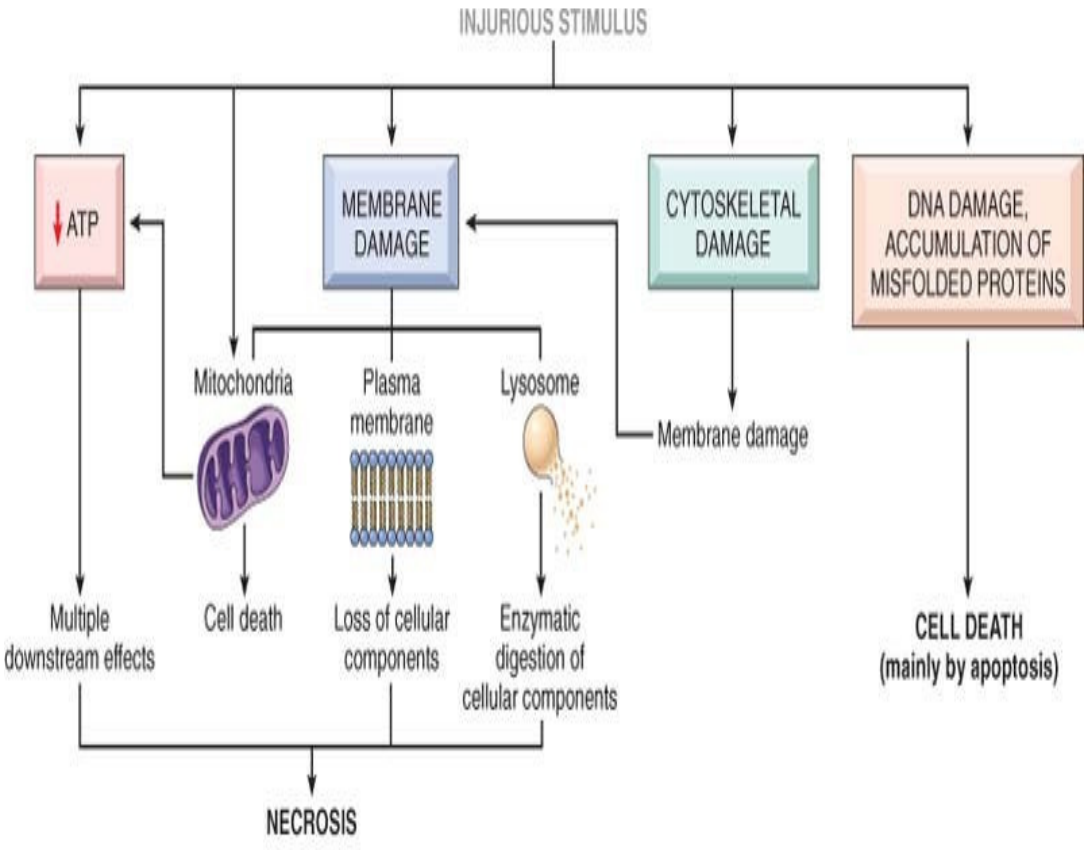
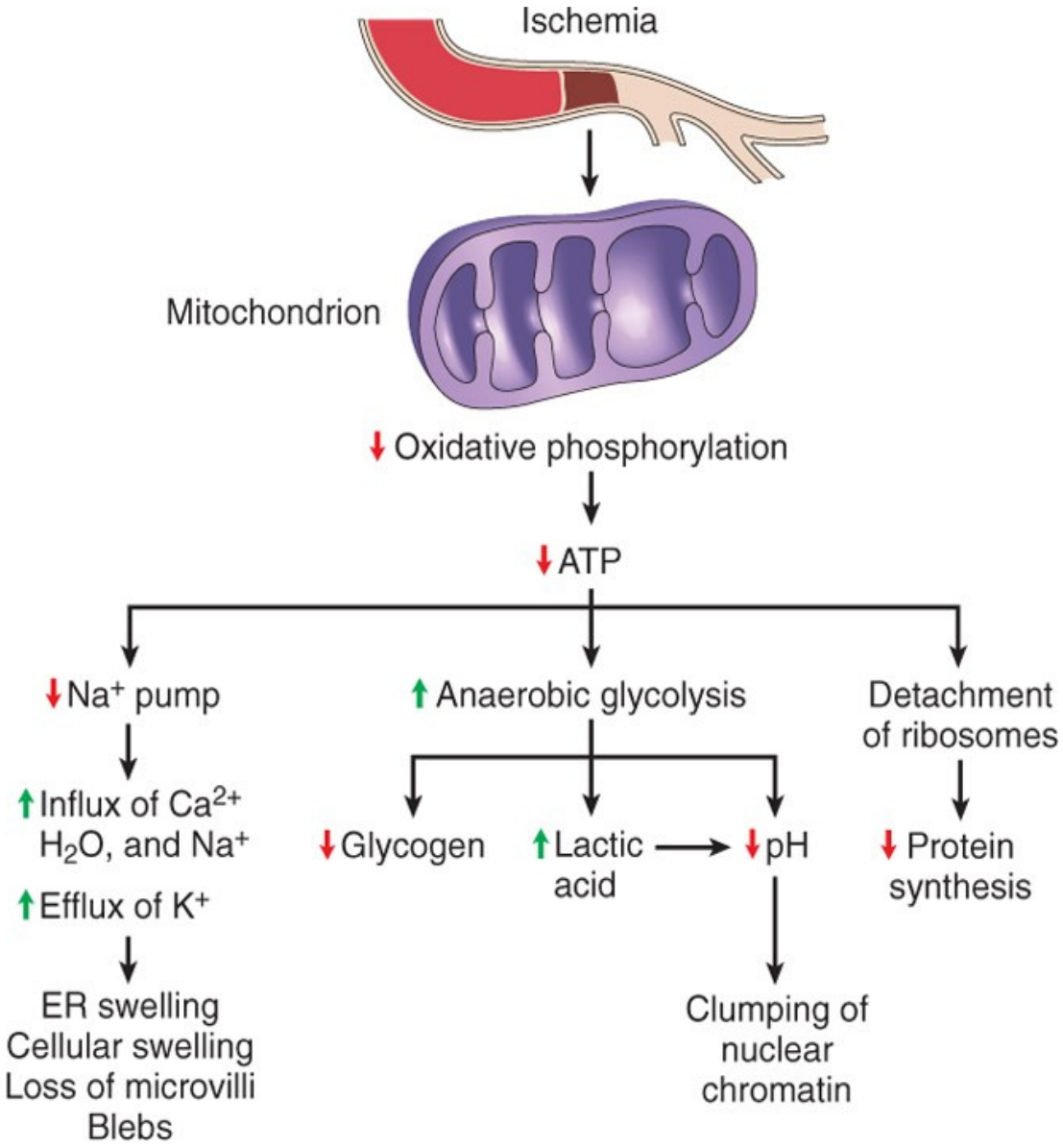


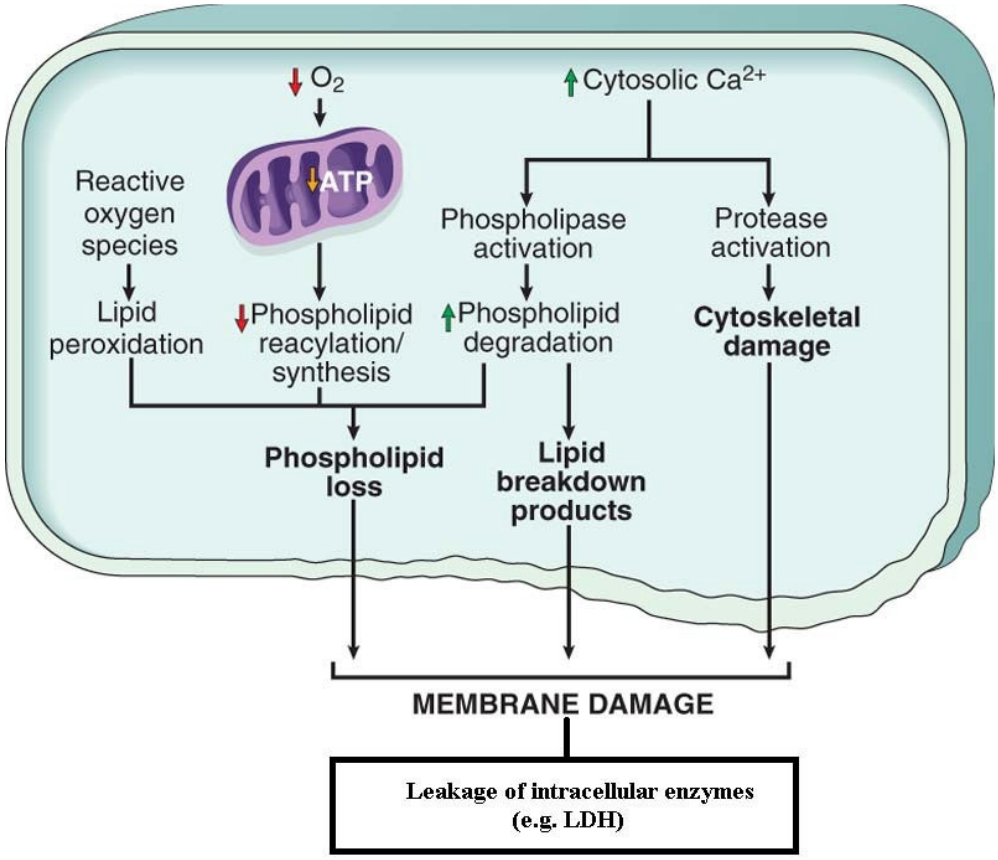
Fig. 2. Mechanism of cellular injury due to hypoxic insult.



Membrane injury

The mechanism of cellular membrane injury in HIE is multi factorial and not exclusively induced by the free radicals. Calcium influx activates phospholipases which has negative impact on the membrane phospholipids and proteases that will damage the cytoskeleton. If the integrity of cell membrane is lost, there will be irreversible damage with massive calcium influx and profound leakage of intracellular enzymes [55] (Fig. 3).

Fig 3. Mechanisms of membrane damage in cell injury. [Adapted from Robbins Basic Pathology]



Specific aspects of Pathophysiology of perinatal asphyxia

Being born is stressful, particularly if it is by vaginal delivery. In normal delivery during each uterine contraction there will be transient fetal hypoxia [56], which results in the fetus becoming more acidemic as the labour progresses. In general, the greater the stress and trauma of labour, higher will be the catecholamine surge. Yet despite enduring this process for several hours, most neonates are pink, vigorous with regular breathing by 1-2 minutes of age [57]. Not all the babies make the transition to extrauterine environment without help. The action which we initiate in these babies in the first few minutes of life will make the difference between death, survival with cerebral palsy or intact neurological survival.

Observed patterns of brain injury following hypoxia-ischaemia:

Cerebral edema

Gross swelling of cerebral tissue with marked flattening and widening of gyri with obliteration of the sulci occurs within 24-48 hours of hypoxia, which is seen in imaging or at post mortem. It arises because of two mechanism, first one is cytotoxic, when membrane failure leads to intracellular fluid accumulation and second one is vasogenic, when the impaired blood brain barrier permits capillary leak and interstitial fluid accumulation [57].

Selective neuronal necrosis

The most common observed pathology after hypoxia is selective neuronal necrosis. The affected neurons appear in a scattered fashion and often widely distributed throughout the grey matter. The cerebral cortex layers 3 and 4 and the hippocampus are particularly vulnerable. This may reflect differing metabolic rates of the various cortical structures [57].

Basal ganglia and brainstem

Basal ganglia injury seems to be responsible for the dyskinetic type of cerebral palsy seen in survivors of hypoxia and there may be abnormal signal intensity in basal ganglia on MRI. Abnormal capillary proliferation and microcalcification are seen in histology within first week. These are detected by ultrasound or CT imaging. An abnormal myelination pattern occurs if the infant survives for several months, which may be detected in MRI. Haemorrhage and haemorrhagic infarction affecting the thalamus are also a well recognized phenomenon [57].

Parasagittal injury

This is an ischaemic injury affecting the cerebral cortex and subcortical white matter in vascular watersheds between the anterior, middle and posterior cerebral arteries, giving rise to a parasagittal distribution, and is often symmetrical [57].

White matter injury

In preterm infants periventricular leukomalacia occurs after hypoxic injury. In term infants subcortical leukomalacia occurs after ischaemic injury. The survivors of most severe insults show a mixed pattern of injury referred to as multi cystic leukoencephalopathy [57].

Focal cerebral infarction

Infarction of major cerebral artery most commonly the left middle cerebral artery has been associated with asphyxia in the past, but it is now realized that this lesion occurs more commonly in infants with no evidence of intrapartum asphyxia (67%) [58].

Laboratory evaluation of asphyxia :

Cardiac evaluation

- **Cardiac troponin I and cardiac troponin T :**

These are the Cardiac regulatory proteins which control the calcium mediated interaction of actin and myosinare markers of myocardial damage. In asphyxiated neonates these protein levels are elevated.

- More than 5-10% of asphyxiated neonates have elevated serum creatine kinase myocardial bound (CK MB), which indicates myocardial injury.

Neurological markers of brain injury:

- In asphyxiated neonates mostly within 12 hrs of the insult, serum CK MB may be increased but it has not been associated with long term neurological outcome. Also other serum markers like protein S-100, neuron specific enolase and urine markers have been measured.
- Serum and urine markers of brain injury are not routinely used for predicting outcome or the presence of brain injury.

Renal evaluation:

- Serum creatinine and blood urea levels may be elevated in neonatal asphyxia especially within 2-4 days of insult.
- Renal insult may also be confirmed with the help of Fractional excretion of sodium.
- Proximal tubular dysfunction may be indicted by urine levels of β -2- microglobulin but not routinely used. This low molecular weight protein is freely filtered through the glomerulus and reabsorbed almost completely in the proximal tubule.
- Renal sonographic abnormalities correlate with the occurrence of oliguria.

Brain imaging :

Cranial ultrasound and Doppler cerebral blood flow:

There are little data to support the use of this modality in the imaging of encephalopathy. However anterior and middle cerebral artery blood flow indices are helpful when measured within 6-24 hrs of age. (Pourcelot's resistive index (PRI) < 0.50-0.60 is suggestive of poor neuro developmental outcome. This is a ratio of end – diastolic flow vs systolic blood flow. This index has a positive predictive value of 80% and is indicative of cerebral vascular, paralysis or impairment of cerebral auto-regulatory mechanisms[59].

Computed tomography:

May be used to detect cerebral edema, hemorrhage and hypoxic ischaemic brain injury. However CT can be performed rapidly and done without sedation but has significant radiation effects. CT can be done only if MRI is unavailable or the baby is too unstable for MRI.

MRI:

Types of MRI are as follows:

- Conventional T1weighted and T2 weighted imaging
- Diffusion weighted imaging
- Proton MRS (Magnetic Resonance Spectroscopy)

Conventional MRI:

Three patterns of injury are most characteristically described in conventional MRI done between 2-8 days of age

- Thalamus or posterior lateral putamen (most severe and most common lesion)
- Parasagital grey and subcentral white matter
- Focal or multifocal brain injury

T1 MRI images show hyperintense signals in less than three days lesion and T2 MRI images show hypointense signals by 6-7 days of life.

Diffusion weighted imaging:

It provides evidence of cerebral injury before conventional MRI can pick up. However DWI imaging can be falsely negative if done earlier than 24 hrs and later than 8 days.

Proton MRS:

This exciting modality provides additional prognostic data by studying the tissue concentration spikes of various metabolites. This modality can play an important role in the assessment of HIE and also can determine the age of the lesion.

Management:

It is important to realize that whatever damage is done cannot be reversed as at present there is no specific molecule ready for therapy in HIE.

Therefore the current standard of management of neonates with HIE has been limited to supportive therapy only.

The Investigation and Management Principles are elucidated here:

- Effective Neonatal Resuscitation (as per NRP by AAP / AHA)[60]
- Respiratory management including ventilation for apnea / hypoventilation (in hypercarbia> 55 mm) or associated respiratory co-morbid conditions like meconium aspiration syndrome (MAS), persistent pulmonary hypertension in newborn (PPHN), atelectasis.
- Correction of hemodynamic processes and maintenance of normal mean BP > 40 mm by use of volume and / or inotropes support as applicable.
- Traditional fluid management has been to restrict fluids for first 48 – 72 hrs in view of possibility of SIADH. Strict input and output charts, serum lactate, daily weights, serum and urinary electrolytes, urine output and urine specific gravity are used to manage a tight fluid balance. The goal is to aim for zero fluid balance.
- Empirical antibiotics (Avoidance of aminoglycosides – nephrotoxic)
- Correction of metabolic abnormalities is important. Common metabolic issues like
    - Hypoglycemia, hyperglycemia
    - Hypocalemia

- Hypomagnesemia
- Hypo and hypernatremia
- Hypo and hyperkalemia

- Controlling seizures with anti seizures medication. Definitely consider therapy if cardio respiratory status is compromised.
- Correction of coagulopathy by FFP or specific factors as applicable.
- Important to note that there is no role for use of steroids in HIE therapy.
- Assessment of end organ damage
  - LIVER : liver failure (increased Aspartate amino transferase , Alanine amino transferase , Gamma glutamyltransferase)
  - KIDNEY: renal failure (anuria/ oliguria / creatinine.125 mmol /L)
  - CARDIAC : cardiac dysfunction (inotropes > 4 hrs , increased level of troponin)

The appropriate management is dictated by the assessment of specific organ system.

The overall guiding principle / goal in management of HIE is to achieve normal hemostasis with maximum prevention of further injury as much as possible.

Perinatal asphyxia is a perilous condition due to its potential in causing severe damage even death of a newborn infant. The values of

present biochemical markers in diagnosing asphyxia is inadequate and controversial [21]. Uric acid is the end product of purine metabolism in humans [61]. It is obtained from either increased breakdown of tissue nucleic acids or from increased turnover of purines. Xanthine oxidase and dehydrogenase are the enzymes that reduce the purines, xanthine and hypoxanthine to uric acid. Uric acid and reduced nicotinamide adenine dinucleotide are produced by Xanthine dehydrogenase. Xanthine oxidase produces uric acid and superoxide. In hypoxia or ischemia, the dehydrogenase form is increasingly converted to oxidized form. Uric acid has poor solubility that needs continuous excretion by the kidneys so as to avoid accumulation of toxic metabolites. The nature of its poor solubility tends to produce high serum levels when its production or excretion is altered.[62,63]

Uric acid excretion has four components; glomerular filteration, reabsorption, tubular secretion and reabsorption beyond secretory sites. Increased elimination of uric acid may be caused by metabolic changes, reflecting cellular hypoxia or changes in renal system. During reoxygenation and reperfusion after asphyxia and ischaemia, hypoxanthine accumulated in both circulating blood and tissues is oxidised to uric acid [64]. Since urinary creatinine can be used as the reference substrate in a spot urine sample, an increased uric acid to creatinine ratio may be an absolute

indicator of severity of tissue hypoxia in patients with intact renal functions[65].

The ratio of urinary uric acid to creatinine helps in rapidly recognizing asphyxia and assessing its severity. Though numerous indicators for asphyxia are available, no single indicator has been found to be effective in predicting subsequent morbitity. The Apgar scores have been used long time since in defining asphyxia and in determing the outcome prognostication [66]. Although many biochemical indicators such as , hypoxanthine, lactate, brain isoenzyme of creatinine phosphokinase, erythropoietin, neuron specific enolase, vasopressin and excitatory amino acids are reported ,they are most useful for the purpose of research and still remain unavailable in most clinical services [67].

MATERIALS AND METHODS

Study design

This is an analytical cross sectional study.

Study area

Neonatal Intensive Care unit of Paediatrics department, Government Rajah Mirasdar Hospital, Thanjavur.

Study population

Case and control group compromised of asphyxiated and non asphyxiated neonates respectively.

The case group: It included 50 neonates fulfilling the following criteria:

Inclusion criteria:

1) Gestational age ≥ 37 weeks.
2) Appropriate for gestational age.
3) The neonates will be identified to have experienced perinatal asphyxia when at least 3 of the following are present:
    A. Intrapartum signs of fetal distress, as indicated by non reassuring NST on continuous electronic fetal monitoring and/or by thick meconium staining of the amniotic fluid.
    B. Apgar score of < 7 at one minute of life
    C. Resuscitation with >1 minute of positive pressure ventilation before stable spontaneous respiration.

D. Umbilical arterial blood gas analysis showing pH <7.20.

E. Mild, moderate or severe hypoxic ischemic encephalopathy (HIE), as defined by Sarnat and Sarnat staging in 1976 [44].

Exclusion Criteria:

1. Congenital malformations.
2. Maternal drug addiction.
3. Neonates born to mothers who received magnesium sulphate within 4 hours prior to delivery or opioids (pharmacological depression).
4. Hemolytic disease of the newborn.
5. Neonates born to mothers who consume alcohol
6. Neonates born to mothers who are smokers
7. Neonates born to mothers on anti epileptics

The control group:

It included 50 term apparently healthy neonates appropriate for gestational age without signs of peinatal asphyxia as evidenced by normal fetal heart rate patterns, clear liquor and one minute Apgar score ≥7.

All neonates included in the study had the following done:

1) Detailed maternal history, assessment of intrauterine fetal well being by continuous electronic fetal monitoring, meconium staining of amniotic fluid, mode of delivery, Apgar score, sex of the baby and

weight of the baby were recorded on the precoded proforma. Gestational age was assessed by New Ballard scoring system. Arterial blood gas analysis (ABG) was done in umbilical arterial blood in all neonates in case group.

2) Thorough clinical and neurological examination was done for all the neonates included in the study. The asphyxiated neonates (case group) were monitored for seizures, hypotonia and HIE in the immediate neonatal period in the NICU. Grading system used to grade the severity of HIE was Sarnat and Sarnat staging in 1976[44].
3) The case group also had other investigation done to rule out other causes of hypotonia, seizures, lethargy other than HIE with relevant investigations like blood glucose, serum electrolytes, blood culture and sensitivity. Peripheral smear study for erythrocyte morphology and reticulocyte count was done to document hemolytic disease of new born.

Study Period

From January 2016 t o July 2016.

Sampling Procedure

Consecutive sampling

Sample size

50 asphyxiated neonates are included in case group and 50 non asphyxiated neonates are included in control group.

Investigations done

Urine samples were collected from the neonates and sent for urinary uric acid and creatinine ratio.The spot urine samples were collected between 6-24 hours of life by catheterization or by attachment of urine collection bags. If there was any delay in analysis it was frozen at (- 20°C) until analysis could be carried out. Uric acid and creatinine in the same urine sample were determined by auto analyzer.

Uric acid

Urine samples were analyzed on the autoanalyzer with automatic sample dilution using 0.9 NaCl. Assay principle: Enzymatic colorimetric assay using uricase was done.

The intensity of the red color was proportional to the uric acid concentration and was measured photometrically [68].

Creatinine

Urine samples were analyzed on the autoanalyzer with automatic sample dilution using 0.9NaCl. Assay principle: Kinetic colorimetric assay (Jaffe Method) as follows:

Creatinine +picric acid = creatinine-picric acid complex.

In an alkaline media, creatinine forms a yellow orange complex with picrate. The color intensity was proportional to the creatinine concentration and was measured photometrically[69].

Statistical Methods: Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean±SE (Min-Max) and results on categorical measurements are presented in proportions (%). Significance is assessed at 5% level of significance.

Analysis of variance (ANOVA) has been used to find the difference in study parameters between three or more groups of patients. Chi-square/ Pearson correlation has been used to find the difference in study parameters.

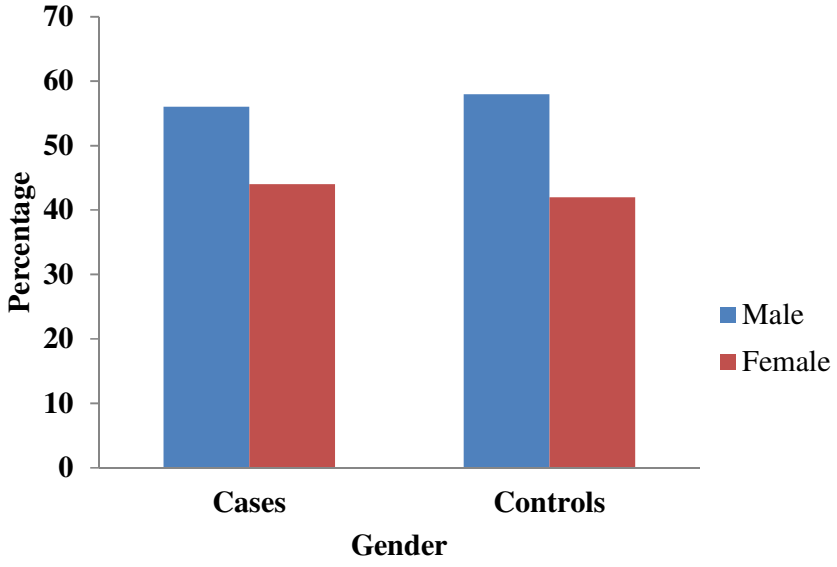
OBSERVATION AND RESULTS

The present study was conducted in Neonatal Intensive care unit of Department of Paediatrics, Rajah Mirasdar Hospital, Thanjavur from January 2016 to July 2016. Cases and Controls comprised of asphyxiated and non-asphyxiated neonates, respectively.

Table 6: Gender distribution of neonates studied

Gender	Cases		Control	
	No	%	No	%
Male	28	56.0	29	58.0
Female	22	44.0	21	42.0
Total	50	100.0	50	100.0

Fig. 4. Gender distribution of neonates studied

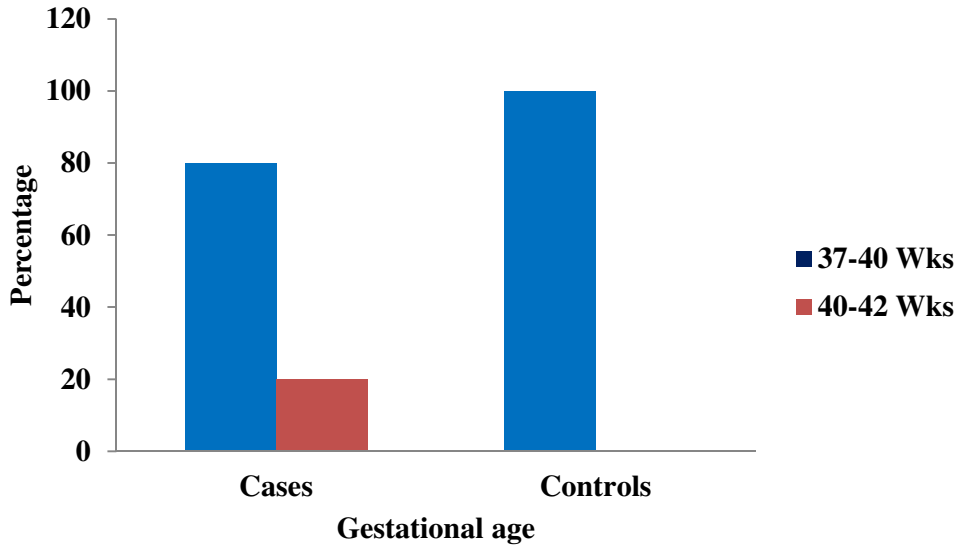


The gender distribution of neonates is shown in Table 6 and Fig 4. Among the 50 neonates in case group, there were 28 (56%) males and 22 (44%) females. Among the control group of 50 neonates, there were 29 (58%) males and 21 (42%) females. Samples are gender matched with p=0.840

Table 7: Gestational age of neonates studied

Gestational age (in weeks)	Cases		Control	
	No	%	No	%
(37-40 weeks)	40	80.0	50	100.0
(40-42 weeks)	10	20.0	0	0.0
Total-	50	100.0	50	100.0

Fig. 5. Gestational age distribution of neonaates studied

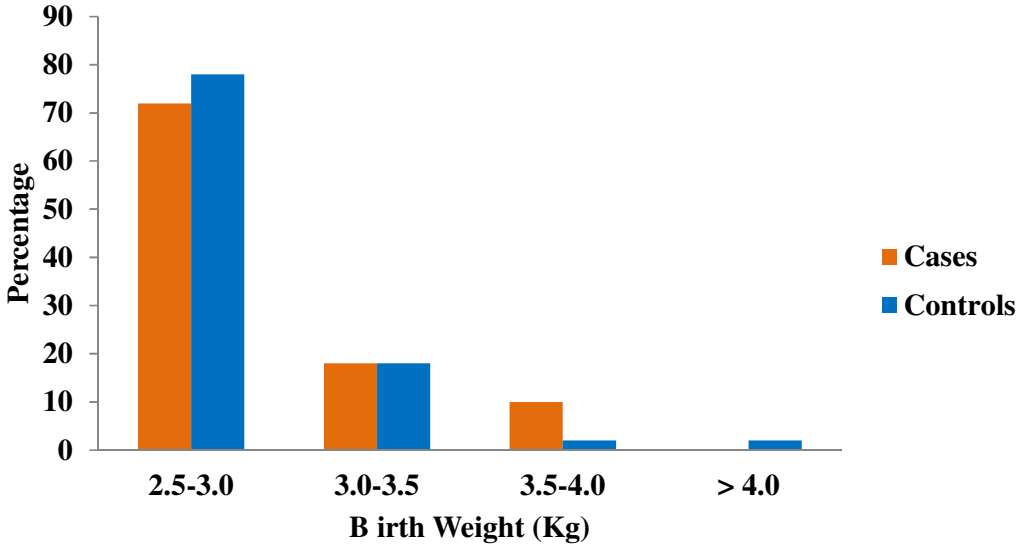


The gestational age of neonates is shown in Table 7 and Fig. 5. Among 50 asphyxiated neonates who formed the case group 40 (80%) were in gestational age of 37-40 weeks, 10 (20%) were in gestational age of 40-42 weeks. In control, all 50 neonates were below 40 weeks of gestation only. The gestational age distribution is statistically similar with p=0.001.

Table 8: Birth weight of neonates studied

BW (kg)	Cases		Controls	
	No	%	No	%
2.50-3.00	36	72.0	39	78.0
3.00-3.50	9	18.0	9	18.0
3.50-4.00	5	10.0	1	2.0
>4.00	0	0.0	1	2.0
Total	50	100.0	50	100.0
Mean ± SD	2.88±0.39		2.83±0.37	

Fig. 6. Birth weight distribution of neonates studied

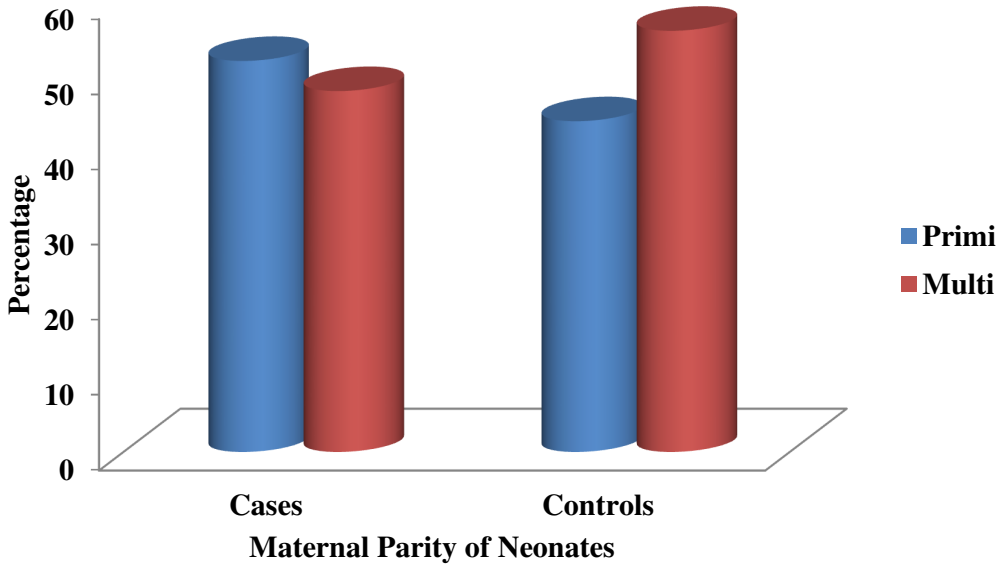


The birth weight of neonates is shown in Table 8 and Fig. 6. Out of the 50 neonates incase group, 36(72%) neonates weighed between 2.5-3.0kg, 9(18%) weighed between of 3.0-3.5kg and 5(10%) weighed between 3.5-40 kg. None of the neonates weighed > 4 kg. Among the control group of 50 neonates, 39 (78%) neonates weighed between 2.5-3.0 kg, 9 (18%) weighed between 3.0-3.5kg, 1 (2%) weighed between 3.5-4.0 kg and 1 (2.0%) weighed > 4 kg. The mean weight incase group was 2.88±0.39 kg and in control group was 2.83±0.37 kg. Birth weight distribution is statistically similar with P=0.285.

Table 9: Maternal parity of neonates studied

Maternal Parity	Cases		Controls	
	No	%	No	%
Primi	26	52.0	22	44.0
Multi	24	48.0	28	56.0
Total	50	100.0	50	100.0

Fig. 7. Shows the maternal parity of neonates studied

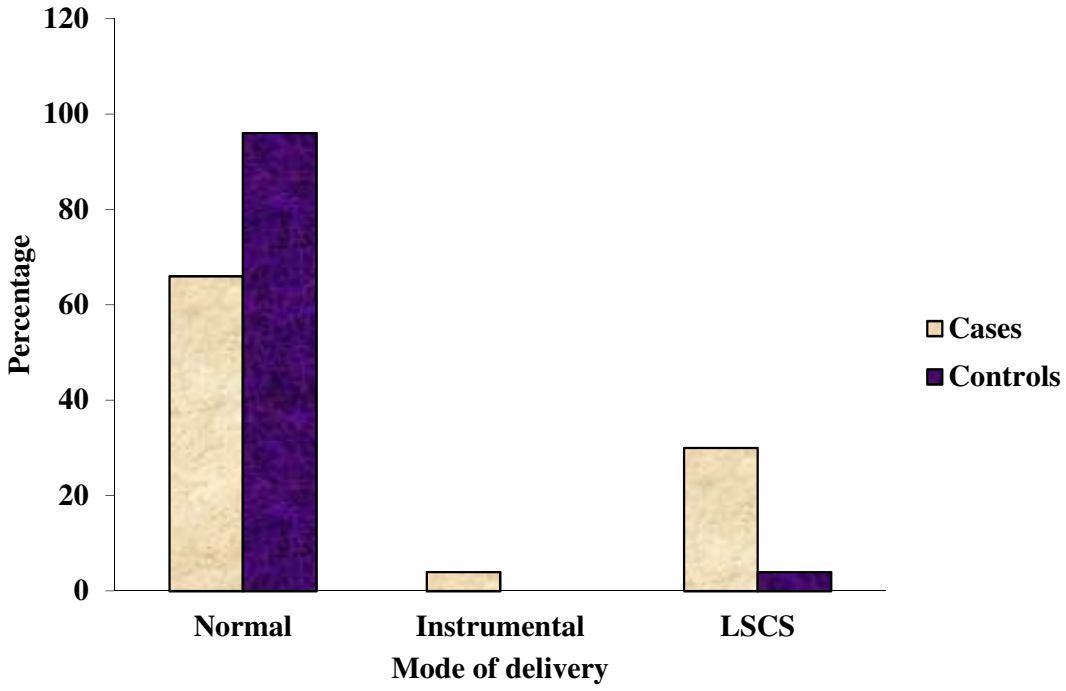


The maternal parity of neonates is shown in Table 9 and Fig. 7. Out of the 50 neonates in case group, 26 (52%) were born to primi mothers and 24 (48%) were born to multi gravida mothers. Among the control group of 50 neonates, 22 (44%) were born to primi mothers and 28 (56%) were born to multi gravid mothers. Proportion of primi and multi gravid mothers are statistically similar with P=0.423.

Table10: Mode of delivery of neonates studied

Mode of delivery	Cases		Controls	
	No	%	No	%
Normal	33	66.0	48	96.0
Instrumental	2	4.0	0	0.0
LSCS	15	30.0	2	4.0
Total	50	100.0	50	100.00

Fig. 8. Mode of delivery of neonates studied

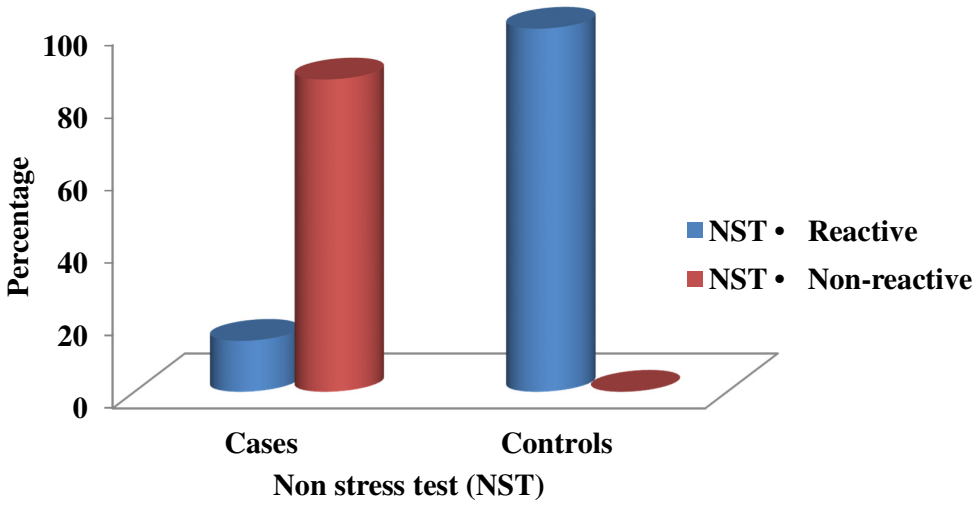


The mode of delivery of neonates is shown in Table 10 and Fig. 8. Among the 50 neonates in case group, 33 (66%) neonates were delivered normally, 15 (30%) were delivered by cesarean section and 2 (4%) neonates through instrumental delivery. While in control group of the 50 neonates, 48 (96%) were delivered normally, 2 (4%) neonates were delivered by cesarean section and none of the neonates was born by instrumental delivery. The Incidence of cesarean section and instrumental delivery are significantly more in cases (34%) compared to controls (4%) with P=0.001.

Table 11: Signs of Fetal Distress of neonates studied

NST FD	Cases		Controls	
	No	**%**	**No**	**%**
Reactive	7	14.0	50	100.0
Non-reactive	43	86.0	0	0.0

Fig. 9. Maternal non stress test (NST) of the neonates studied

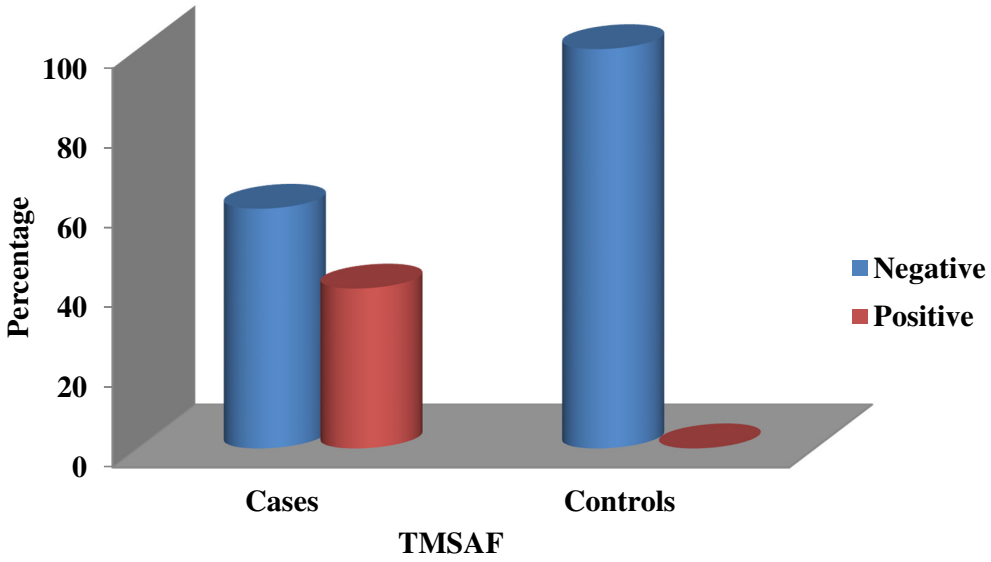


The signs of fetal distress of neonates are shown in Table 11 and Fig. 9. Of the 50 neonates in case group, 7 (14%) had Reassuring NST and 43 (86%) had Non Reassuring NST suggestive of fetal distress. All the 50 (100%) neonates in control group had Reassuring NST. The Incidence of Non Reassuring NST is significantly more in cases (86%) against controls with P< 0.001.

Table 12: Thick Meconium Stained Amniotic Fluid (TMSAF)status of the neonates studied

TMSAF	Cases		Controls	
	No	%	No	%
Negative	30	60.0	50	100
Positive	20	40.0	0	0.0

Fig. 10. TMSAF status of the neonates studied

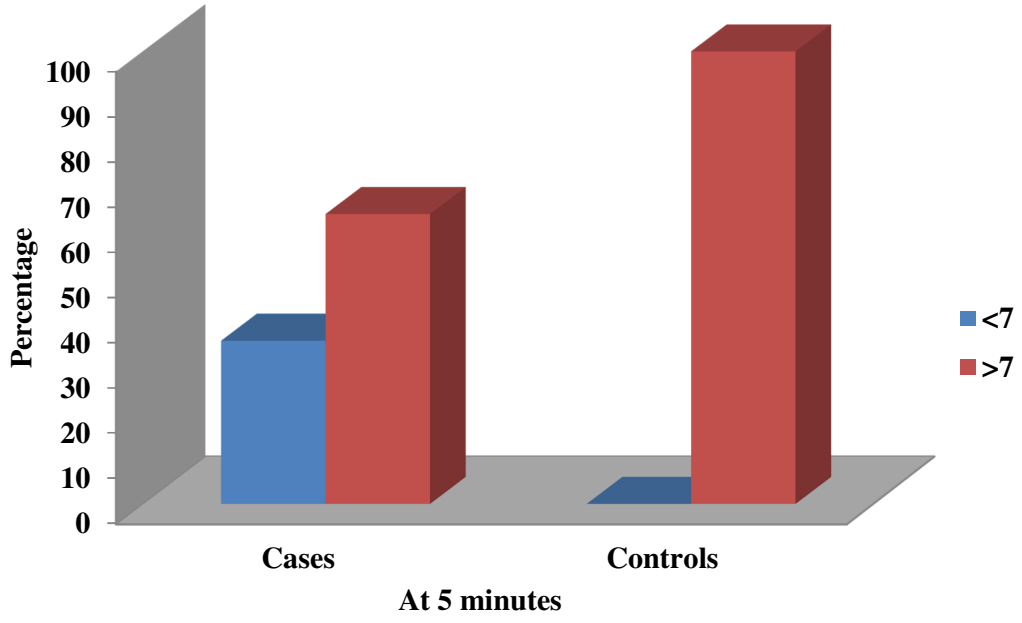


Of the 50 neonates in case group, 20 (40%) had Thick MSAF and 30 (60%) had clear amniotic fluid. All the 50 (100%) neonates in control group had clear amniotic fluid (Table 12 and Fig.10). The Incidence of Thick MSAF is significantly more in cases against controls with P< 0.00I.

Table 13: Apgar score of neonates studied at 1, 5 and 10 min

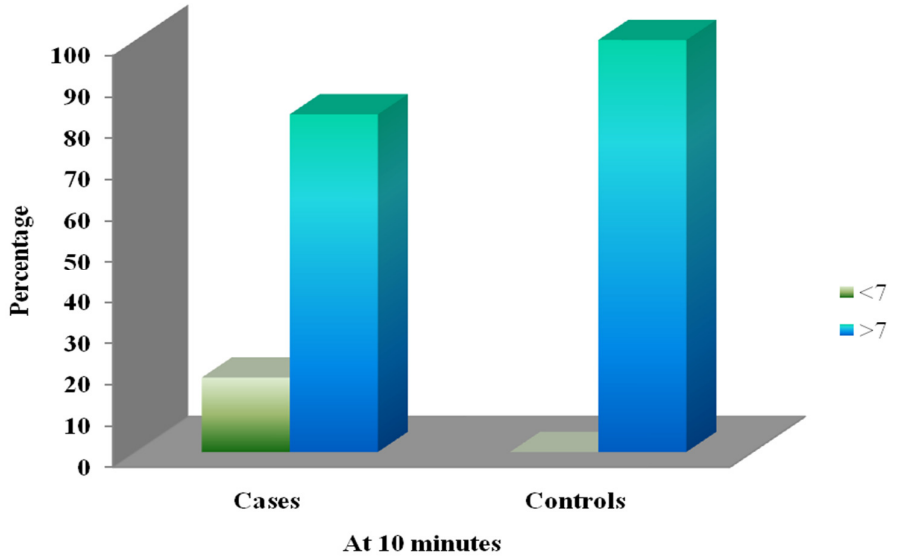
Apgar score	Cases		Controls	
	No	%	No	%
At 1minute				
<7	50	100.0	0	0.0
>7	0	0.0	50	100.0
At 5minutes				
<7	18	36.0	0	0.0
>7	32	64.0	50	100.0
At 10minutes				
<7	9	18	0	0.0
>7	41	82	50	100.0

Fig. 11a. Showing the APGAR score at 5 minutes of the neonates studied



Of the 50 neonates in case group, 18 (36%) neonates had an Apgar score of <7 at 5 min and 32 (64%) had Apgar score above 7. All the 50 (100%) neonates in the control group had an Apgar score of ≥7.0 (Table 13 and Fig. 11a).

Fig. 11b. Showing the APGAR score at 10 minutes of the neonates studied



Among the 50 neonates in case group, 9 (18%) neonates had an Apgar score of <7at10 min and 41 (82%) had above 7 Apgar score. All the 50(100%) neonates in the control group had an Apgar score of ≥7.0 (Table 13 and Fig. 11b).

Table 14: Severity of HIE based on Apgar score of neonates studied

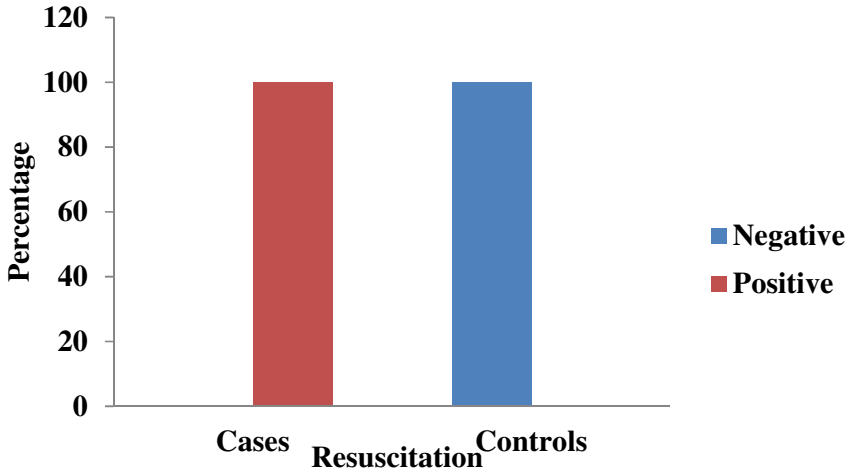
Apgar score	Cases (n=50)		Controls (n=50)	
	No	**%**	**No**	**%**
Apgar score at 1 min				
0-3	31	62.0	0	0.0
4-6	19	38.0	0	0.0
≥7.0	0	0.0	50	100.0
Apgar score at 5 min				
0-3	2	4.0	0	0.0
4-6	16	32.0	0	0.0
≥7.0	32	64.0	50	100.0
Apgar score at 10 min				
0-3	0	0.0	0	0.0
4-6	9	18.0	0	0.0
≥7.0	41	82.0	50	100.0

The severity of HIE based on Apgar score of neonates studied is shown in Table 14. Of the 50 neonates in the case group, 31 (62%) neonates had an Apgar score between 0-3 (severe birth asphyxia) at 1 min, 19 (38%) had an Apgar score between 4-6 (Moderate birth asphyxia) and none of the neonates had an Apgar score of ≥ 7 at 1 min. Of the 50 neonates in case group, 2 (4%) neonates had an Apgar scores between 0-3 (severe birth asphyxia) at 5 min, 16 (32%) neonates had an Apgar score between 4-6 (moderate birth asphyxia) at 5 min and a majority of 32 (64%) neonates had an Apgar score of ≥ 7 at 5 min. Out of 50 neonates in case group, 9 (18%) neonates had an Apgar score between 4-6 (moderate birth asphyxia) at 10 min, 41 (82%) had an Apgar score of ≥ 7 and none had an Apgar score between 0-3 (severe birth asphyxia) at 10 min.

Table 15: Resuscitation with >1 minute of positive pressure ventilation required for the neonates studied

Resuscitation	Cases		Controls	
	No	%	No	%
Negative	0	0.0	50	100.0
Positive	50	100.0	0	0.0

Fig. 12. Showing the need for resuscitation with >1 min of PPV of the neonates studied

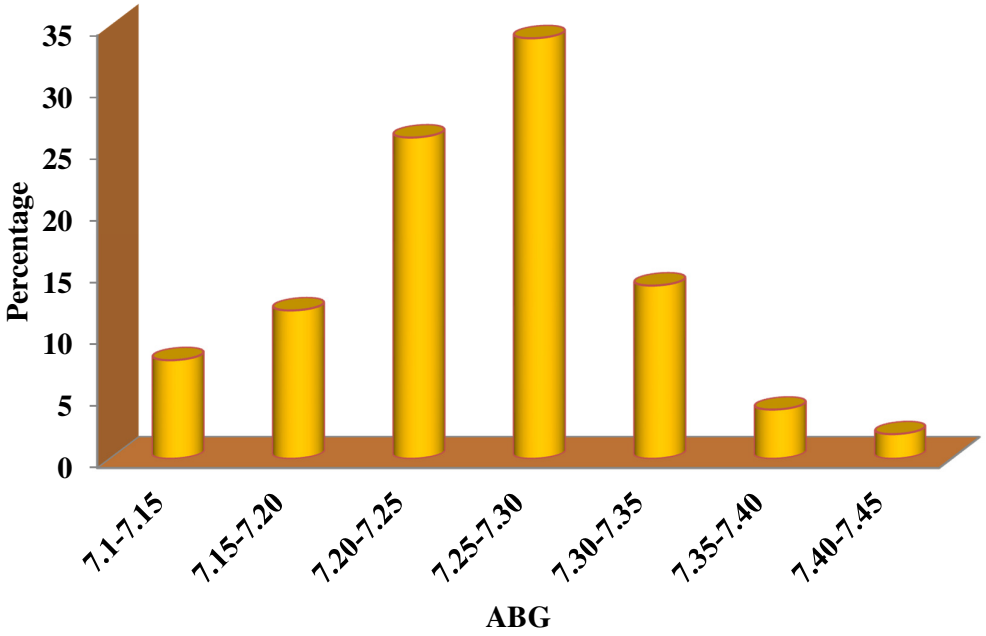


The resuscitation with >1 minute of positive pressure ventilation required is shown in Table 15 and Fig. 12. Among the 50 neonates in case group, all the 50(100%) neonates were in need of resuscitation with>1minute of positive pressure ventilation before stable spontaneous respiration. All the50 (100%) neonates in control group were not in need of any such intervention (100.0%) with p=0.002.

Table 16: Showing the arterial pH of the neonates studied

ABG	No of patients (n=50)	%
7.10-7.15	4	8.0
7.15-7.20	6	12.0
7.20-7.25	13	26.0
7.25-7.30	17	34.0
7.30-7.35	7	14.0
7.35-7.40	2	4.0
7.40-7.45	1	2.0

Fig. 13. Showing the arterial pH of the neonates studied

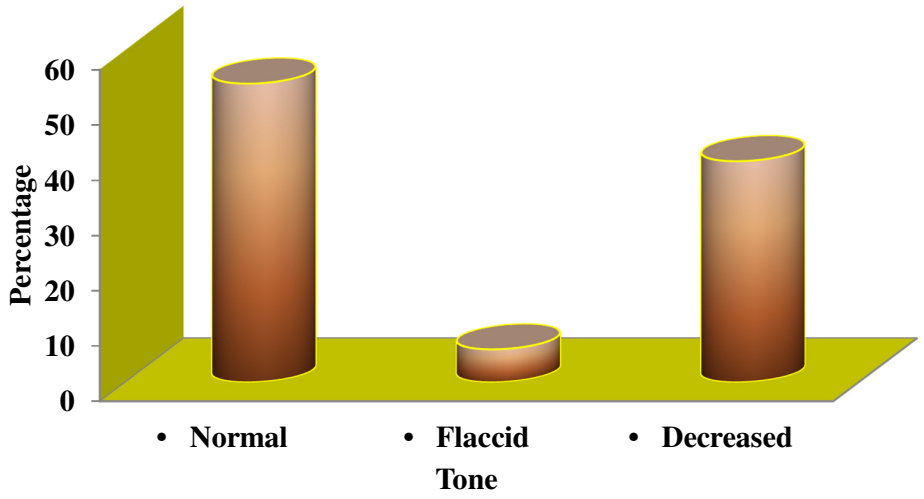


The arterial pH of the neonates is shown in Table 16 and Fig. 13. Among the 50 cases of neonatal asphyxia studied 4(8%) of the neonates had arterial pH between7.10-7.15, 6 (12%) of the neonates had arterial pH between 7.15-7.2, 13 (26%) of the neonates had arterial pH between 7.2-7.25, 17 (34%) of the neonates had arterial pH between 7.25-7.3, 7 (14%) of the neonates had arterial pH between7.3-7.35, 2(4%) of the neonates had arterial pH between 7.35-7.4 and 1 (2%) of the neonates had arterial pH between 7.4-7.45.

Table 17: Neurological Examination of the neonates studied

Tone	No of patients (n=50)	%
Normal	27	54.0
Decreased	20	40.0
Flaccid	3	6.0

Fig. 14. Tone of neonates studied

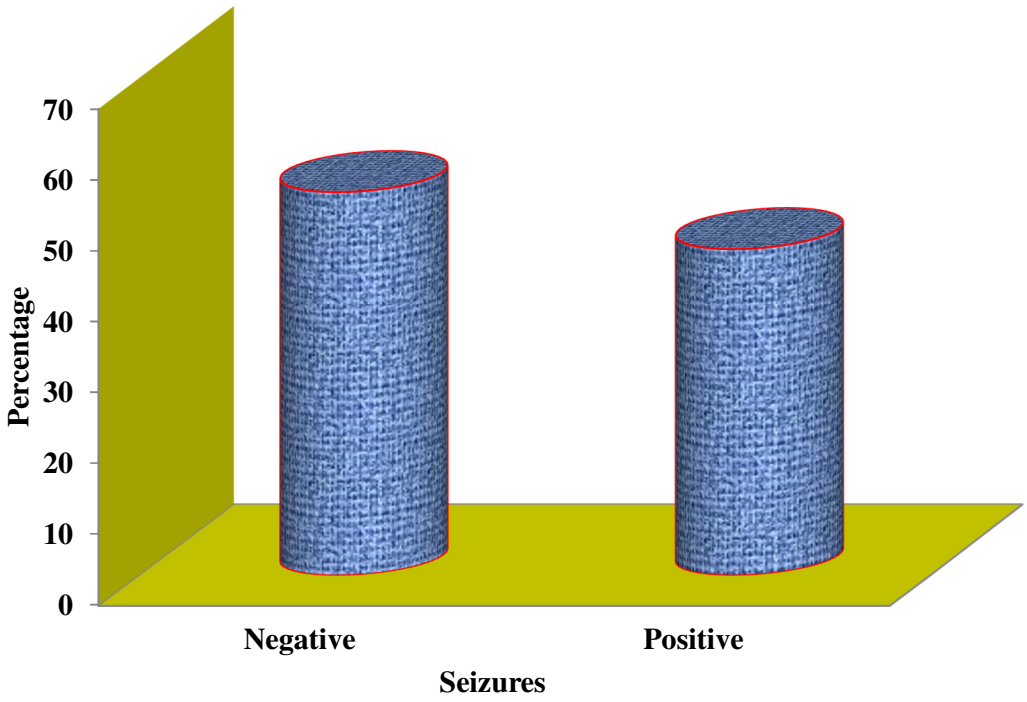


The tone of the neonates is shown in Table 17 and Fig14. Out of the 50 neonates in case group, 27 (54%) had normal tone, 20 (40%) had hypotonia and 3 (6%) were flaccid. In control cases, 50 (100%) neonates had normal neurological examination. Abnormal neurological examination is significantly more (46%) in cases compared to controls with $p<0.001$.

Table 18: Neonates having seizures in this study

Seizures	No of patients (n=50)	%
Negative	27	54.0
Positive	23	46.0

Fig. 15. Shows percentage of neonates having seizures



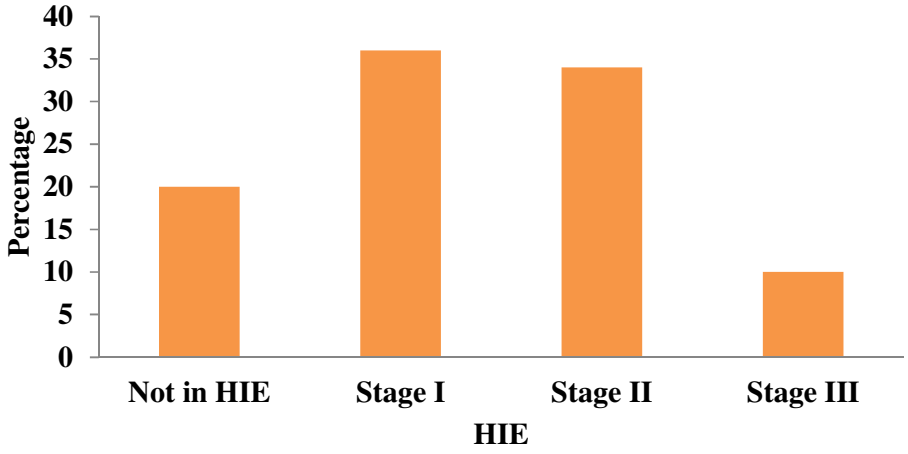
Of the 50 neonates in case group, 27 (54%) had no seizures, 23 (46%) had seizures (Table 18 and Fig. 15). Seizures are significantly more (46%) in cases compared to controls with $p<0.001$.

Table 19: Incidence of HIE (Hypoxic Ischemic Encephalopathy) among neonates studied

HIE	No of patients (n=50)	%
Not in HIE	10	20
Stage I	18	36
Stage II	17	34
Stage III	5	10

Stages classified as per Sarnat and Sarnat classification of hypoxic ischemic encephalopathy 1976.

Fig. 16. Showing HIE staging of asphyxiated neonates

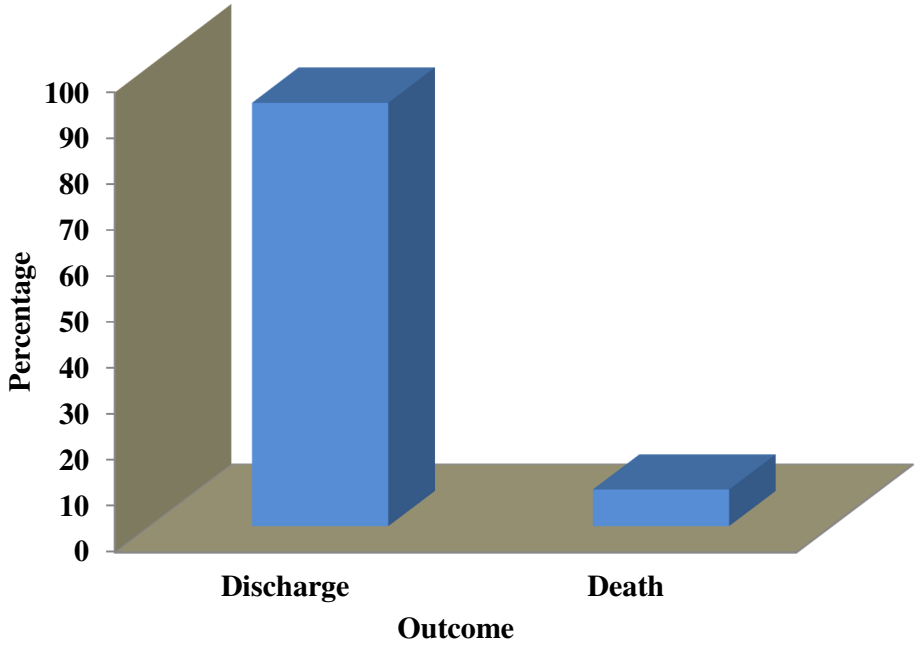


The incidence of HIE among neonates is shown in Table 19 and Fig.16. Among the 50 neonates in the case group, 10(20%) were not in HIE, 18(36%) had mild HIE, 17(34%) had moderate HIE and 5(10%) had severe HIE in the immediate neonatal period in the Neonatal Intensive Care Unit.

Table 20. Outcome of neonates in the case group (Asphyxiated)

Outcome	No. of patients (n=50)	%
Discharge	46	92%
Death	4	8.0%

Fig. 17. Outcome of neonates in the case group

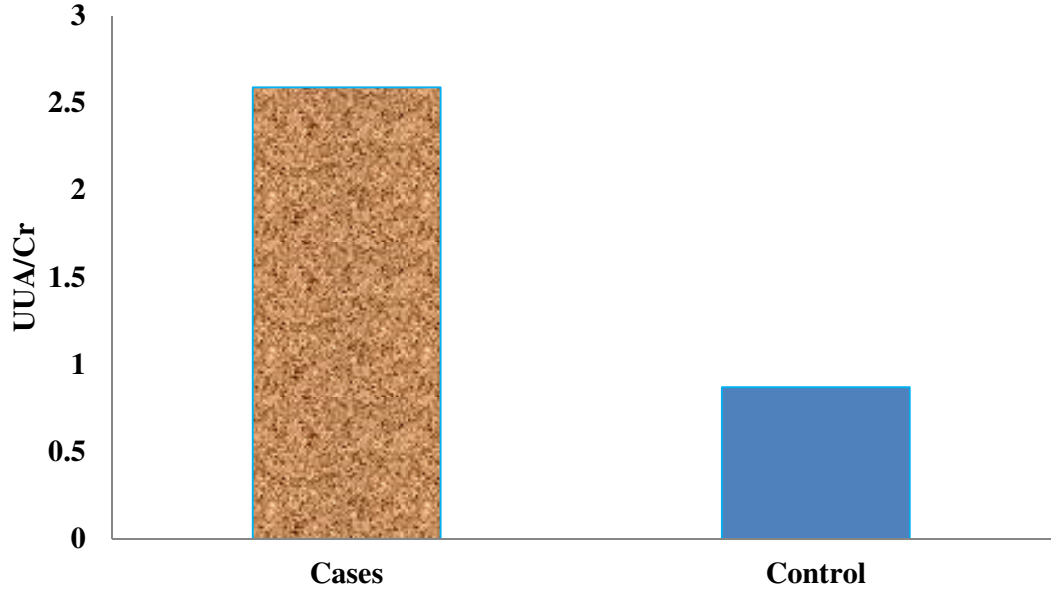


The outcome of neonates enrolled in the case group having suffered asphyxia is shown in Table 20 and Fig. 17. Among the 50 neonates enrolled in the case group, 46 (92%) neonates were discharged and 4 (8%) died.

Table 21: Comparison of Urinary uric acid/creatinine (UUA/Cr) ratio in two groups studied

UUA/Cr	Cases	Controls
Min-Max	0.78-4.74	0.42-1.23
Mean ± SD	2.59±1.04	0.72±0.16
Inference	UUA/Cr ratio is significantly higher in study group compared to Control with P<0.001	

Fig. 18. Comparison of Urinary uric acid/creatinine (UUA/Cr) ratio in two groups studied



The comparison of UUA/Cr ratio in two groups studied is shown in Table 21 and Fig. 18. UUA/Cr ratio is significantly higher in study group compared to Control with P<0.001.

Table 22: Correlation of urinary uric acid and creatinine ratio (UUA/Cr) with HIE status in cases studied

UUA/Cr	Total number of patients (n=50)	HIE Stage				P value
		Not in HIE (n=1)	Stage I (n=18)	Stage II (n=17)	Stage III (n=5)	
Min-Max	0.78-4.74	0.78-2.65	1.62-3.48	1.11-3.92	3.52-4.74	<0.001**
Mean ± SD	2.59±1.04	1.28±0.53	2.66±0.70	2.79±0.74	4.29±0.46	

Fig. 19. Comparison of UUA/Cr raatio with HIE status in cases studied

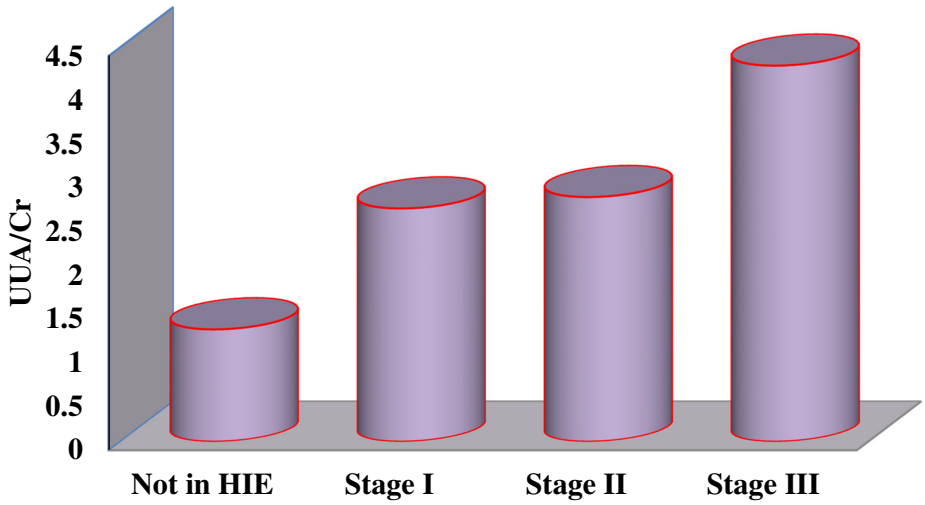


Table 22 and Fig. 19 showed the correlation of UUA/Cr ratio with HIE status in cases studied and it was found to be statistically significant with the p value of < 0.001.

Table 23. Diagnostic value of UUA/Cr ratio

Variables	Values
True positive	43
True Negative	46
False Positive	4
False Negative	7
Sensitivity	86%
Specificity	92%
PPV	91.49%
NPV	86.49%
Accuracy	89%

PPV-Positive predictive value, NPV-Negative predictive value

Table 24: Shows sensitivity, specificity and predictive values of UUA/Cr in prediction of Neonatal asphyxia

UUA/Cr	Sensitivity	Specificity	PPV	NPV	Accuracy	P value
>1.22	86.0	92.0	91.49	86.49	89.00	<0.001**

The sensitivity, specificity and predictive values of UUA/Cr in prediction of Neonatal asphyxia is shown in Table 24.

Urinary UA/Cr value of >1.22 has 86% sensitivity, 92% specificity, positive predictive value of 91.49%, negative predictive value of 86.49% and an accuracy of 89% in diagnosing asphyxia among term neonates.

DISCUSSION

Perinatal asphyxia is a common neonatal condition contributing significantly to neonatal morbidity and mortality. Although asphyxia is a commonly made diagnosis at birth there is no accepted definition. It is a devastating condition because of its potential to cause permanent damage and even death of the neonate. The value of biochemical markers for diagnosing asphyxia is inadequate and controversial [21]. Many studies have shown cerebral function monitoring using EEG, cranial ultrasonography, MRI and estimation of markers such as CK-BB, brain specific LDH isomer glutamide and neuron specific enolase in CSF are useful in predicting both the immediate dysfunction and the long term outcome [70, 71], but they are not easily available. Due to limitations, the Apgar score cannot be used as an useful tool for the evaluation of asphyxia in newborns. Various factors especially prematurity has an effect on it as a result of which it may not predict mortality and morbidity definitely. The signs of asphyxial injury are nonspecific and overlap with other illnesses. In the absence of perinatal records, it is difficult to diagnose neonatal asphyxia retrospectively. The current problem is our inability to precisely distinguish the false positively diagnosed from the true positive asphyxiated neonates. Several studies have been conducted to evaluate better markers which would help to differentiate asphyxiated and non-asphyxiated neonates.

In our study an attempt is made to ascertain whether UUA/Cr ratio can distinguish an asphyxiated from Non-asphyxiated term neonate. These tests are routinely available in most centers and hence the study was done to establish its usefulness.

Uric acid is the end product of purine metabolism in humans. Under certain conditions like hypoxia or ischaemia, there will be increased conversion of the Xanthine dehydrogenase to the oxidized form. Because of its poor solubility, any alterations in production or excretion will produce high serum levels [62, 63]. During reoxygenation after asphyxia or reperfusion after ischemia, hypoxanthine that accumulated in both circulating blood and tissues is oxidized to uric acid [64].

The present study showed significant increase in UA/Cr ratio in early urine samples from asphyxiated full term neonates and the study revealed positive correlation between the UA/Cr ratio and the severity of HIE.

Table 25: Comparison of gender, birth weight and UUA/Cr ratio between our study and Reem Mahmoud and Dina El Abd study[20]

Characteristics		Reem Mahmoud and Dina EI Abd		Present study		P value
		Cases	**Controls**	**Cases**	**Controls**	
Sex	Male	40%	70%	56%	58%	Not significant
	Female	60%	30%	44%	42%	
Birth weight		3.25±0.54kg	3.32±0.44kg	2.88±0.39kg	2.83±0.37 kg	Not significant
UUA/Cr ratio		2.9±0.73	0.72 ±0.35	2.59±1.04	0.72±0.16	<0.001

UUA/Cr ratio was significantly elevated in asphyxiated neonates when compared with controls ($p<0.001$) in Reem Mahmoud and Dina El Abd study which was similar to the findings in our study (Table 25).

Table 26: Comparison of UUA/Cr ratio in various HIE stages of Reem Mahmoud and Dina EI Abd[20] study and present study

UUA/Cr	Reem Mahmoud and Dinaa EI Abd[20]	Present study
Mild HIE		
Min-Max	1.02-2.11	1.62-3.48
Mean ± SD	1.53±0.25	2.66±0.70
Moderate HIE		
Min-Max	1.68-2.69	1.11-3.92
Mean ± SD	2.19±0.32	2.79±0.74
Severe HIE		
Min-Max	2.25-4.54	3.52-4.74
Mean ± SD	3.18±0.61	4.29±0.46
Controls		
Min-Max	0.20-1.22	0.42-1.23
Mean ± SD	0.72±0.35	0.72±0.16

Asphyxiated neonates were classified into 3 groups as per Sarnat and Sarnat staging 1976 in both the studies.

The highest UA/Cr ratio was found in severe HIE in our study which is similar to Reem Mahmoud and Dina EI Abd study (Table 26).

Table27. Comparative study of UUA/Cr ratio between our study and Basu *et al*[13], Bader *et al*[17]

Characteristics	Basu *et al*		Bader *et al*		Present study		P value
	Cases (n=31)	Controls (n=31)	Cases (n=18)	Controls (n=50)	Cases (n=50)	Controls (n=50)	
UUA/Cr ratio	3.1±1.3	0.96±0.54	2.06±1.12	0.64±0.48	2.59±1.04	0.72±0.16	<0.001

The urinary UA/Cr ratio was significantly higher in cases than controls in our study which is similar to Basu *et al* and Bader *et al.*

Table 28: Comparative study of results of our study and Bader *et al*[17]

	UUA/Cr cutoff	Sensitivity	Specificity	PPV	NPV	P value
Present study	>1.22	86%	92%	91.49%	86.49%	<0.001
Bader *et al*	>1.2	74%	76%	78%	72%	<0.001

The positive predictive value of UUA/Cr with a cut off > 1.2 in a study by Bader et al was 78% and the negative predictive value was 72%. The sensitivity was 74% and specificity 76% which was similar to our study.

Ciler Erdag and Vitrinel reported that the mean uric acid and creatinine ratio within 24 hours of birth was more in asphyxiated neonates than non asphyxiated neonates [14].

The results of present study were in concordance with Akisu *et al* (2007), who reported elevated UA/Cr ratio in full term infants with asphyxia and it correlated with the severity of HIE. The UA/Cr ratio was higher in asphyxiated neonates than non asphyxiated neonates (2.11±0.83 vs 0.72±0.39 p< 0.001). The UA/Cr ratio was found to be a good, simple screening test for the early assessment of perinatal asphyxia[16].

Mehes *et al*[72] reported that the UA/Cr ratio was elevated in term infants with asphyxia and the ratio correlates with the severity of HIE. They concluded that UA/Cr ratio is a good and simple screening test for early assessment of perinatal asphyxia.

Dong Wen Bin, *et al* [19] reported in his study that asphyxiated neonates have higher UA/Cr ratio than non asphyxiated neonates. It might be used as an indicator for early assessment of severity of asphyxia and post asphyxia renal injuries.

Jensen *et al* [22] and Hasday and Grum[23] found increased uric acid in urine of asphyxiated neonates.

The UA/Cr ratio allows rapid recognition of asphyxia and assessment of its severity. While many indicators for asphyxia are recognized, no single indicator was found to be predictive of subsequent morbidity. Although several biochemical indicators such as lactate, hypoxanthine,brain isoenzyme of creatinine phosphokinase, neuron specific enolase, excitatory

amino acids and erythropoietin are reported, they are mostly useful in research and are not available in most clinical services [67].

However, we found that the urinary uric acid to creatinine ratio to be a good, simple screening test for the early assessment of neonatal asphyxia. Furthermore there is correlation between the UUA/Cr ratio and the severity of the encephalopathy, indicating the degree of injury at early stage when other quantitative methods frequently cannot be carried out. However, this ratio does not provide further prognostic information that must be obtained by other methods.

SUMMARY

- This is an analytical cross sectional study conducted from January 2016 to July 2016 in the Department of Pediatrics, Rajah Mirasdar Hospital, Thanjavur.
- Cases and Controls comprised of asphyxiated and non asphyxiated neonates, respectively. The spot urine samples collected between 6-24 hours of life and sent for urinary uric acid to creatinine ratio analysis constituted the material for the study.
- A urinary uric acid to creatinine (UA/Cr) ratio value of >1.22 was taken as the cut-off level. The sensitivity, specificity, Positive predictive value (PPV), Negative predictive value (NPV) was calculated.
- Among the 50 neonates in case group, there were 28 (56%) males and 22 (44%) females. Among the control group of 50 neonates, there were 29 (58%) males and 21 (42%) females. Samples are gender matched with p=0.840
- Among 50 asphyxiated neonates which formed the case group 40(80%) cases were in gestational age of 37-40 weeks, 10 (20%) cases were in gestational age of 40-42 weeks, where as all normal neonates which constituted the control group were in gestational age of 37-40

weeks. The correlation with gestational age was found to be statistically significant with p value of 0.001.

- Among the 50 neonates in case group 36(72%) neonates weighed between 2.5-3.0kg, 9(18%) weighed between 3.0 3.5kg and 5(10%) weighed>3.5kg. Among the control group of 50 neonates, 39(78%) neonates weighed between 2.5-3.0kg, 9(18%) weighed between3.0-3.5 kg and 1 (2%) weighed between 3.5-4.0 kg, 1(2%) > 4kg. The mean weight in case group was 2.88±0.39 kg and in control group was 2.83±0.37 kg. Birth weight distribution is statistically similar with P=0.285.

- Among the 50 neonates in case group, 26(52%) were born to primi mothers and 24(48%) were born to multi gravida mothers. Among the control group of 50 neonates, 22 (44%) were born to primi mothers and 28 (56%) were born to multi gravida mothers. The correlation with maternal parity was found to be statistically not significant with a p value of 0.840.

- Among the 50 neonates in case group, 33(66%) neonates were delivered normally, 15(30%) were delivered by cesarean section and 2(4%) had instrumental delivery. Among the control group of 50 neonates, 48(96%) had normal delivery, 2 (4%) neonates were delivered by cesarean section. Incidence of cesarean section and

instrumental delivery are significantly more in cases compared to controls with P=0.001

- Of the 50 neonates in case group, 7(14%) had Reassuring NST and 43 (86%) had Non Reassuring NST suggestive of fetal distress. All the 50 (100%) neonates in control group had Reassuring NST. Incidence of Non Reassuring NST is significantly more in cases (86%) against controls with P<0.001.
- Of the 50 neonates in case group, 20(40%) had Thick MSAF and in 30 (60%) the amniotic fluid was clear. All the 50(100%) neonates in the control group had clear amniotic fluid. Incidence of thick MSAF was significantly more in case group when compared to control group.
- All the 50 neonates were in need of >1 minute of positive pressure ventilation before stable spontaneous respiration in the case group. All the 50 (100%) neonates in control group were not in need of any such intervention with a P<0.001
- Out of the 50 cases of neonatal asphyxia studied 4(8%) of the neonates had arterial pH between 7.10-7.15, 6(12%) of the neonates had arterial pH between 7.15-7.2, 13(26%) of the neonates had arterial pH between7.2-7.25, 17(34%) of the neonates had arterial pH between 7.25-7.3, 7(14%) of the neonates had arterial pH between 7.3-7.35,

2(4%) of the neonates had arterial pH between 7.35-7.4, 1(2%) neonate had arterial pH between 7.4-7.45.

- Of the 50 neonates in case group, 27(54%) had normal neurological examination with normal tone, 20(40%) had hypotonia and 3(6%) were flaccid. All the 50 (100%) neonates in control group had normal neurological examination. Abnormal neurological examination is significantly more (46.0%) in cases when compared to controls with P<0.001.

- Of the 50 neonates in case group, 27(54%) had no seizures. 23(46%) had seizures. Seizures are significantly more (46.0%) in case group when compared to control group with P<0.001.

- Of the 50 neonates in the case group, 10(20%) were not in HIE, 18(36%) had mild HIE, 17(34%) had moderate HIE and 5(10%) had severe HIE in the immediate neonatal period in Neonatal Intensive Care Unit.

- Out of 50 asphyxiated neonates enrolled in the case group, 46(92%) were discharged after recovery while discharge, 4(8%) died.

- UUA/Cr ratio is significantly higher in study group compared to Control with P<0.001. The correlation of urinary UA/Cr ratio with

HIE status was found to be statistically significant with a p value of <0.001.

Urinary UA/Cr cut of value of >1.22 has 86% sensitivity,92% specificity, positive predictive value of 91.49%, negative predictive value of 86.49% and an accuracy of 89% in diagnosing asphyxia among term neonates.

CONCLUSION

1. Urinary uric acid to creatinine ratio is higher in asphyxiated infants than non asphyxiated infants.
2. Urinary uric acid to creatinine ratio can be used as a quick, inexpensive, non invasive, reliable, early biochemical marker of birth asphyxia.
3. Estimation of urinary uric acid to creatinine ratio had good correlation with severity of HIE.
4. This ratio does not provide further prognostic information which must be obtained by other biochemical markers or neuroimaging.

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PROFORMA OF THE DISSERTATION

STUDY OF URINARY URIC ACID / CREATININE RATIO AS A MARKER OF NEONATAL ASPHYXIA

BABY OF : D.O.A.:

SEX : D.O.D.:

TIME AND

DATE OF BIRTH :

BIRTH WEIGHT :

ASSESSMENT OF GESTATIONAL AGE :

METHOD	LMP	USG	NEW BALLARD SCORE
PERIOD OF GESTATION			

MATERNAL HISTORY :

NON STRESS TEST : REASSURING / NON REASSURING

BIRTH NOTES :

THICK MECONIUM STAINED AMNIOTIC FLUID : YES / NO

APGAR score	1 MIN	5 MIN	10 MIN

EXAMINATION OF THE BABY :

HEAD TO TOE EXAMINATION :

ANY OBVIOUS EXTERNAL CONGENITAL ABNORMALITIES:

NEUROLOGICAL EXAMINATION :

OTHER SYSTEMIC EXAMINATION :

COURSE IN NICU :

HIE STAGE :

INCLUSION CRITERIA	YES	NO
1) Gestational age ≥ 37 weeks		
2) Appropriate for gestational age		
3) The neonates will be identified to haveexperienced perinatal asphyxia when at least 3of the following are present:		
A) Intrapartum signs of fetal distress, as indicated by late decelerations on fetal monitoring or by thick meconium staining ofthe amniotic fluid		
B) APGAR score of <7 at one minute of life		
C) RESUSCITATION with >1 minute of positive pressure ventilation before stable spontaneous respiration.		
D) Profound metabolic or mixed acidemia (pH<7.20) in an arteryblood sample, if obtained		
E) Mild, moderate or severe hypoxic ischemic encephalopathy (HIE), as defined by Sarnat & Sarnat, 1976		

EXCLUSION CRITERIA	YES	NO
1) Congenital malformations		
2) Maternal drug addiction		
3) Neonates born to mothers who would have received magnesium sulphate within 4 hours prior to delivery or opiods		
4) Congenital or acquired infections		
5) Hemolytic disease of the newborn		
6) Neonates born to mothers consuming alcohol		
7) Neonates born to mothers who are smokers		
8) Neonates born to mothers on anti epileptics.		

Investigations:

1) **Umbilical Artery Ph:**

2)

Markers	Levels in urine sample
a) uric acid	
b) creatinine	

3) Urinary Uric Acid And Creatinine Ratio :

MASTER CHART OF CASES																	
SL. NO	**IPNO**	**SEX**	**GA**	**BW**	**MH**	**MOD**	**FD**		**Apgar**			**RES**	**ABG**	**NE**	**HIE**	**D**	**UUA/CR**
□							**NST**	**TMSAF**	**1'**	**5'**	**10'**						
1.	415389	M	T	2.80 Kg AGA	MG	CS	NR	-	5/10	8/10	8/10	+	7.29	T N S-	1	D	3.04
2.	415391	Fch	T	2.45 Kg AGA	P	ND	NR	-	1/10	6/10	7/10	+	7.21	T↓ S+	2	D	1.92
3.	415478	F	T	2.6 0Kg AGA	P	CS	NR	-	5/10	8/10	8/10	+	7.28	T N S-	1	D	2.55
4.	415646	F	T	2.6 0Kg AGA	P	ND	NR	-	2/10	4/10	6/10	+	7.16	T↓ S+	3	D	4.22
5.	415663	F	PD	3.78 Kg AGA	MG	ND	NR	-	5/10	7/10	9/10	+	7.30	T N S-	1	D	3.02
6.	415738	F	T	3.0 0Kg AGA	MG	CS	NR	-	1/10	6/10	7/10	+	7.21	T↓ S+	2	D	3.92
7.	415897	F	T	3.12Kg AGA	P	ND	R	+	5/10	9/10	9/10	+	7.34	T N S-	-	D	2.65
8.	415912	F	T	2.67 Kg AGA	MG	CS	NR	-	2/10	8/10	8/10	+	7.23	T↓ S+	2	D	2.68
9.	415928	F	T	3.52 Kg AGA	P	CS	NR	-	3/10	8/10	9/10	+	7.45	T N S-	1	D	1.20
10.	415948	M	T	2.63 Kg AGA	P	ND	NR	-	1/10	4/10	6/10	+	7.14	T F S+	3	D	3.52
11.	417183	M	T	2.6 0Kg AGA	MG	CS	NR	-	2/10	8/10	8/10	+	7.25	T N S-	1	D	3.48
12.	417779	F	T	2.80Kg AGA	MG	ND	NR	-	5/10	8/10	8/10	+	7.29	T N S-	1	D	3.14
13.	417941	M	PD	2.60Kg AGA	P	ND	NR	+	1/10	5/10	7/10	+	7.22	T↓ S+	2	D	3.71
14.	418665	M	T	3.90Kg AGA	MG	ND	NR	-	1/10	8/10	8/10	+	7.28	T N S-	1	D	3.28
15.	418870	M	T	3.40Kg AGA	MG	ND	NR	-	1/10	4/10	6/10	+	7.20	T↓ S+	2	D	2.80
16.	413287	M	T	3.00Kg AGA	P	ND	NR	+	4/10	8/10	8/10	+	7.20	T↓ S+	2	D	2.87
17.	418916	M	T	2.5Kg AGA	P	CS	NR	-	1/10	3/10	5/10	+	7.10	T F S+	3	Expired	4.74
18.	419455	M	T	2.90Kg AGA	MG	ND	R	-	2/10	6/10	6/10	+	7.22	T↓ S+	2	D	2.88

19.	419667	F	PD`	3.10Kg AGA	P	ID	NR	+	1/10	7/10	9/10	+	7.26	T N S-	1	D	1.62
20.	419245	F	T	2.80Kg AGA	MG	ND	NR	-	5/10	8/10	8/10	+	7.29	T N S-	1	D	3.14
21.	419954	M	T	2.60Kg AGA	MG	ND	NR	-	4/10	8/10	8/10	+	7.20	T N S-	-	D	0.78
22.	420015	M	T	2.60Kg AGA	P	ND	NR	+	5/10	8/10	8/10	+	7.28	T N S-	1	D	3.38
23.	415692	N	T	2.50Kg AGA	P	CS	NR	-	1/10	6/10	8/10	+	7.20	T↓ S+	2	D	1.11
24.	421007	M	T	2.70Kg AGA	MG	ND	NR	+	3/10	7/10	8/10	+	7.22	T↓ S+	2	D	2.93
25.	421305	M	PD	2.60Kg AGA	MG	ND	NR	-	3/10	8/10	8/10	+	7.21	T↓ S+	2	Expired	3.82
26.	421806	F	PD	3.40Kg AGA	MG	ND	R	+	4/10	8/10	8/10	+	7.32	T N S-	-	D	1.32
27.	413452	F	T	2.70Kg AGA	P	ND	R	-	2/10	4/10	6/10	+	7.24	T↓ S+	2	D	2.18
28.	430324	M	T	2.50Kg AGA	P	ND	NR	+	1/10	7/10	8/10	+	7.26	T N S-	1	D	3.32
29.	430331	F	T	2.40Kg AGA	MG	ND	NR	+	1/10	5/10	6/10	+	7.14	T F S +	3	Expired	4.50
30.	430401	M	PD	2.55Kg AGA	MG	ND	NR	-	3/10	8/10	8/10	+	7.21	T↓ S+	2	D	3.82
31.	430480	M	T	2.50Kg AGA	P	ND	NR	-	5/10	8/10	8/10	+	7.27	T N S-	1	D	3.06
32.	430638	F	T	2.90Kg AGA	P	CS	NR	-	4/10	9/10	9/10	+	7.29	T N S-	1	D	2.90
33.	431046	M	T	3.20Kg AGA	MG	CS	NR	+	3/10	8/10	9/10	+	7.26	T N S-	1	D	3.10
34.	431134	F	T	3.05Kg AGA	P	CS	NR	+	4/10	8/10	8/10	+	7.29	T N S-	1	D	1.78
35.	431284	F	T	2.67Kg AGA	MG	CS	NR	-	3/10	6/10	7/10	+	7.26	T N S-	1	D	2.10
36.	431295	F	PD	2.76Kg AGA	MG	ND	NR	-	4/10	6/10	8/10	+	7.19	T↓ S+	2	D	2.98
37.	431591	F	T	3.65Kg AGA	P	ID	NR	+	1/10	8/10	8/10	+	7.31	T N S-	1	D	2.12
38.	431607	M	T	2.60Kg AGA	P	ND	R	-	3/10	9/10	9/10	+	7.32	T N S-	-	D	1.32

39.	431989	M	T	2.76Kg AGA	MG	CS	NR	-	5/10	6.10	7/10	+	7.30	T N S-	-	D	1.02
40.	423477	M	T	2.77Kg AGA	MG	ND	NR	+	3/10	6/10	7/10	+	7.22	T↓ S+	2	D	2.98
41.	432583	M	T	2.50Kg AGA	MG	ND	NR	+	6/10	8/10	8/10	+	7.32	T N S-	-	D	1.53
42.	432714	M	T	2.80Kg AGA	P	CS	NR	+	1/10	8/10	8/10	+	7.28	T N S-	1	D	1.78
43.	432502	M	PD	3.00Kg AGA	P	ND	NR	-	5/10	9/10	9/10	+	7.35	T N S+	-	D	1.20
44.	433398	F	T	3.96Kg AGA	MG	ND	R	-	4/10	8/10	8/10	+	7.30	T N S-	-	D	1.24
45.	433575	M	T	3.05Kg AGA	MG	ND	NR	+	2/10	5/10	7/10	+	7.24	T↓ S+	2	D	2.38
46.	432720	M	PD	3.00Kg AGA	P	ND	R	+	2/10	8/10	8/10	+	7.31	T↓ S+	2	D	2.20
47.	423766	M	PD	2.80Kg AGA	P	ND	NR	+	1/10	3/10	6/10	+	7.14	T↓ S+	3	Expired	4.48
48.	423924	F	T	3.20Kg AGA	P	ND	NR	-	1/10	5/10	6/10	+	7.22	T↓ S+	2	D	2.38
49.	424593	M	T	3.50Kg AGA	P	CS	NR	+	6/10	9/10	9/10	+	7.38	T N S-	-	D	0.78
50.	424491	F	T	2.50Kg AGA	P	ND	NR	+	3/10	9/10	9/10	+	7.36	T N S-	-	D	0.98

MASTER CHART OF CONTROLS															
SL. NO	**IP NO**	**SEX**	**GAA**	**BW**	**MH**	**MOD**	**FD**		**APGAR**			**RES**	**ABG**	**NE**	**UUA/CR**
							NST	**MSAF**	**1′**	**5′**	**10′**				
1.	427653	F	T	2.50 Kg AGA	P	LSCS	R	-	8/10	9/10	9/10	-	-	T N S-	0.76
2.	427654	F	T	2.50 Kg AGA	MG	ND	R	-	7/10	8/10	8/10	-	-	T N S-	0.82
3.	429020	M	T	2.80 Kg AGA	MG	ND	R	-	7/10	9/10	9/10	-	-	T N S-	0.81
4.	428424	F	T	2.50Kg AGA	P	ND	R	-	7/10	8/10	8/10	-	-	T N S-	0.91
5.	427542	F	T	3.50 Kg AGA	P	ND	R	-	7/10	8/10	8/10	-	-	T N S-	1.18
6.	427549	F	T	3.20 Kg AGA	MG	ND	R	-	7/10	8/10	8/10	-	-	T N S-	1.22
7.	427652	M	T	2.60Kg AGA	MG	ND	R	-	7/10	9/10	9/10	-	-	T N S-	0.98
8.	427456	M	T	2.70Kg AGA	MG	ND	R	-	7/10	8/10	8/10	-	-	T N S-	0.87
9.	427662	M	T	2.80Kg AGA	P	ND	R	-	7/10	9/10	9/10	-	-	T N S-	0.90
10.	427659	M	T	3.00 Kg AGA	P	LSCS	R	-	7/10	8/10	8/10	-	-	T N S-	1.22
11.	427661	F	T	3.70Kg AGA	MG	ND	R	-	7/10	9/10	9/10	-	-	T N S-	0.60
12.	427810	M	T	2.40Kg AGA	MG	ND	R	-	8/10	9/10	9/10	-	-	T N S-	0.70
13.	427536	F	T	2.90Kg AGA	MG	ND	R	-	7/10	8/10	8/10	-	-	T N S-	1.00
14.	427467	M	T	2.80Kg AGA	P	ND	R	-	8/10	9/10	9/10	-	-	T N S-	0.70
15.	427772	F	T	2.60Kg AGA	MG	ND	R	-	8/10	9/10	9/10	-	-	T N S-	0.70
16.	427779	M	T	3.07Kg AGA	MG	ND	R	-	7/10	8/10	8/10	-	-	T N S-	0.90
17.	427814	F	T	2.40.Kg AGA	MG	ND	R	-	7/10	9/10	9/10	-	-	T N S-	0.70

18.	427818	M	T	2.70Kg AGA	P	ND	R	-	8/10	9/10	9/10	-	-	T N S-	1.08
19.	427823	M	T`	2.80g AGA	P	ND	R	-	8/10	9/10	9/10	-	-	T N S-	0.80
20.	427826	M	T	3.00Kg AGA	MG	ND	R	-	7/10	8/10	8/10	-	-	T N S-	1.00
21.	427827	M	T	3.10Kg AGA	P	ND	R	-	7/10	8/10	8/10	-	-	T N S-	0.60
22.	427835	F	T	2.70Kg AGA	P	ND	R	-	7/10	9/10	9/10	-	-	T N S-	0.90
23.	427838	F	T	2.90Kg AGA	P	ND	R	-	7/10	9/10	9/10	-	-	T N S-	0.79
24.	427894	F	T	2.80Kg AGA	MG	ND	R	-	8/10	9/10	9/10	-	-	T N S-	0.91
25.	427911	M	T	2.50Kg AGA	MG	ND	R	-	7/10	9/10	9/10	-	-	T N S-	0.76
26.	427812	M	T	2.80Kg AGA	P	ND	R	-	8/10	9/10	9/10	-	-	T N S-	0.68
27.	427912	M	T	2.60Kg AGA	MG	ND	R	-	7/10	8/10	8/10	-	-	T N S-	1.23
28.	430082	F	T	2.50Kg AGA	P	ND	R	-	8/10	9/10	9/10	-	-	T N S-	0.60
29.	430489	F	T	2.50Kg AGA	P	ND	R	-	7/10	8/10	8/10	-	-	T N S-	0.72
30.	430638	F	T	2.70Kg AGA	MG	ND	R	-	7/10	9/10	9/10	-	-	T N S-	0.61
31.	430534	M	T	2.70Kg AGA	MG	ND	R	-	7/10	8/10	9/10	-	-	T N S-	0.82
32.	437715	M	T	2.90Kg AGA	MG	ND	R	-	8/10	9/10	9/10	-	-	T N S-	0.94
33.	431239	M	T	2.60Kg AGA	P	ND	R	-	7/10	8/10	8/10	-	-	T N S-	0.76
34.	431326	M	T	3.20Kg AGA	MG	ND	R	-	7/10	8/10	9/10	-	-	T N S-	0.84
35.	431076	M	T	3.20Kg AGA	P	ND	R	-	7/10	8/10	8/10	-	-	T N S-	1.01

36.	431640	M	T	4.20Kg AGA	MG	ND	R	-	7/10	9/10	9/10	-	-	T N S-	0.66
37.	431874	M	T	2.50Kg AGA	P	ND	R	-	7/10	9/10	9/10	-	-	T N S-	1.00
38.	431862	M	T	2.30Kg AGA	P	ND	R	-	7/10	9/10	9/10	-	-	T N S-	0.78
39.	431428	M	T	3.00Kg AGA	MG	ND	R	-	7/10	9/10	9/10	-	-	T N S-	0.64
40.	432080	M	T	3.30Kg AGA	MG	ND	R	-	8/10	9/10	9/10	-	-	T N S-	0.42
41.	432169	M	T	2.60Kg AGA	MG	ND	R	-	8/10	9/10	9/10	-	-	T N S-	0.55
42.	432239	F	T	2.60Kg AGA	P	ND	R	-	7/10	8/10	8/10	-	-	T N S-	0.61
43.	433240	M	T	3.50Kg AGA	P	ND	R	-	7/10	8/10	8/10	-	-	T N S-	0.42
44.	432282	F	T	3.00Kg AGA	MG	ND	R	-	7/10	9/10	9/10	-	-	T N S-	0.83
45.	423477	F	T	3.20Kg AGA	MG	ND	R	-	8/10	9/10	9/10	-	-	T N S-	0.81
46.	432491	F	T	2.80Kg AGA	MG	ND	R	-	7/10	9/10	9/10	-	-	T N S-	0.92
47.	432237	M	T	2.90Kg AGA	P	ND	R	-	7/10	9/10	9/10	-	-	T N S-	0.99
48.	432214	M	T	2.50Kg AGA	P	ND	R	-	8/10	9/10	9/10	-	-	T N S-	1.01
49.	432314	F	T	2.50Kg AGA	MG	ND	R	-	7/10	8/10	8/10	-	-	T N S-	1.22
50.	432350	F	T	3.10Kg AGA	MG	ND	R	-	7/10	9/10	9/10	-	-	T N S-	0.45