Introduction

Perinatal asphxia is, after prematurity and sepsis, the third main cause of neonatal death worldwide (*Schlapbach et al., 2011).*

Hypoxic injury results in the fetal and neonatal mortality, morbidity or long term sequel such as cerebral palsy, mental retardation, epilepsy and learning disability. In term neonate, 1-4 % of infants suffer birth asphyxia and one third manifest significant neurological deficits *(Delivoria-Papadopoulos et at., 2011) .*

Vasopressin is one of the most important physiological stress and shock hormones, Arginine vasopressin, is a nonapeptide acting as a main regulator in the homeostatis of the cardiovascular and renal system *(Treschan and Peters, 2006)* .

Vasopressin is highly instable with a short half-life of 4-20 minute *) Treschan and Peters, 2006)* , therefore reliable determination of vasopressin concentration is not used in clinical practice. Vasopressin is derived from a larger precursor peptide which contains also C-terminal pro-vasopressin, called copeptin *) Schlapbach et al., 2011)* . The secretion of vasopressin can be estimated by measuring copeptin *(Wellmann et al., 201 0)* .

Upon release of vasopressin, equal amounts of copeptin are secreted. Copeptin is relatively stable in serum and thereby reliably mirrors vasopressin levels *(Jochberger et al, 2009)* .

Copeptin concentrations were strongly related to factors associated with perinatal stress such as birth acidosis, asphyxia *(Schlapbach et al., 2011)* .

Aim of the Work

The aim of the work is to investigate the diagnostic value of cord blood copeptin in neonates with perinatal asphyxia .

Perinatal Asphyxia

Definitions:

A) Asphyxia

Asphyxia is a Greek word which means "stopping of the pulse" *(Dutta AK, 2007) .*

Perinatal asphyxia refers to a condition in which impaired gas exchange leads, if persistent, to fetal hypoxemia and hypercarbia *(Hansen and Soul, 2012) .* If the hypoxemia is severe enough, initially peripheral tissues (muscle and heart) and then brain tissue develop an oxygen debt, leading to anaerobic glycolysis and production of lactic acidosis, causing metabolic acidemia. This can be measured by blood gas analysis *(Levene and de Vries, 2011).*

B. Hypoxia, Anoxia

Anoxia is a term used to indicate the consequences of complete lack of oxygen (O2) as a result of a number of primary causes *(Ambalavanan and Carlo , 2011).*

Hypoxia is a condition in which there is a decrease of O_2 supply to the tissues in spite of adequate blood flow to the tissue *(Rajan et al., 2010).*

Hypoxemia is a condition where arterial oxygen tension (Pao2) is below normal *(* Samuel *and* Franklin *, 2008)* .

Ischemia refers to blood flow to cells or organs that is insufficient to maintain their normal function *(Biban and Silvagni, 2012).*

C. Encephalopathy

This is a clinical and not an etiologic term that describes an abnormal neurobehavioral state consisting of decreased level of consciousness and usually other signs of brain stem and/or motor dysfunction. It does not imply a specific etiology, nor does it imply irreversible neurologic injury as it may be caused by such

reversible conditions as maternal medications or hypoglycemia *(Hansen and Soul , 2012) .*

Neonatal encehalopathy (NE) characteristically begins within the first postnatal day and may be associated with seizure-like activity, hypoventilation or apnea, depressed primitive reflexes and the appearance of brain stem reflexes *(Mahajan and Wazir , 2012).*

D. Hypoxic Ischemic Encephalopathy (HIE)

An abnormal neurobehavioral state in which the predominant pathogenic mechanism is impaired cerebral blood flow *(Adcock and Papile, 2008).*

HIE is an important cause of permanent damage to central nervous system (CNS) tissues that may result in neonatal death or manifest later as cerebral palsy or developmental delay *(Ambalavanan and Carlo, 2011).*

The terms HIE and PA have been used synonymously in the past, rather loosely . Since establishing the relationship between asphyxia and HIE is not always possible, the term NE was proposed as an alternative to remove t he medicolegal implications of HIE. The term birth asphyxia is also imprecise, and its use is not recommended *(Soni and Katewa , 2007).*

Incidence

Inspite of major advances in monitoring technology, obstetric care and knowledge of fetal and neonatal pathologies, neonatal HIE remains a serious condition causing significant mortality and long term morbidity *(Biban and Silvagni , 2012) .*

According to the World Health Organization (WHO), between 4 and 9 million newborns develop birth asphyxia each year. Of these, an estimated 1.2 million die and at least same number develop severe consequences such as cerebral palsy, epilepsy and developmental delay (The World Health Report, 2005) *(Dursun et al, 2012).*

The Frequency of PA is inversely related to gestational age and birth weight. It occurs in 0.5% of newborns ch presentation, and postdates *(Hansen and Soul , 2012) .*

In Egypt and other developing countries, PA is the most important cause of hypoxic ischemic (H-I) brain damage in th e full-term newborn infants *(Boo , et al., 2000).* In Egypt it is not an un-common health problem. It is one of the direct causes of infant mortality rate ranking only second to sepsis. HIE in ci dence in Egypt is 4.5-5.5 cases per 1000 term births *(El Metwa lly , 2006).*

In the developing world, the incidence of asphyxia is believed to be considerably higher due to the increased prevalence of risk factors *(Biban and Silvagni, 2012).*

Risk Factors and Etiology :

Adverse clinical situations in the antepartum and intrapartum periods may reflect on the fetus (Table 1) .

Table 1: Antepartum and intrapartum risk factors for asphyxia

Antepartum	Intrapartum
Pregnancy-induced h ypertension . Maternal diabetes . Chronic hypertension . Anemia or isoimmunisation . Previous fetal neonatal death . Bleeding in 2nd or 3rd trimester .	Premature labor . Emergency cesarean section . Forceps or vacuum-assisted delivery . Precipitous labor . Chorioamnionitis .

Maternal infection . Polyhydramnios . Oligohydramnios. I ntrauterine growth retardation Diminished fetal activity . Maternal cardiac, renal, pulmonary, thyroid or neurological disease. Post-term gestation . Multiple gestation. Drug therapy, for example, magnesium and lithium . Maternal substance abuse . Fetal malformation. No prenatal care . Age of mother years. Premature rupture of membranes (PROM).	Prolonged rupture of membranes (before delivery) . Prolonged labour (Prolonged second stage of labor (. Fetal heart rate abnormality . Malpresentation. Use of general anesthesia. Uterine tetany. Meconiun-stained amniotic fluid. Prolapsed cord. Abruptio placentea. Narcotics given before delivery .

(Nanavati and Rao, 2009)

Chapman and Stoll (2007) divided the factors causing hypoxia into fetal factors and postnatal factors (Table 2) .

Table 2 : Factors causing hypoxia .

(A) Fetal factors may be caused by: (1) Inadequate oxygenation of maternal blood as a result of hypoventilation during anesthesia, cyanotic heart disease, respiratory failure, or carbon monoxide poisoning. (2) Low maternal blood pressure as a result of the hypotension that may complicate spinal anesthesia or that may result from compression of the vena cava and aorta by the gravid uterus. (3) Inadequate relaxation of the uterus to permit placental filling as a result of uterine tetany caused by the administration of excessive oxytocin. (4) Premature separation of the placenta. (5) Impedance to the circulation of blood through the umbilical cord as a result of compression or knotting of the cord. (6) Uterine vessel vasoconstriction by cocaine. (7) Placental insufficiency from numerous causes, including toxemia and postmaturity.	(B) After birth hypoxia may be caused by : (1) Anemia severe enough to lower the oxygen content of the blood to a critical level, as after severe hemorrhage or hemolytic disease. (2) Shock severe enough to interfere with the transport of oxygen to vital organs as a result of overwhelming infection, massive blood loss, and intracranial or adrenal hemorrhage. (3) A deficit in arterial oxygen saturation from failure to breathe adequately postnatally because of a cerebral defect, narcosis, or injury. (4) Failure of oxygenation of an adequate amount of blood as a result of severe forms of cyanotic congenital heart disease or pulmonary disease.

Pathophysiology of asphyxia:

Whenever oxygen deprivation occurs, there is initial period of rapid breathing as well as a rise in heart rate and blood pressure (Figure 1) *(Nanavati and Rao, 2009).*

If hypoxia continues the respiratory center become unable to continue initiating breathing and breathing stops, usually within 2-3 minutes (primary apnea). After a latent period of apnea (primary), primitive spinal centers exert an effect by initiating primitive gasping breaths *(Samuels and Wieteska , 2011) .*

After a while, if hypoxia continues, even these activities cease (terminal apnea). The time taken for such activity to cease is up to 20 minutes *(* Grady , Howell *and* Cox *, 2007).*

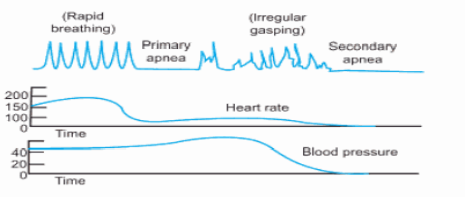

Fig ure (1): Effects of asphyxia *(Nanavati and Rao, 2009).*

The initial compensatory adjustment to an asphyxial event is an increase in cerebral blood flow (CBF). This is accompanied by a redistribution of cardiac output to essential organs, including the brain, heart, and adrenal glands. The blood pressure (BP) increases due to increased release of epinephrine. These are classically compensatory responses to asphyxia *(Mahajan and Wazir, 2012).*

After the early compensatory adjustments fail, loss of cerebral autoregulation occurs as result of hypercapnia, hypoxemia and/or acidosis. CBF autoregulation is a protective mechanism that maintains stable cerebral blood flow velocity (CBFV) in normal infants, regardless of variations of systemic arterial pressure *(Distefano and Praticò , 2010) .*

So the CBF becomes pressure-passive, at which time brain perfusion depends on systemic BP, leaving the infant at risk for both cerebral ischemia and cerebral hemorrhage. With prolonged asphyxia there is a decrease in cardiac output resulting in hypotension. As BP falls, CBF falls below critical levels, and the brain injury occurs. This leads to intracellular energy failure (1ry energy failure) *(Mahajan and Wazir, 2012)*.

The pathology of hypoxic ischemia is dependent on the affected organ and the severity of the insult *(Ambalavanan and Carlo , 2011) .*

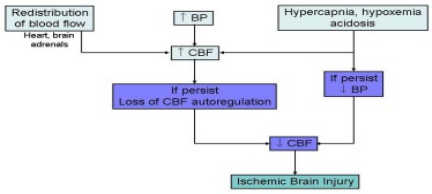

Figure (2): Fetal response to asphyxia *(Shah et al., 2007).*

Mechanisms of neuronal cell death and injury following hypoxia-ischemia

Brain hypoxia and ischemia due to systemic hypoxemia, reduced CBF, or both are the primary physiological processes that lead to HIE *(Mahajan and Wazir, 2012).*

The severity and extension of brain damage are strictly related to intensity, timing and duration of H-I insult. *(Distefano and Praticò, 2010),* with severe injury resulting in necrosis, whereas milder insults result in apoptosis *(Kasdorf and Perlman, 2013) .*

The brain injury that develops is an evolving process so that a combination of biochemical *(Wong* et *al., 2011).*

Acute H-I insult leads to events that can be broadly categorized as early (primary) and delayed (secondary) neuronal death *(Levene and de Vries, 2011).*

The first phase (primary neuronal cell death) is during the acute insult. It is associated with related events: cellular hypoxia, energy failure, and cellular membrane depolarization. *(Perlman, 2007) .*

Depletion of oxygen precludes oxidative phosphorylation and results in a switch to anaerobic metabolism, which is an energy-inefficient state resulting in: (1) Accumulation of lactic acid (2) Inability to maintain cellular functions (3) Rapid depletion of high-energy phosphate reserves including adenosine triphosphate (ATP) *(Perlman, 2007)*.

Depletion of ATP, even during mild episodes of hypoxia-ischemia, may initiate a cascade of events ultimately resulting in neurona l death *(Morales et al., 2011).*

The second phase (delayed neuronal cell death) is during the recovery period following circulatory restoration *(Perlman JM, 2007).* It is associated with reperfusion injury (oxidative stress), excitotoxicity, accumulation of intracellular calcium (Ca 2+), activation of numerous enzymes and pathways, cytotoxic actions of activated microgli a, inflammation, and apoptosis *(Wong et al., 2011).*

This new phase of neuronal damage starts at about 6-24 hours after the initial injury *(McHale et al. , 2012)*

The duration of the delayed phase is not precisely known in the human fetus and newborn but appears to increase over the first 24-48 hours and then start to resolve thereafter. In the human infa nt, the duration of this phase is correlated with adverse neurodevelopmental outcomes at 1 year and 4 years after insult *(Morales et al., 2011).* Clinically, it is the latter phase that is amenable to potential intervention(s) *(Kasdorf and Perlman, 2013).*

The combined effects of cellular energy failure, acidosis, glutamate release, intracellular Ca 2+ accumulation, lipid peroxidation, and nitric oxide (NO) neurotoxicity disrupt essential components of the cell, resulting in its death *(Lai and Yang , 2011)*.

Figure (3): Potential biochemical mechanisms of hypoxic ischemic cerebral injury *(Sangkae and Perlman, 2000).*

Specific mechanisms of cell injury

A. Excitatory amino acids release (Excitotoxicity):

Excitotoxicity refers to the excitatory amino acid (EAA) receptor over activation which plays a critical role in the pathogenesis of perinatal H-I injury *(Li et al., 2011)*.

Hypoxia- ischemia stimulates the release of glutamate which accumulates within the synaptic cleft as a result of (1) failure of energy-dependent glutamate reuptake at presynaptic nerve endings and (2) increased glutamate release from presynaptic nerve terminals *(Wong et al., 2011).*

This result in high synaptic levels of glutamate and EAA receptor overactivation, including N-methyl-D-aspartate (NMDA), amino-3-hydroxy-5-methyl-4 isoxazole propionate (AMPA), and kainate receptors. These receptors are linked to ion channels and are therefore called ionotropic receptors.Their activation results in influx of sodium (Na +) and Ca 2+ into post- synaptic neurons. This leads to rapid cytotoxic edema and necrotic cell death. Intracellular Ca 2+ accumulation leads to further pathologic cascades activation *(Mahajan and Wazir, 2012).*

Figure (4): Schematic representation of the cell surface glutamate (Glu) receptor *(Palmer and Vannucci, 2003).*

B. Cytosolic calcium accumulation:

Increased intracellular Ca 2+ is very detrimental to neurons and other cells, it has been implicated as a major contributor to NE and ischemia-reperfusion injury, and is associated with Ca 2+ dependent activation of various pathways, cell or neuron swelling, injury *(Wong et al., 2011).*

Cytosolic Ca 2+ is increased by influx through 1) open NMDA and Ca 2+ permeable AMPA receptor channels and other voltage-dependent Ca 2+ channels, (2) the release of Ca 2+ from intracellular stores (mitochondria and endoplasmic reticulum [ER]), and (3) failure of Ca 2+ efflux mechanisms due to energy failure *(Lai and Yang, 2011)*.

The increase in cytosolic Ca 2+ in turn, activates proteases, lipases, endonucleases, and nitric oxide synthases (NOS) *(Morales et al., 2011).*

In selected neurons, the intracellular Ca 2+ induces the production of NO through activation of NOS *(Perlman, 2007).*

Also increased intracellular Ca 2+ activates enzymatic pathways involved in the production of reactive oxygen species (ROS), including the conversion of xanthine deh ydrogenase to xanthine oxidas *(Wong et al., 2011).*

C. Free radicals and nitric oxide generation:

Reperfusion injury is an important factor responsible for brain injury in asphyxiated infants via increased production of ROS and NO *(Wong et al., 2011)*.

The resulting damage, which is unavoidable, is referred to oxidative stress caused by free rad icals *(Gitto et al., 2013)*. It results when the critical balance between free radical generation and antioxidant defenses is unfavorable *(Lobo et al., 2010).*

The newborn is especially vulnerable to oxidative stress and reperfusion injury due to immature antioxidant defense mechanisms and incre ased vulnerability to apoptosis *(Gill et al., 2012)*.

A direct relation has been demonstrated between the degree of hypoxia and the severity of oxidative stress *(Gitto et al., 2013).*

During H-I injury, s ources of free radicals is (1) the reaction of free ferric iron with peroxide, 2) NO from the activation of NOS , 3) increased intracellular Ca 2+ and mitochondrioal injury, 4) activation of proteases leading to conversion of xanthine dehydrogenate to xanthine oxidase, 5) activation of phospholipase A2 leading to increased generation of oxygen free radicals from cyclo-oxyg enase and lipoxygenase pathways *(Folkerth and Kinney, 2008).*

Free radicals can lead to lipid peroxidation as well as DNA and protein damage and can trigger apoptosis. Free radicals (superoxide radicals) can combine with NO to form perox ynitrite a highly toxic oxidant *(Mahajan and Wazir, 2012).*

Figure (5): Effect of accumulation of cytosolic calcium and free radicals formation *(Sang kae and Perlman , 2000)*.

D. Inflammatory mediators

Inflammatory mediators appear to play a criti cal role in the pathogenesis of H-I brain injury *(Perlman , 2007).* Microglial cells can be activated by H-I insults and subsequently produce proinflammatory cytokines *(Wong et*

al., 2011).

A relationship has been established between pro-inflammatory cytokine serum level and outcome for infants with PA. Infants who die or develop cerebral palsy had high plasma levels of pro-inflammatory cytokines *(Morales et al., 2011).*

Proposed mechanisms by which increased proinflammatory cytokines may damage the CNS include direct cytotoxic effects; increased blood-brain barrier permea bility; increased production of NOS, cyclooxygenase, and free radicals, increased release of excitatory amino acids, and induction of systemic inflammatory response syndrome, resulting in the deleterious effects associated with i nflammation *(Wong et al., 2011).*

E. Apoptosis

In severe H-I brain injury; necrosis is the predominant modalities of cell death but in less severe injury apoptosis seems to prevail *(Martin et al., 2003).*

Fetal/ neonatal adjustments to insult:

The fetus is highly adapted to intrauterine conditions, which include low partial pressures of O_2 and relatively limited supply of substrates compared with postnatal life *(Bennet et al., 2009).*

For the fetus, hypoxia is perhaps the greatest challenge to its well-being in utero and consequently it has many adaptive features which help it to maximize O_2 a vailability to its tissues *(Bennet et al., 2009).*

The fetus cannot store O_2 and is wholly dependent on steady supply of O_2, but thanks to these adaptations the fetus normally exists with a surplus of O_2 relative to its metabolic needs. Thus, during hypoxia the fetus can maintain normal O_2 consumption down to the equivalent of approximately 50% of uterine artery blood flow *(Bennet and Gunn, 2009).*

The fetuses and newborn are much more resistant to hypoxia than adults because of increased neonatal cardiac glycogen stores, the ability of the neonatal brain to utilize fatty acids as energy sources and the vasodilator effect of carbon dioxide on neonatal cerebral circulation. Susceptibility of various organs to hypoxia varies depending on the gestational age. The newborn brain is generally resistant to hypoxia, but the process of autoregulation is not. Thus, loss of autoregulation leads to development of ischemia as a result of PA *(Gieron- Korthals and Colon , 2005).*

The ability of an organ to maintain aerobic metabolism is dependent on the amount of energy needed to maintain the functional activity of the organ, the amount of the O_2 delivered to the tissues and the amount of O_2 extracted by the tissue *(Connolly , 2010).*

These adaptive features include: higher basal blood flow to organs, left shift of the O_2 dissociation curve, the capacity to reduce significantly energy-consuming processes, greater anaerobic capacity in many tissues, and the capacity to redistribute blood flow towards essential organs away from the periphery *(Bennet and Gunn , 2009).*

Thus the fetus is quite capable of adjusting to episodes of hypoxemia with synchromized response which involves behavioral, cardiovascular, hormonal, auton omic and metabolic adjustments *(Tooley, 2008).*

A. Behavioral adjustment:

The fetus can make changes to conserve energy. It expends considerable energy making fetal breathing movements (FBMs), particularly in late gestation. In the fetus hypoxia abolishes FBMs *(Bennet and Gunn , 2009).*

During acute hypoxemia, fetal movements decrease. Loss of fetal movement raises concern for ongoing CNS hypoxia and injury *(Si gnore et al. , 2009).*

B- Cardiovascular adjustment

During asphyxia, initially th ese circulatory effects occur, 1) an alteration in the fetal circulation that a larger proportion of the cardiac outpu t is distributed to the brain, 2) an incre ase in total and regional CBF, 3) a loss of vascular autoregulation, (4) and later a diminution in cardiac output with the occurrence of systemic hypotension, (5) and as a consequence a decrease in CBF *(Volpe, 2008a).*

This redistribution of blood flow, by shunting of blood to the essential organs, is designed to protect the most critical and vulnerable organs *(Volpe, 2008a).*

Prolongation of hypoxemic episodes for 6-8 hours causes progressive metabolic acidemia with both the fetal O_2 consumption and cardiovascular performance maintained until the pH falls below 6.9 *(Alonso-Spilsbury et al., 2005).*

C) Hormonal adjustment:

Sympathetic response, c atecholamines are secreted by the fetal adrenal glands in response to stress. These substances may mediate some of the vascular effects seen in the normal fetus during period of hypoxia. Both noradrenaline and adrenaline are released. Also, high levels of circulating cortisol are produced *(Tooley, 2008)*

D) Metabolic adjustment:

Metabolism can switch to anaerobic glycolysis during periods of hypoxia using glucose and glycogen. It soon leads to accumulation of lactic acid in tissues and blood giving rise to an increasing acidaemia. The mobilization of liver glycogen stores to increase blood glucose levels duri ng hypoxia is important for maintenance of brain and myocardial functions *(Volpe, 2008a).*

The immature CNS can more readily utilize the lactate, pyruvate and ketones generated by anaerobic glycolysis as an alternative to glucose *(Nordström et al., 2001) .*

Diagnosis of perinatal asphyxia:

Seven clinical features are used as possible markers of PA:

1) Fetal distress.

2) Intrauterine passage of meconium in term infant.

3) Metabolic acidosis.

4) Failure to establish spontaneous respiration.

5) Depression of Apgar scores.

6) HIE

7) Multiorgan involvement.

The more features that are present, the more the confident the diagnosis can be. The presence of fetal distress, passage of thick meconium, or fetal acidosis together with HIE, are absolute criteria for the diagnosis and the others are supportive *(Volpe , 2008b) .*

Assessment of perinatal asphyxia

A. Antepartum assessment

Antepartum fetal surveillance is warranted for women at increased risk for fetal distress. The predominant cause of antepartum fetal distress is uteroplacental insufficiency.

The goals of antepartum fetal surveillance are to prevent intrauterine fetal demise and prevent hypoxic brain injury *(Carlo , 2011a) .*

The techniques used for evaluating the fetus during the antepartum period are best divided into those are shown in (T able 3) .

Table 3 : Major means of antepartum assessment

Fetal movement
- Detection by maternal perception or by Real- time ultrasonagraphy

Fetal heart rate - Non stress test (NST): response of fetal heart rate to movement. - Contraction stress test (CST): response of fetal heart rate to stimulated (oxytocin and nipple stimulation) or spontaneous uterine contraction. Fetal biophysical profile - Combination of fetal breathing, movement, tone, heart rate reactivity, and amniotic fluid volume. Fetal growth - Detection of intrauterine growth retardation Fetal blood flow velocity - Detection by Doppler technique of flow velocity in umbilical and fetal systemic and cerebral vessels

(Volpe, 2008b)

(1) Fetal movement monitoring

This is the simplest method of fetal assessment .This is done by making the mother lies quietly for an hour and records each perceived fetal movement. Active periods average 30 to 40 minutes, periods of inactivity *(Wilkins-Haug and Heffner, 2012).*

Techniques used for monitoring fetal movement also includes electro mechanical device (tocodynamometry), and real time ultrasonography *(Volpe , 2008b) .*

2-Fetal heart rate (FHR) :

The nonstress test (NST) is a reliable means of fetal evaluation. It is simple to perform, relatively quick, and noninvasive. It is based on the principle that fetal activity results in a reflex acceleration in heart rate. The test is performed by monitoring FHR and uterine activity is simultaneously recorded. The test result may be reactive, nonreactive, or inadequate *(Wilkins-Haug and Heffner , 2012).*

A reactive NST is 2 accelerations of at least 15 beats/minute lasting for not less than 15 secconds each within a 20 min period *(*Littleton-Gibbs *and* Engebretson *, 2012).*

CST may be used as a backup or confirmatory test when the NST is nonreactive or inadequate. The CST is based on the idea that uterine contractions can compromise an unhealthy fetus *(Wilkins-Haug and Heffner, 2012).* It observes the fetal heart rate response to spontaneous, nipple-, or oxytocin-stimulated uterine contractions. Fetal compromise is suggested when three contractions in 10 min are followed by late decelerations *(Carlo, 2011a).*

3. Fetal Biophysical Profile:

The biophysical profile (BPP) assesses fetal breathing, body movement, tone, heart rate, and amniotic fluid volume, and it is used to improve the accurate and safe identification of fetal compromise *(Carlo, 2011a).*

The presence or absence of these markers determine the level of fetal compromise at the time of testing. Each of the five components of the BPP is assigned a score of either 2 or 0 for its absence or presence *(Davidson, 2012).*

(4) Fetal growth :

Advances in ultrasound technology have provided the capability of accurate quantitative assessment of fetal growth. Growth retarded infants are less to tolerate labor than do normally growth infants. Therefore, antepartum detection of such infants is important in formulating rational decisions *(Volpe, 2008b).*

(5) Fetal blood flow velocity

Signs of compromise seen on Doppler ultrasonography include reduced, absent or reversed diastolic waveform velocity in the fetal aorta or umbilical artery *(Carlo, 2011a).*

B. Intrapartum assessment

Brain injury in the intrapartum period represents a large source of potentially preventable neurological morbidity (Table 4

Table 4 : Major means of intrapartum assessment of the fetus

Meconium passage
Fetal heart rate
Fetal acid –base status
Other techniques
Transcutaneous monitoring of blood gases and p H
Near infrared spectroscopy
Doppler measurements of fetal blood velocity
Fetal electroencephalogram

(Volpe, 2008b)

(1) Passage of meconium :

Meconium-stained amniotic fluid occurs in approximately 10 -20 % of apparently normal pregnancies at term and 25–50% of postdate deliveries *(Volpe , 2008b).*

Passage of mecoinum in utero is generally considered as a sign of fetal distress.The stress can be acute as in cord compression or chronic as in placental insufficiency *(Hiremath et al., 2012) .*

Fetal hypoxia may lead to meconium passage in utero secondary to increased intestinal prestalsis and perhaps also relaxation of the anal sphincter *(Volpe , 2008b).* Intrauterine asphyxia also produces a gasping response by which meconium enters the trachea *(Kumari et al., 2012).*

(2) Intrapartum fetal heart rate monitoring:

Electronic fetal heart rate monitoring (EFM) is the most widely used method of intrapartum surveillance *(Graham et al., 2006)*

It has been used to predict fetal distress or well-being. Fetal bradycardia being one of the most serious. Newer technologies, such as fetal pulse oximetry and fetal electrocardiography may more accurately identify fetuses at risk *(Biban and Silvagni, 2012) .*

When EFM is used, the monitors simultaneously record FHR and uterine activity for ongoing evaluation *(Wilkins-Haug and Heffner, 2012).*

The major aspects of the FHR pattern evaluated are divided into baseline features (i.e., rate, beat-to-beat variability) and periodic features (i.e., accelerations or decelerations), usually in r elation to uterine contractions (Table 5).

Table 5 : The major aspects of the FHR pattern

i. Baseline heart rate:	Assessment of the FHR begins with the finding that the normal heart rate is 120 to160 beats/minute. Normal fetal heart exhibits fluctuations of approximately 6 to 25 beat/ min.
ii. Beat-to-beat variability:	The presence of normal beat-to-beat variability is considered the best single assessment of fetal well-being.
iii.Accelerations:	Increase in FHR during the uterine contractions of labor, as in the case of antepartum contractions or with fetal movement, are not of concern and in fact

	are generally considered a sign of fetal well-being.
iv. Decelerations *a. Early Deceleration* b. Late decelerations: c.Variable decelerations:	Decrease in FHR associated with uterine contractions and are of three major ty pes: early, late, and variable. - It begins with the onset of a contraction, reaches its peak with the peak of the contraction, and then returns to normal baseline levels as the contraction ends - Related to compression of the fetal head and are mediated by vagal input to the heart. - They are benign and require no intervention. - Begin after a contraction starts but reaches a peak well after the peak of contraction is reached and does not return to baseline until 30 to 60 seconds after the contraction is completed. - Result from uteroplacental insufficiency and possible fetal hypoxia. - The most commonly observed deceleration. - This characteristically abrupt slowing of the fetal heart rate may begin before, with, or after the onset of the contraction and is varaiable in duration. - R esult from fetal umbilical cord compression. - A cause for concern if 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.

(Volpe, 2008b)

The loss of beat-to-beat variability coupled with variable or late decelerations significantly enhances the likelihood that the fetus is undergoing significant hypoxia. Baseline bradycardia as a feature of fetal hypoxia is accompanied by loss of beat-to-beat variability and decelerations *(Volpe, 2008b)*.

(3) Fetal acid base status

Acid-base analysis of umbilical cord blood provides an objective method of evaluating a depressed newborn's condition, especially with regard to hypoxia and academia *(Nageotte, 2013)*.

Blood gas analysis immediately after birth is a direct measure and accurate reflection of fetal acid-base balance during the time period immediately preceding birth *(Blackburn , 2012).*

Although the exact cord blood pH value that defines significant fetal acidemia is unknown, an umbilical artery pH *(Carlo, 2011a)*.

(4) Fetal monitoring with lactate :

Lactate concentration in umbilical cord blood at delivery may be a better tool than pH or base deficit to assess metabolic acidosis. A lactate level greater than 8 mmol/L ma y indicate intrapartum asphyxia *(Dyer and Schoeman, 2013)*.

C . Postnatal Diagnosis:

(1) Depression of Apgar score :

In 1952, Dr Virginia Apgar devised a scoring system that was a rapid method of assessing the clinical status of the new born infant at 1 minute of age *(ACOG and APP, 2006).*

The AAP is currently recommending an expanded Apgar score reporting form which details both the numeric score as well as concurrent resuscitative interventions *(Ringer, 2012).*

The Apgar score was not designed to predict neurologic outcome *(Carlo, 2011b).* It is not appropriate to use it alone to establish the diagnosis of asphyxia, but, when combined with other conventional markers, such as arterial umbilical cord pH and base deficits, it has some predictive value for the development of HIE *(Biban and Silvagni, 2012).*

This scoring system provides a standardized assessment for infants after delivery. The Apgar score comprises of 5 components, each of which is given a score of 0, 1, or 2. The score is now reported at 1 and 5 minutes after birth *(ACOG and APP, 2006)* (Table 6).

Table (6): Apgar scoring system

Score	Signs		
2	1	0	
>	<	Absent	Heart rate
Good crying	Slow (irregular)	Absent	Respiratory effort
Active motion	Some flexion of extremities	Limp	Muscle tone
Cough or sneeze	Grimace	No response	Reflex irritability
All pink	Pink body, blue extremities	Blue, pale	Color

(Carlo, 2011b)

One minute Apgar score generally correlates with umbilical cord blood pH and is an index of intrapartum depression. It does not correlate with outcome. Apgar scores beyond 1 minute are reflective of the infant's changing condition and the ad equacy of resuscitative efforts *(Ringer, 2012).*

The more prolonged the period of severe depression (i.e., Apgar score 3), the more likely is an abnorma l long-term neurologic outcome *(Ringer, 2012).* Apgar score of 0 to 3 beyond 5 minutes is one suggestive criterion for an intrapartum asphyxial insult. However, a persistently low Apgar score alone is not a specific indicator for intrapartum compromise *(ACOG and APP, 2006).*

A low score may be due to a number of factors (Table 7). Regardless of the etiology, a low Apgar score identifies an infant needing immediate resuscitation

Table (7): Factors affecting Apgar score.

False Negative (Acidosis; Normal Apgar)	False positive (No fetal acidosis or hypoxia ; Low Apgar)
	• Immaturity • Analgesics, narcotics • Magnesium sulphate • Acute cerebral trauma • Percipitous delivery • Congenital myopathy

• Metabolic acidosis • High fetal catecholamines • Some full-term infant	• Congenital neuropathy • Spinal cord trauma • C.N.S. anomaly • Lung anomaly (diaphragmatic hernia) • Airway obstruction (choanal atresia) • Congenital pneumonia,sepsis • Prior episodes of asphyxia (recovered) • Hemorrhage-hypovolemia

(Carlo, 2011b)

(2) Failure to establish spontaneous respiration:

The time to the onset of spontaneous breathing or the first breath, or alternatively, the need for intubation has been used by many as an alternative marker of immediate neonatal condition. Failure to establish spontaneous respiration by 30 minutes carries a very high risk of handicap or death. It may be influenced by other factors that cause depression of respiration, such as the administration of maternal drugs and neuromuscular disease of the newborn *(Cornette and Levene, 2009).*

(3) Hypoxic-ischemic encephalopathy:

Hypoxic ischemic brain injury is the most important consequence of PA. HIE has a spectrum of manifestations from mild to severe *(Ramji, 2009).*

The diagnosis of perinatal HIE requires an abnormal neurologic examination on the first day following birth. It is important to note that no significant neurologic abnormality diagnosed later in childhood (e.g. cerebral palsy) can be described to PA in the absence of evidence in the immediate neonatal period of neurologic abnormality and severe multiorgan dysfunction *(Hansen and Soul, 2012) .*

Three features are important in considering this intra partum insult is the likely cause of neonatal brain injury

1) evidence of fetal distress, 2) depression at birth and , 3) an overt neonatal neurological syndrome in th e first hours and days of life *(Volpe, 2008c).*

One of the most utilized definitions of perinatal asphyxia (PA) is that promulgated in 2003 by The American Academy of Pediatrics *(AAP)* and the American College of Obstetricians and Gynecologists *(ACOG) ,* which include certain criteria that must be all present to confirm the occurrence of PA severe enough to result in acute neurological injury . Those Essential criteria are:

1) Profound metabolic or mixed acidemia (p H <
2) Persistence of an Apgar score of 0 - 3 for

3) Clini cal neurologic sequelae in the immediate neonatal period (e.g., seizures, hypotonia, coma or HIE).

4) Evidence of multiorgan system dysfunction in the immediate neonatal period. (e.g. kidney, lungs, liver, heart, intestine) *(ACOG and AAP , 2003).*

(3) Presence of multiorgan dysfunction:

Often; asphyxiated neonate will develop dysfunction of organs other than the CNS while showing minimal evidence of H-I brain injury. In such instance, the brain is spared at the expense of cardiac output to the affected organs *(Gieron –Korthals and Colon, 2005).*

In a minority of cases (dysfunction *(Hansen and Soul, 2012).*

The occurrence of manifestations from other organs can at times assist a clinician in estimating the time of the

insult *(Gieron –Korthals and Colo n , 2005) .*

Table (8): Effect of asphyxia on different systems:

System	Effects
Renal system	Acute tubular or cortical necrosis.
Central nervous system	HIE , infarction, intracranial hemorrhage, seizures, cerebral edema, hypotonia and hypertonia.
Cardiovascular system	Myocardial ischemia, poor contractility, tricuspid insufficiency, hypotension,
Pulmonary	Pulmonary hypertension, pulmonary hemorrhage and respiratory distress syndrome.
Adrenal	Adrenal hemorrhage.
Gastrointestinal system	Perforation, ulceration with hemorrhage and necrosis.
Metabolic	S yndrome of inappropriate antidiuretic hormone secretion (SIADH), hyponatremia, hypoglycemia, hypocalcemia and myoglobinuria.
Integument	Subcutaneous fat necrosis.
Hematology	Disseminated intra vascular coagulation (DIC).

(Ambalavanan and Carlo, 2011)

Effects of perinatal asphyxia on different systems:

(A) Central nervous system (CNS) effects:

The CNS manifestations include HIE, seizures and intracranial hemorrhage *(Ramji , 2009) .*

Neonatal seizures: in an asphyxiated neonate, can be caused by asphyxia or associated metabolic problems such as hypoglycemia, hyponatremia and intracranial bleeding. Intracranial hemorrhage: can occur in an asphyxiated neonate. This can be secondary to alterations in cerebral blood flow or, rarely, due to direct trauma *(Ramji , 2009) .*

Several topographic patterns of involvement have been observed. Term infants demonstrate neuronal necrosis of the cortex (later, cortical atrophy) and parasagittal ischemic injury. Preterm infants demonstrate periventricular leucomalaca (PVL) (later, spastic diplegia), status marmoratus of the basal ganglia, and intraventricular hemorrhage. Term more often than preterm infants have focal or multifocal cortical infarcts that produce fo cal seizures and hemiplegia *(Ambalavanan and Carlo, 2011).*

(B) Effects of asphyxia on renal system:

The kidney is the most common organ to be affected in PA *(Fanos et al. , 201 4) .*

Asphyxia in newborns cause marked reduction in renal blood flow with significant increase in vascular resistance of the kidney, and renal failure is relatively a common complication of severe H - I insult *(Cornette and Levene, 2009) .* The proximal tubule of the kidney is especially affected by decreased perfusion, leading to acute tubular necrosis (ATN) with oliguria *(Hansen and Soul, 2012) .*

(C) Effects on cardiovascular system:

Cardiac dysfunction is caused by transient myocardial ischemia. It may present as reduced myocardial

contractility, severe hypotension or passive cardiac dilatation *(Mahajan and Wazir, 2012).*

Echocardiographic findings include decreased left ventricular contractility ; elevated ventricular end-diastolic pressures; tricuspid insufficiency and pulmonary hypertension *(Adcock and Papile, 2008).*

In severely asphyxiated infants, dysfunction more commonly affects the right ventricle *(Hansen and Soul, 2012).*

(D) Pulmonary affection in asphyxia:

Effects include increased pulmonary vascular resistance leading to persistant pulmonary hypertension, pulmonary hemorrhage, pulmonary edema due to cardiac dysfunction, secondary respiratory distress syndrome (RDS) due to failure of surfactant prod uction, and meconium aspiration *(Adcock and Papile, 2008)* .

They are also more prone to aspiration pneumonia and sepsis *(Ramji, 2009).*

(E) Gastrointestinal affection in asphyxia:

Necrotizing enterocolitis (NEC) is the major complication affecting the bowel in asphyxiating infants. *(Cornette and Levene, 2009).* If a term neonate develops features of NEC one must suspect asphyxia *(Ramji, 2009).*

Intestinal injuries may not be apparent in the first few days of li fe or until feeds are initiated *(Mahajan and Wazir, 2012).*

(F) Hepatic affection in asphyxia:

Asphyxia may cause significant hepatic damage. One of the fetal responses to hypoxia is increased shunting of blood through the ductus venosus, with subsequent hepatic hypoxia and elevation of serum gl utamic-oxaloacetic transaminase (SGOT) and glutamic-pyruvic transaminase (SGPT) *(Cornette and Levene, 2009)* .

Hepatic systems can manifest as conjugated hyperbilirubinemia and coagulpathy *(Ramji , 2009).* More extensive damage may occur, leadin g to DIC , inadequate glycogen stores with resultant hypoglycemia, or altered detoxifi cation or elimination of drugs *(Hansen and Soul, 2012).* Cholestasis is also present in approximately 10% of asphyxiated infant *(Shah et al. , 2004).*

G) Hematological affection in asphyxia:

I nclude increased nucleated RBCs, neutropenia or neutrophilia, thrombocytopenia, and coagulopathy *(Mahajan and Wazir , 2012)* .

Polycythemia is not an uncommon finding in the asphyxiated neonate. The high hematocrit may be a reflection of the hypoxic environment of the fetus. In contrast an affected infant will experience anemia due to bone marrow suppression secondary to asphyxia or an acute blood loss may exacerbate the anemia. Clinically, anemia will present with hypox emia, tachycardia and acidosis *(Tekin, 2003) .*

Hematologic effects also include DIC due to damage to blood vessels, poor production of clotting factors due to liver dysfunction, and poor production of platelets by the bone marrow *(Hansen and Soul, 2012).*

(H) Metabolic affection in asphyxia:

Asphyxiated neonates can develop various metabolic problems such as metabolic acidosis, hypoglycemia (hyperinsulinism), hyperglycemia, hypocalcaemia, and hyponatremia. Hyponatremia is usually caused by SIADH *(Ramji, 2009) .*

I) Endocrinal effects of asphyxia:

PA trigger rapid alteration in the concentration of several hormones , such as catecholamines, glucocorticoids, adrenocorticotropic hormones (ACTH), beta endorphins, antidiuretic hormones, aldosterones, rennin and insulin. Asphyxia also affects thyroid hormone secretions *(Pereira and Procianoy, 2003).*

J) Infections:

These neonates are more prone to infections *(Ramji , 2009).*