Introduction

Although, the rate of premature birth appears to vary by geographic region, the reported incidence varies between 6 and 10% **(Balaraman, 2003).**

Maternal medical conditions increase the risk of Preterm birth, and often labor has to be induced for medical reasons; such conditions include high blood pressure **(Goldenberg et al., 1998)**, Preeclampsia **(Bánhidy et al., 2007)**, maternal diabetes**(Rosenberg et al., 2005)**, Asthma, thyroid disease, and heart disease **(Simhan and Caritis, 2007)**.

Preterm birth is a high risk factor for perinatal morbidity, mortality, and later on neurodevelopmental disabilities and adverse respiratory outcome (**Chellani, 2007)**.

Apnea of prematurity is mainly due to immature mechanisms of respiratory control**(Martin et al., 2002)**, incidence is inversely related to gestational age, It has been reported to occur in 25% of infants <2500 grams and up to 80% of infants <1,000 grams. Apnea may be present on the first day of life, but peak incidence occurs around day 5-7 of life **(Baird et al., 2002).**

Caffeine is a methylxanthine used extensively as first-line pharmacotherapy in apnea of prematurity **(Erenberg et al., 2000)**. Its efficacy in reducing the frequency of apneic episodes

and the need for mechanical ventilation is well established **(Erenberg et al., 2000).**

Caffeine has been shown to reduce the rates of cerebral palsy and neurodevelopmental impairment in preterm infants **(Schmidt et al., 2007).** The mechanisms underlying this neuroprotection are incompletely understood.

Benefits of amplitude- integrated electroencephalography (aEEG) available in neonatal intensive care units of some tertiary hospitals include limited number of electrodes, readily applicable, easy to operate, relatively short training required for interpretation, immediate interpretation available at the bedside, lower cost, continuous and long-term recording, and condensed recording output, Amplitude-integrated EEG is feasible as a clinical and research tool for continuous brain monitoring in the NICU **(Hellstrom-Westas et al., 2008).**

Aim of the Work

1) In a way to elucidate the effect of caffeine administration on cerebral cortical activity in preterm infants, Amplitude-integrated electroencephalography will be used to monitor cerebral function changes during caffeine administration.

2) To study the effect of caffeine administration on preterm infants' electroencephalographic maturational changes by conventional EEG.

Prematurity

Definition:

The preterm neonate is the one whose birth occurs before the end of 37th week (258th day) following onset of the last menstrual period **(Cloherty et al., 2012).**

Infants can be classified according to birth weight into:

1. Normal birth weight: 2500-3999 gm.
2. Low birth weight: 1500-2500 gm.
3. Very low birth weight: 1000- up to 1500 gm.
4. Extremely low birth weight :< 1000 gm.

(Stoll and Chapman, 2008).

Incidence:

The incidence of prematurity shows variation from one area to another ranging from 2.3% in the developed countries up to 25-35 % in some developing countries and on average about 8% of all births are premature births **(Delfos et al., 2003).**

The incidence of preterm delivery is higher in low socioeconomic population and in women who don't receive prenatal care **(Fiore et al., 2001).**

Etiological factors of prematurity:

Table (1): Causes of preterm birth.

Fetal	.Fetal distress . Multiple gestation . Erthroblastosis. . Non immune hydrops fetalis
Placental	. Placental dysfunction . Placenta previa . Abruptio placenta
Uterine	. Bicornuate uterus . Incompenent cervix(premature dilatation)
Maternal	. Pre ecalampsia . Chronic medical illness (e.g. cyanotic heart disease, renal disease) .Infection (e.g. listeria monocytogenes, group B streptococcus) .Urinary tract infection, bacterial vaginosis, chorioaminiotitis . Drug abuse(e.g. cocaine)
Others	. Premature rupture of membranes . Polyhydraminos . Iatrogenic . Trauma

(Carlo, 2011).

Assessment of prematurity:

I-Antenatal assessment:

a) Date of last menstrual period:

The expected date of delivery can be quickly calculated by McDonal`s rule; add 7 days and subtract 3 months. This method can be of great help especially if the mother has regular menstrual periodwith standard cycle and can remember exactly the date of the last menstrual period **(Chen et al., 1999).**

b) Data of first recorded fetal heart sounds:

These are first detected at approximately 10-12 weeks by ultrasonic Doppler and at about 20 weeks by fetoscope **(Sebling, 1999).**

c) Data of first recorded fetal activity (quickening):

A primigravida typically feels fetal movements at about 18–20 weeks, whereas a multigravida woman will typically feel movements around 15–17 weeks **(Levene et al., 2000).**

d) Fundal height:

Most caregivers will record their patient's fundal height on every prenatal visit, Measuring the fundal height can be an indicator of proper fetal growth (**Morse et al., 2008).**

e) Ultrasonic examination during pregnancy:

Ultrasonographic estimate is based upon crown rump length whose measurement can provide an estimate of the gestational age accurate to within 3-5 days at the period of 7-12 weeks of gestation. Biparietal diameter can help in estimating the gestational age between 20 and 30 weeks of gestation (**Chervenak et al., 1998).**

II-Postnatal assessment:

Clinical assessment of neonatal gestational age can be obtained by use of modified Dubowitz examination which has been further modified to achieve greater accuracy. The newly expanded new Ballard score provides valid and accurate assessment of gestational age for extreme premature infants that were not previously available (**Ballard et al., 1991).**

The score now spans from -10 (correlating with 20 weeks gestation) to 50(correlating with 44 weeks gestation). It is best performed at< 12 h of age if the infant < 26 weeks gestation. If the infant is > 26 weeks gestation there is optimal age of examination up to 96 h (**Gomella, 2009).** New Ballard

Score is illustrated in figure (1).

Neuromuscular Maturity

	−1	0	1	2	3	4	5
Posture							
Square Window (wrist)	>90°	90°	60°	45°	30°	0°	
Arm Recoil		180°	140°–180°	110°–140°	90°–110°	90°	
Popliteal Angle	180°	160°	140°	120°	100°	90°	<90°
Scarf Sign							
Heel to Ear							

Physical Maturity

Skin	Sticky triable transparent	gelatinous red, transtucent	smooth pink, visible veins	superficial peeling &/or rash, few veins	cracking pale areas rare veins	parchment deep cracking no vessels	leathery cracked wrinkled
Lanugo	none	sparse	abundant	thinning	bald areas	mostly bald	
Plantar Surface	heel–toe 40–50 mm:–1 <40 mm:–2	>50mm no crease	faint red marks	anterior transverse crease only	creases ant. 2/3	creases over entire sole	
Breast	imperceptible	barely perceptible	flat areola no bud	stippled areola 1–2 mm bud	raised areola 3–4 mm bud	full areota 5–10 mm bud	
Eye/Ear	lids fused loosely:–1 tightly:–2	lids open pinna flat stays folded	sl. curved pinna; soft; slow recoil	well–curved pinnal; soft but ready recoil	formed & firm instant recoil	thick cartilage ear stiff	
Genitals male	scrotum flat, smooth	scrotum empyt faint rugae	testes in upper canal rare rugae	testes descending few rugae	testes down good rugae	testes pendulous deep rugae	
Genitals female	clitoris prominent labia flat	prominent clitoris small labia minora	prominent clitoris enlarging minora	majora & minora equally prominent	majora large minora small	majora cover clitoris & minora	

Maturity Rating

score	weeks
−10	20
5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

Fig. (1): Expanded Ballard Scoring System for neuromuscular and physical maturity (assessment of gestational age) **(Ballard et al., 1991).**

Problems associated with prematurity:

Preterm delivery is a major cause of prenatal mortality and morbidity. The problems of prematurity are related to difficulty in extra-uterine adaptation due to immaturity of organs and systems (**Watts and Saigal, 2006).**

1-Respiratory problems:

Preterm infants usually adapt poorly to air breathing and present with prenatal depression in the delivery room. Several studies have shown that even in the absence of neonatal respiratory distress, preterm delivery is associated with altered lung functions. Compared to healthy term infants, preterm infants have lower specific compliance and impaired gas mixing deficiency; this suggests that preterm birth affects alveolization and formation of elastic tissue in lungs associated with altered airway development during infancy (**Thomas et al., 2006).**

I-Respiratory distress syndrome (RDS):

The primary cause of RDS, also known as hyaline membrane disease, is inadequate pulmonary surfactant due to preterm birth. The main manifestations of the disease are caused by the resultant diffuse alveolar atelectasis, edema, and cell injury. Subsequently, serum proteins that inhibit surfactant function leak to the alveoli. The increased water content,

immature mechanisms for clearance of lung liquids, leak of alveolar capillary opposition and low surface area for gas exchange typical of immature lung also contribute respiratory distress syndrome (**Escobedo et al., 2004).**

In uncomplicated mild RDS these membranes disappear quickly. In ventilated newborns, the healing process is altered and delayed, and hyaline membranes may remain prominent. In most severe cases of RDS, progressive scaring, fibrosis and emphysema of alveoli and air ways leads to chronic lung disease (CLD) (**Hjalmorson and Sandberg, 2002).**

II-Apnea of prematurity (AOP):

*Definition***:** AOP is defined as cessation of breathing by a premature infant that lasts for more than 15 seconds and/or is accompanied by hypoxia or bradycardia **(Martin et al., 2002).**

AOP is a common problem affecting premature infants, likely secondary to a "physiologic" immaturity of respiratory control that may be exacerbated by neonatal disease. These include altered ventilatory responses to hypoxia, hypercapnia, and altered sleep states, while the roles of gastroesophageal reflux and anemia remain controversial (**Zhao et al., 2011).**

Classification: Apnea is traditionally classified as either obstructive, central, or mixed. Obstructive apnea may occur when the infant's neck is hyperflexed or conversely,

hyperextended. It may also occur due to low pharyngeal muscle tone or to inflammation of the soft tissues, which can block the flow of air though the pharynx and vocal cords. Central apnea occurs when there is a lack of respiratory effort. This may result from central nervous system immaturity, or from the effects of medications or illness. Many episodes of apnea of prematurity may start as either obstructive or central, but then involve elements of both, becoming mixed in nature (**Martin et al., 2002).**

Incidence: AOP occurs in at least 85 percent of infants who are born at less than 34 weeks of gestation. The incidence is inversely related to the gestational maturity of the infant, but has considerable individual variability (**Martin et al., 2002).**

Pathophysiology: immaturity of respiratory control, because apnea is seen most commonly in the premature infant, some type of immaturity of respiratory control mechanism is thought to play a role in most cases **(Gomella, 2009).**

Ventilatory drive is primarily dependent on response to increased levels of carbon dioxide (CO2) and acid in the blood. A secondary stimulus is hypoxia. Responses to these stimuli are impaired in premature infants due to immaturity of specialized regions of the brain that sense these changes. In addition, premature infants have an exaggerated response to laryngeal

stimulation (a normal reflex that closes the airway as a protective measure) (**Martin et al., 2002).**

Pathological states can also lead to apnea in the infant as: hypothermia , hyperthermia, metabolic disturbances such as hypoglycemia or hyponatremia, sepsis, anemia, hypoxemia, inter ventricular hemorrhage or stroke, necrotizing enterocolitis, gastroesophageal reflux, drug withdrawal and drug effects (e.g., maternal antepartum magnesium therapy) **(Gomella, 2009).**

III- Bronchopulmonary dysplasia (BPD):

Definition: Infants are considered to have BPD if they continue to require supplemental oxygen to maintain adequate oxygenation at 36 weeks of age after conception and if their lung parenchyma appears abnormal on chest X-ray (**Jobe and Bancalari, 2001)**.

Table (2): Definition of BPD and diagonistic criteria.

Gestational age	< 32 weeks	> 32 weeks
Time of point assessment	36 week PMA or discharge home, whichever comes first. Treatment with >21% oxygen for at least 28days plus.	>28days but<56 days postnatal age or discharge home, whichever comes first. Treatment with >21% oxygen for at least 28 days plus.
Mild BPD	Breathing room air at 36 week PMA or discharge, whichever comes first.	Breathing room air by 56 days postnatal or discharge, whichever comes first.
Moderate BPD	Need for <30% oxygen at 36 week PMA or discharge, whichever comes first.	Need for<30% oxygen at 56 days postnatal age or discharge, whichever comes first.
Severe BPD	Need for ≥ 30% oxygen and⁄or positive pressure(PPV or NCPAP) at 36 week PMA or discharge, whichever comes first.	Need for≥ 30 oxygen and⁄ or positive pressure(PPV or NCPAP) at 56 day postnatal age or discharge, whichever comes first.

(Job and Bancalari, 2001).

2-Neurological problems:

Preterm infants have poorer neuro-developmental outcomes than term infants and have increased odds to have a mental and/or physical developmental delay (**Woythaler et al., 2011).**

The incidence of intraventricular hemorrhage and periventricular leucomalacia (PVL) are inversely related to gestational age (**Ward and Beachy, 2003).**

Prematurely born children with a higher degree intracranial hemorrhage have a greater risk for the loss of hearing and development of visual handicap (**Filipovic, 2011).**

Periventricular leukomalacia (PVL) is necrosis of the white matter due to arterial ischemia in the cerebral artery water shed area as opposed to venous congestion seen in periventricular hemorrhagic infarction (**Arthur, 2006).**

Prematurity may be considered as significant risk factors for developing psychopathology (**Hallin et al., 2011).**

3-Cardiovascular problems:

One out of four very preterm infants will present with circulatory maladaptation during the first two days of life, with an increased risk of early complication and long term sequlae. Appreciation of those transitional difficulties can not be limited

to blood pressure. Assessment of blood pressure itself must be done in relation with gestational age and birth weight adapted norms (**Rigo et al., 2007).**

Premature infants may be hypotensive due to hypovolemia, cardiac dysfunction and/or vasodilatation due to sepsis. Congenital malformations and PDA may risk the preterm infants **(De Santis and Clyman, 2006).**

A hemodynamically significant patent ductus arteriosus has a negative effect on cerebral oxygenation in premature infants. Subsequent and adequate treatment of a patent ductus arteriosus may prevent diminished cerebral perfusion and

Subsequent decreased oxygen delivery, which reduces the changes of damage to the vulnerable immature brain (**Lemmers et al.**, **2008**).

4-Gastro- intestinal problems:

Necrotizing enterocolitis (NEC) is an inflammatory disorder of the gastrointestinal tract that occurs in early life. Prematurity represent the single greatest risk for NEC (**Sanglid et al., 2006).**

The exact etiology of NEC remains uncertain, however the majority of cases of NEC occur in formula fed, premature neonates with the age of onset inversely related to gestational age, frequently after 2-3 weeks after birth for infants with