نسبة الكارنيتين فى البلازما للمبتسيرين الذين يعانون من لازمة الكرب التنفسى

رسالة

توطئة للحصول على درجة الماجيستر فى طب الأطفال

مقدمة من

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INTRODUCTION

Respiratory distress syndrome (RDS) remains to be a common and distressing problem facing neonatologists.It occurs in 60-80% of infants less than 28 weeks of gestational age and in 15-30% of those born between32 and 36 weeks. RDS is a cause of considerable mortality in the neonatal period. An estimated 30% of all neonatal deaths result from RDS or its complications ***(Stoll and Kliegman, 2004).***

Carnitine (L-3hydroxy-4-N-trimethylaminobutyrate) a small water soluble molecule plays a key role in transporting long chain fatty acids across the inner mitochondrial membrane for B oxidation via a carnitine acyl transferase enzyme system ***(Scaglia and longo, 1999).***

Pulmonary surfactant production is an important process in fetal lung maturation ***(Arenas et al., 1998).***

As carnitine is an integral component of the membrane phospholipids fatty acid turnover in human cells, it is possible that carnitine causes lung maturation via membrane phospholipids repair activity ***(Korkmaz et al., 2005).***

AIM OF THE WORK

The aim of this work is to assess free plasma carnitine levels, both cord and maternal, in preterm infants who developed respiratory distress syndrome and those who did not and to evaluate its role in the pathogenesis of respiratory distress syndrome (RDS).

PREMATURITY

Definition

A preterm infant is any infant born before 37 completed weeks gestation as before 259 days following onset of the last menstrual period, regardless of birth weight ***(Graham, 2002).***

Premature infants can be classified by birth weight and appropriateness for gestational age into: premature but appropriate size for gestational age (preterm AGA), preterm but with weight small for gestational age (preterm SGA), preterm but with weight large for gestational age (preterm LGA) ***(Lee and Cloherty, 2004).***

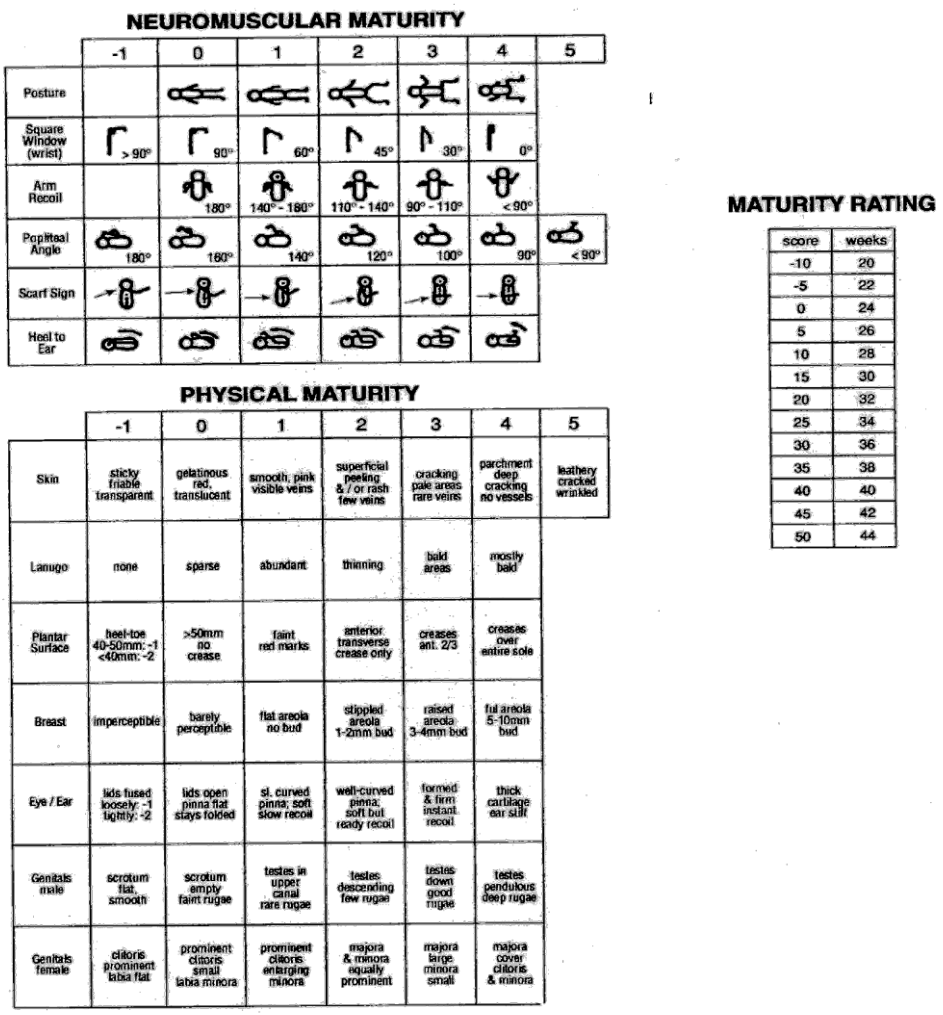
Description of prematurity

Gestational age at birth is now recognized as a reference standard related to the outcome and prognosis of the preterm infant, together with birth weight. Mild prematurity refers to 32-36 weeks, which could be further subdivided into moderate (32-33 weeks) and mild (34-36 weeks) preterm birth. Although immediate neonatal outcomes are usually reported to be encouraging, this small group contributed significantly to an excessive infant mortality in the post neonatal period (up to one year of age) from asphyxia related conditions, infection and sudden infant death syndrome ***(Kramer et al., 2000).***

Birth at 28-31 weeks gestation is defined as very preterm and accounts for less than 1% of all deliveries and about 10% of preterm births of short to long term morbidity. Below 28 week is regarded as extremely preterm (less than 5% of all preterm births) where early neonatal mortality is high up to 50% with severe handicaps occurring among survivors born below 26 weeks ***(Effer et al., 2002).*** Recent reports described survival rates among extremely low gestational ages (24-25 weeks) according to obstetrical variables at admission ***(Moutquin et al., 2003).***

Clinical assessment of prematurity

Clinical assessment of neonatal gestational age can be obtained by the use of modified Dobowitz examination, which has been further modified to achieve greater accuracy. The newly expanded new Ballard score (NBS) provides of valid and accurate assessment of gestational age for extremely premature infants that were not previously available ***(Ballard et al., 1991).*** The system is used to evaluate the gestational age through recording physical criteria that might differentiate extremely premature infants from more mature infants and a final score is obtained following the addition of each category's score. The system is accurate ± 2 weeks confirmed gestational last menstrual period and gestational age by prenatal ultra-sonography ***(Lee and Clohery, 2004).***



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

	-1	0	1	2	3	4	5
Skin	sticky friable transparent	gelatinous red, translucent	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 40-50mm: -1 <40mm: -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 1-2mm bud	raised areola 3-4mm bud	full areola 5-10mm bud	
Eye / Ear	lids fused loosely: -1 tightly: -2	lids open pinna flat stays folded	sl. curved pinna; soft slow recoil	well-curved pinna; soft but ready recoil	formed & firm instant recoil	thick cartilage ear stiff	
Genitals male	scrotum flat, smooth	scrotum empty 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): Scoring system: Ballard JL, et al: New Ballard Score, expanded to include the extremely premature infants ***(Ballard etal., 1991).***

Incidence and prevalence

Preterm birth is the major clinical problem associated with perinatal mortality, serious neonatal morbidity and moderate to severe childhood disability ***(Kramer et al., 2000).***

Prematurity comprises 6-10%of all births in westerns countries, and comprises more than two thirds of all perinatal deaths ***(Lumley, 2003).***

In order to have incidence of prematurity in Egypt we should have national or seminational survey and this was not conducted, but from documented files it was proved to be 11% in El Menia governorate and 50% in Qalyubia Governorate and much less in Cairo ***(El-Rafie, 2002).***

Prevalence of prematurity is affected by the way in which gestational age is assessed, associated practices, and by the perceived viability of extremely preterm infants. Despites these uncertainities, there is reliable evidence that preterm births are increasing, especially births before 28 weeks gestation. Contributing factors to such increase include births following assisted reproductive therapy and ovulation induction, and the increasing proportion of births among women older than 31 years. On the other hand, improvements in neonatal care have substantially increased survival of preterm infants during the last 15 years ***(Fiore et al., 2001).***

Etiological factors for prematurity

Prematurity results from three clinical conditions: *medically indicated preterm birth (iatrogenic), preterm premature rupture of membranes (PPROM) and spontaneous preterm births (idiopathic)* ***(Goffinet, 2005).***

Medically indicated preterm birth (iatrogenic) in absence of PROM or spontaneous preterm labour occurs in about 25% of all preterm births with variations from 8.7%-35.2% according to reports and studied populations ***(Zeitlin et al., 2004)***. Medical indications are related to maternal complication and/or endangering fetal well being. Iatrogenic risk factors involves: Maternal causes as pre eclampsia, eclampsia, antepartum bleeding, Chronic medical illness, obstetrical complication and maternal age > 35 years ***(Dole et al., 2003).***Fetal causes as intrauterine growth restriction, unstable fetal conduction, fetal anomalies, and multiple pregnancies ***(Mattison et al., 2001).***

Preterm premature rupture of membranes, accounts for another 25% of all preterm births (range 7.1%-51.2%). This condition occurs more often in the disadvantaged population, and among Afro-American women ***(Hogue et al., 2001).*** Infection is usually regarded as the main cause of PROM ***(Klaus Friese, 2003).***

Spontaneous or idiopathic preterm delivery accounts for at least 50% of all preterm deliveries (range 23.2%-64.1%), being more frequent in the population without any established risk factors, where it represents up to 50%-70% of all preterm deliveries according to studied populations ***(Moutquin et al., 2003)***.

Risk factors for Spontaneous preterm birth includes previous preterm labour, low body mass (BMI < 20) and poor weight gain, strenuous physical workload, it's suggested that standing up more than 2 hours a day predisposes to preterm labour, uterine anomalies, lifestyle as smoking, maternal age below 18 years and recently the possibility of genetic predisposition emerges ***(Varner and Esplin, 2005).***

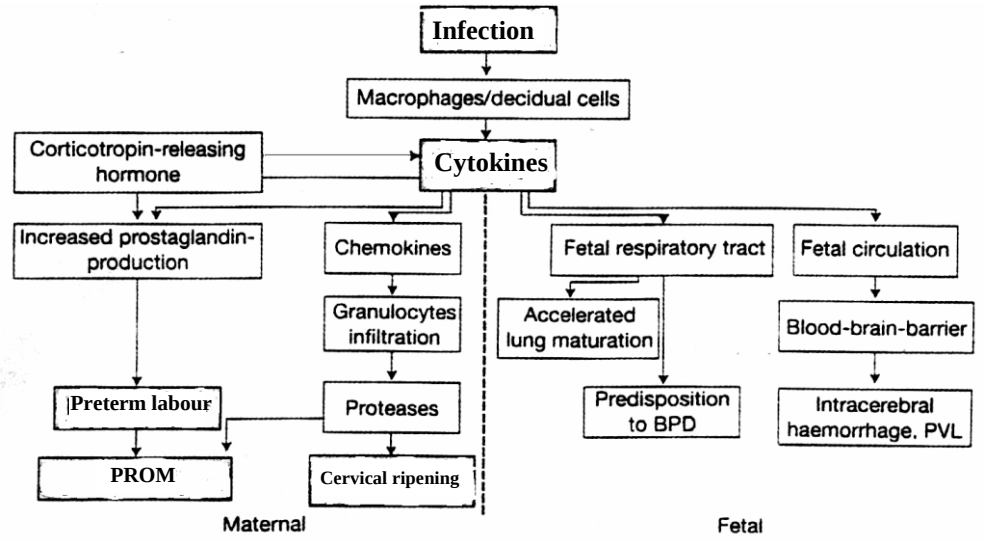


Fig. (2): Association between infection, cytokine and preterm delivery ***(Moutquin et al., 2003)***.

Table (1): Currently recognized etiological risk factors associated with clinical presentation of preterm birth ***(Moutquin, 2003).***

Medically induced preterm birth
Maternal
Pregnancy hypertension and vascular disorder
Medical acute illness or chronic conditions
Obstetrical complication
Antepartum bleeding
Maternal age > 35 years
Fetal
Intrauterine growth restriction
Unstable fetal condition
Fetal anomaly
Multiple pregnancies
Preterm premature rupture of membranes
Infection
Uterine distension
Cervical anomalies
Afro American ethnicity
Disadvantaged population
Spontaneous preterm birth
Previous preterm birth, preterm labour
Low body mass, poor weight gain
Sternouous physical workload, ergonomic factors
Uterine anomalies.
Psychosocial stress
Lifestyle, smoking
Drug abuse
Maternal age < 18 years
Unknown

Clinical outcomes and problems of prematurity

Preterm delivery is a major cause of perinatal mortality and morbidity. The premature child from the anatomo-physiological deficiencies represents one of the most important medical problems. The problems of prematurity are related to the difficulty in extrauterine

adaptation due to immaturity of organ and systems ***(Watts and Saigal, 2006).***

It has been reported that the preterm infants with birth weight average 796 gram about 37% of them had mental developmental indices < 70%, 29% had psychomotor developmental indices < 70%, and 25% had abnormal findings on neurological examination. These adverse assessments did not vary much with decreasing birth weight but also correlate with intraventricular hemorrhage, periventricular leukomalacia ***(Vohr etal., 2005).***

Some maternal diseases are predictors of good outcome such as preterm infants born to mothers with preeclampsia do better because they have less intraventricular hemorrhage and periventricular leukomalacia (PVL) than other preterm infants ***(Baud et al., 2000)***.

Intubation and ventilation on the first day of life were associated with more bronchopulmonary dysplasia ***(Jobe and Bancalari, 2001).*** As over inflation of the lungs during resuscitation initiates an injury sequence that probably leads to bronchopulmonary dysplasia. Pulmonary inflammation may in turn promote a systemic inflammatory reaction resulting in brain injury ***(Bancalari et al., 2003)***.

Bronchopulmonary dysplasia, patent ductus arteriosus, intraventricular hemorrhage, periventricular

leukemalacia, respiratory distress syndrome, and necrotizing enterocolitis are certain diseases associated with prematurity, where short term outcomes and 2 years outcomes are influenced by the severity of the disease ***(Hack et al., 2000).***

Intraventricular hemorrhage, periventricular leukomalacia, inflammatory process such as chorioamnionitis, postnatal sepsis and postnatal glucocorticoid use for bronchopulmonary dysplasia are associated with bad neurodevelopmental outcomes ***(Dammann et al., 2005)***. Low birth weight infants in populations of term infants predict stroke heart attack and diabetes in later life. The mechanisms proposed are that cell populations in critical organs are modified by changes in cell type, cell distribution, and cell numbers. These effects are even more in the very preterm infants who inevitably have growth retardation when compared with term infant ***(Ehrenkranz et al., 1999).***

a) Respiratory problems

Preterm infants usually adapt poorly to air breathing and present with perinatal 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 function. Compared to healthy term infants, preterm infants have lower specific compliance and impaired gas mixing efficiency. This suggests that preterm birth per se affects alveolization and formation of elastic tissue in lungs associated with altered airway development during infancy ***(Thomas et al., 2006).***

Respiratory handicaps in preterm infants include:

i. ***Respiratory distress syndrome (RDS)***

ii. ***Apnea of prematurity:*** apnea in the neonatal period is frequently associated with prematurity and is a common problem in the neonatal intensive care nurseries. 25% of neonates weighing less than 1800 gm (± 34 wk gestation) and the majority of neonates under 30 weeks gestation will have at least one apneic episode.

Apnea of prematurity, in absence of identifiable predisposing cause, occuring on the second to seventh day is mainly due to immaturity of brain stem. It was found that preterm infants with a greater number of apneic episodes exhibit an increased ventilatory response to hypoxia exposure, suggesting that apnea of prematurity may be associated with enhanced peripheral chemoreceptor activity ***(Nock et al., 2003).***

iii. Bronchopulmonary dysplasia (BPD) and chronic lung disease

BPD is a result of lung injury in infants resulting from mechanical ventilation and supplemental oxygen. 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 diagnostic criteria

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

(Stoll and Kliegman, 2004).

Risk factors including prolonged periods of mechanical ventilation and oxygen therapy, LBW, low gestational age, male sex, low pCO2 at 48 hr, PDA, high peak inspiratory pressure (PIP), increased airway resistance in the first week of life, increased pulmonary artery pressure, and possibly a family history of asthma ***(Dammann et al., 2005).***

Clinical presentation :

Instead of showing improvement on the 3rd - 4th day, consistent with the natural course of RDS, infants who have been on intermittent positive pressure ventilation, shows increased concentration of oxygen roentgenographically yet with worsening pulmonary function ***(Bancalari et al., 2003)***.

This table summarizes in short the possible causes of respiratory failure in preterm infant.

Table (3): Possible causes of respiratory failure in premature infants.

Problem area	Possible causes
Pulmonary	Respiratory distress syndrome Aspiration syndrome Pneumonia Pulmonary hemorrhage Pulmonary alveolar proteinosis Wilson-Mikity syndrome Bronchopulmonary dysplasia Pulmonary insufficiency of prematurity Pneumothorax Tumor Diaphragmatic hernia Chylothorax Cogneital malformations (labor emphysema, cystic adenoma malformation, lymphangiectasis)
Airway	Laryngomalacia Choanal atresia Pierre robin syndrome Micrognathia Nasopharyngeal tumor Subglottic stenosis
Abnormalities of muscles of respiration	Phrenic nerve palsy Spinal cord injury Myasthenia gravis Werding-Hoffmann syndrome
Central problems	Apnea of prematurity Drugs; morphine, magnesium sulfate, mepivacaine, meperidine Seizures Birth asphyxia Hypoxic encephalopathy Intracranial hemorrhage Odines curse Rapid eye movement sleep
Miscellaneous	Congestive heart failure Persistent fetal circulation Postoperative anesthesia/sedation Tetanus neonatorum Extreme immaturity Shock Sepsis Hypoglycemia Electrolyte abnormalities Acid base imbalance Infant botulism Hydrops fetalis

(Goldsmith and Karothkin, 2003)

b) Neurological problems

Premature infants are at an increased risk of acute neurologic problems as intracranial hemorrhage, hypoxic