

# **The Value of Umbilical Cord Blood Interleukin-6 Measurement for Prediction of Intraventricular Hemorrhage in Preterm Infants**

***Thesis***

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## LIST OF ABBREVIATIONS

<b>AD</b>	Alzheimer disease.
<b>AGA</b>	Appropriate for gestational age.
<b>BAFF</b>	B-cell activating factors belonging to the tumor necrosis factor family.
<b>BCMA</b>	B cell maturation antigen.
<b>CAC</b>	Colitis-associated colon cancer.
<b>CBF</b>	Cerebral blood flow.
<b>CISS</b>	Constructive interference in the steady state.
<b>CLC</b>	Cardiotrophin-like cytokine.
<b>CNS</b>	Central nervous system.
<b>CNTF</b>	Ciliary neurotrophic factor.
<b>CT</b>	Computed tomography.
<b>CT-1</b>	Cardiotrophin-1.
<b>CTL</b>	Cytotoxic T Lymphocytes.
<b>DC</b>	Dendritic cells.
<b>EAE</b>	Experimental Autoimmune Encephalomyelitis
<b>EPO</b>	Erythropoietin
<b>GM-CSF</b>	Granulocyte-Monocyte Colony Stimulating Factor.
<b>GM-IVH</b>	Germinal Matrix-intraventricular hemorrhage.
<b>gp130</b>	Glycoprotein 130.
<b>IBD</b>	Inflammatory bowel disease.
<b>IFN</b>	Interferon.
<b>IG</b>	Immunoglobulin.
<b>IKK<math>\beta</math></b>	Inhibitor of NF- $\kappa$ B kinase.
<b>IL</b>	Interleukin.
<b>IL-6R</b>	Interleukin-6 receptor.

<b>IL-6R<math>\alpha</math></b>	IL-6 $\alpha$ -receptor.
<b>IVH</b>	Intraventricular hemorrhage.
<b>JAK</b>	Janus kinase.
<b>LIF</b>	Leukemia inhibitory factor.
<b>LPS</b>	Lipopolysaccharide
<b>MAPK</b>	Mitogen-activated protein kinase.
<b>MHC</b>	Major Histocompatibility complex.
<b>MRI</b>	Magnetic resonance imaging. .
<b>MS</b>	Multiple sclerosis.
<b>NEC</b>	Necrotizing enterocolitis
<b>NK</b>	Natural killer.
<b>NO</b>	Nitric oxide.
<b>OSM</b>	Oncostatin M.
<b>PBMCs</b>	Peripheral blood mononuclear cells.
<b>PC</b>	Procalcitonin.
<b>PDA</b>	Patent ductus arteriosus.
<b>PG</b>	Prostaglandin.
<b>PIVH</b>	Periventricular Intraventricular hemorrhage .
<b>PT</b>	Preterm.
<b>PVH/IVH</b>	Periventricular/ Intraventricular hemorrhage.
<b>PVL</b>	Peri-ventricular leukomalacia.
<b>RA</b>	Rheumatoid arthritis.
<b>RANKL</b>	RANK-Ligand.
<b>RDS</b>	Respiratory distress syndrome.
<b>RR-MS</b>	Recurrent relapsing - Multiple sclerosis.
<b>SGA</b>	Small for gestational age.
<b>SIRS</b>	Systemic inflammatory response syndrome.
<b>SLE</b>	Systemic lupus erythematosus



<b>SSc</b>	Systemic sclerosis.
<b>STAT</b>	Signal transducers and activators of Transcription.
<b>T1D</b>	Type 1 Diabetes.
<b>TACI</b>	Transmembrane activator, calcium modulator and cyclophilin ligand interactor.
<b>TALL1</b>	APOL-related leukocyte expressed ligand 1.
<b>TGF</b>	Tumor Growth Factor.
<b>Th</b>	T helper lymphocytes
<b>THPO</b>	Thrombopoietin
<b>TNF</b>	Tumor Necrosis Factors.
<b>TNF-<math>\alpha</math></b>	Tumor Necrosis Factors -alpha.
<b>TRAIL</b>	TNF-related apoptosis-inducing ligand.
<b>U/S</b>	Ultrasound.
<b>VLBWI</b>	Very low birth weight infants.
<b>WMD</b>	White matter brain damage
<b>X-SCID</b>	X-linked form of severe Combined Immunodeficiency.

# INTRODUCTION

The etiology of preterm birth is multifactorial and involves a complex interaction between fetal, placental, uterine and maternal factors (Stoll and Kliegman, 2004). Advanced of perinatal and natal care, including the use of antenatal steroids and exogenous surfactant, have resulted in increased survival of smaller and more immature infant (Vohr et al., 2000; Gillard et al.; 2001).

However, the improved rates of survival have been associated with increased rates of neurodevelopment morbidity in certain groups such as extremely premature infants (Volpe, 2001).

Intracranial hemorrhage is probably the most commonly encountered accident to the brain in preterm infants. Most authorities would agree that 30 – 50% of preterm infants suffer some form of intracranial bleeding (Burstein et al: 1989).

Early detection of abnormalities in brains of newborn infants is important as significant insults to the brain, especially in preterm babies; are most often clinically silent (Schellinger and Grant, 1986).

The introduction of high resolution real time ultrasonography has revolutionized intracranial diagnosis in the neonatal and early infancy periods. It is an easy, safe, noninvasive and relatively cheap method of diagnosis (Grant et al., 1982).

Kassal et al. (2005) hypothesized that some inflammatory markers; namely interleukins can be a useful tool to predict the later development of intraventricular hemorrhage in preterm infants especially those of very low birth weight.

## **AIM OF THE WORK**

The aims of this study are to assess the value of measurement of umbilical cord blood interleukin-6 levels for prediction of the occurrence of intraventricular hemorrhage in preterm infants and to determine whether these levels can be correlated with cranial ultrasound results or not.

## **SUBJECTS AND METHODS**

The study will include 90 preterm infants (gestational age <37 Weeks) born in the pediatrics Hospital of Alexandria University and in other governmental pediatrics hospitals of Alexandria.

### **Exclusion criteria**

- Preterm babies born to mothers with preterm premature rupture of membranes or those with suspected or proved chorioamnionitis.
- Preterm babies born to mothers who received antenatal steroids.
- Full term babies (gestational age >37 weeks).

### **Cases will be subjected to the following**

1. Adequate history taking especially regarding calculated gestational age, any maternal disease, antenatal steroids treatment and symptoms suggesting chorioamnionitis.
2. Thorough clinical examination stressing on birth weight, signs of early neonatal sepsis, and Ballard score to assess the gestational age.
3. Collection of umbilical cord blood samples for measurement of interleukin-6 levels using commercially available kits.
4. Cranial ultrasound examination during the first week of life for detection of intraventricular hemorrhage.
5. Statistical analysis of the results.

# PREMATURITY

Infants born before 37 weeks gestation are considered premature. The more preterm an infant is born, the greater the risk that the infant will experience complications of prematurity. High rates of morbidity and mortality in preterm infants can be attributed to complications associated with prematurity. Approximately one third of infant deaths can be associated with prematurity. Extremely premature infants have a mortality rate around 50 percent (the highest of any gestational age group), as well as having the greatest risk of morbidity in the long-term. Prematurity accounts for 25% of children with hearing or cognitive impairments, 35 percent of those with visual impairments, and 45% of children with cerebral palsy (**Eichenwald & Stark, 2008**).

Three standard subdivisions classify underweight infants and three are designated for the degree of immaturity (approximate gestational age at birth). Infants born weighing less than 1000 g are considered to be extremely low birth weight (ELBW). An infant born weighing between 1000 g and 1500 g is considered to be very low birth weight (VLBW). Infants born weighing between 1500 g and 2500 g are considered to be low birth weight (LBW) (WHO, 2011). An infant born before 25 weeks gestation is referred to as being extremely preterm (**Nicolas et al., 2000**).

Infants born between 25 and 32 weeks gestation is referred to as being very preterm. An infant born from 32 to less than 37 weeks gestation is referred to as being late preterm (**Pamela et al., 2004**).

## **Short term complications of prematurity**

It is important to quickly stabilize infants in the delivery room to reduce their risk of developing short term complications (**Lemons et al., 2001**).

Short term complications of prematurity are defined as those occurring during the neonatal period (**Eichenwald & Stark, 2008**).

Premature infants are increasingly susceptible to developing short term complications with decreasing birth weight and gestational age, and are the result of anatomical or functional immaturity (**Faranoff et al., 2007**).

Overall, the more short term complications seen in an infant, the greater the chances that the child will experience long term complications of prematurity (**Eichenwald and Stark, 2008**).

## **Preterm Brain Complications**

A child born very preterm uses different regions of the brain to process information than those regions a term infant uses. When an infant is born prematurely, the brain compensates for being underdeveloped to function properly in its new environment. These changes can have detrimental effects in long term (**Jobe, 2010**).

The preterm infant born at 24 weeks gestational age has a brain weight around 100g with a smooth surface with no external architecture (gyri). While at full term, an infant's brain weighs about 350g and has a convoluted surface and great complexity (**Ment et al., 2009**).

The brain of an ELBW neonate grows, but the surface structure is less complex than the full term brain (**Ajayi-Obe et al., 2000**).

A preterm brain has a lower volume of deep nuclear grey matter, which can be further damaged by white matter injury (**Inder et al., 2005**).

Preterm infants are predisposed to brain injury due to factors including hypoxia, ischemia, hyperoxia, and maternal-fetal infection. Perinatal impacts to the brain can result in inflammation, excitotoxicity, and oxidative stress. Genetic factors cause some infants to be more susceptible to these complications. These factors contribute to encephalopathy of prematurity, which is white and grey matter damage of the premature brain (**Kaindl et al., 2009**).