Introduction

During the last few decades, the survival of preterm infants has increased dramatically **(Fanaroff et al., 2007).** This improvement is mainly due to advances in perinatal medicine and neonatal intensive care. Nevertheless, the incidence of neurological impairment remains high among preterm survivors. The most important neurological manifestations of brain damage in preterm infants are cognitive and motor disabilities. Periventricular- intraventricular hemorrhage (PV-IVH) is one of the major causes of the development of cerebral palsy and mental retardation, and the incidence ranges from 15% to 40%, depending on the center in spite of the many efforts to reduce the incidence **(Heuchan et al., 2002).**

Large intraventricular hemorrhage (IVH) has a high risk of neurological disability and over 50 % of these children go on to develop progressive ventricular dilatation **(Volpe, 2001).**

Posthemorrhagic ventricular dilatation (PHVD) remains a complication of prematurity which is associated with high rate of disability, multiple impairments and adverse effect of shunt surgery for hydrocephalus**(Whitelaw et al., 2004). Murphy et al**., have provided evidence that PHVD in the 1990s has a more

aggressive course than previously with appreciable mortality and morbidity in extremely premature infants. Treatment is much more difficult than other types of hydrocephalus because the large amount of blood in the ventricle combined with the small size and instability of the patient make an early ventriculoperitoneal shunt operation impossible **(Murphy et al ., 2002).** Experimental studies have suggested that acute parenchymal compression, ischemic damage, increased parenchymal and perivascular deposition of extracellular matrix proteins are probably due to upregulation of transforming growth factor beta and vascular endothelial growth factor which are further important contributors to the development of the hydrocephalus **(Cherian et al., 2004).**

Transforming growth factor ß1 is a polypeptide member of the transforming growth factor beta super-family of cytokines. It is a secreted protein that performs many cellular functions, including the control of cell growth, cell proliferation, cell differentiation and apoptosis **(Ghadami et al., 2000).**

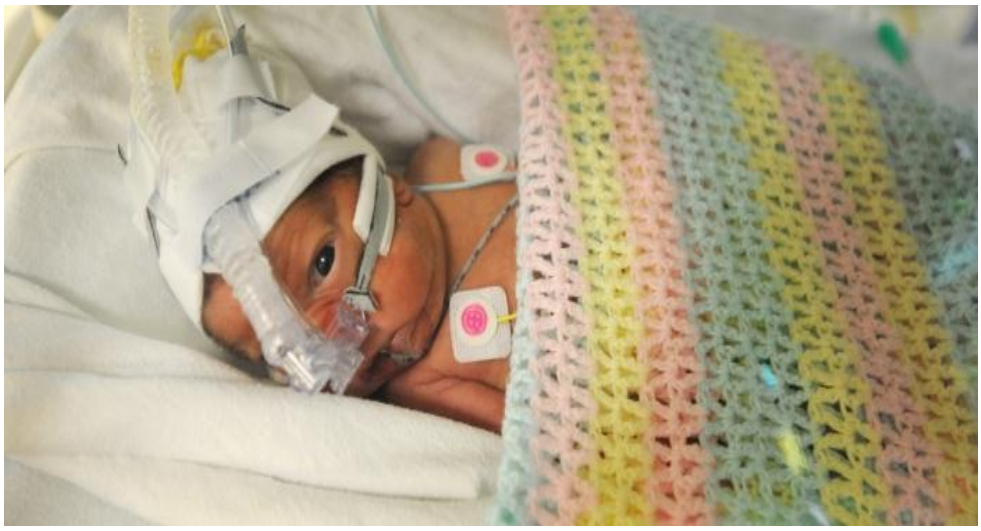
Transforming growth factor-ß1 (TGF-ß1) plays a pivotal role during a variety of normal or pathologic processes, including tissue repair **(Roberts et al., 1986).**

TGF-ß1 is expressed from endothelial, hematopoietic, and connective tissue cells **(Blobe et al., 2000).** It plays an important role in the regulation of tissue proliferation, embryonic development, wound healing, and angiogenesis **(Roberts et al., 1986).**

Aim of the Work

The aim of this study is to evaluate the prognostic value of serum transforming growth factor beta 1 for the development of intra-ventricular hemorrhage in preterm newborns.

Prematurity



For more than 50 years, science has faced the challenging problem of prematurity and its impacts on the health and development of children **(Zelkowitz et al., 2008).**

Infants born before 37 weeks from the first day of the last menstrual period are considered premature. The more preterm an infant is born, the greater the risk that the infant will experience complications of prematurity **(Eichenwald & Stark, 2008).**

Preterm birth is associated with more than one third of all infant deaths **(MacDorman & Mathews, 2008).**

Prematurity and low birth weight (LBW less than 2500 g) accounted for 16.5% of all infant deaths in 2005 and was the second leading cause of infant mortality **(Limperopoulos et al., 2008).**

Preterm births are at significantly increased risk of adverse neurodevelopmental sequelae **(Petrini et al., 2009)** , although the majority of preterms survive, studies of short and long outcomes find significantly higher rates of neurodevelopmental morbidities, sensoneural impairement and other disabilities (e.g., cerebral palsy and visual, auditory and intellectual impairement) and higher rate of complications of the respiratory, gastrointestinal and renal systems **(Honein et al., 2009).**

Three standard subdivisions classify under weight infants and three are designated for the degree of immaturity (approximate gestational age at birth). Infants born weighing less than 1000g are considered to be extremely low birth weight (ELBW). An infant born weighing between 1000 and 1500 g is considered to be very low birth weight (VLBW). Infants born weighing between 1500 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 .An infant 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 **(Nicholas et al., 2000).**

Incidence:

Preterm birth rates available from some developed countries, such as the United Kingdom, the United States and the Scandinavian countries, show a dramatic rise over the past 20 years (**Lawn et al., 2006).** Factors possibly contributing to but not completely explaining this upward trend include increasing rates of multiple births, greater use of assisted reproduction techniques, increases in the proportion of births among women over 34 years of age and changes in clinical practices, such as greater use of elective caesarean section. For example, the increasing use of ultrasonography rather than the date of the last menstrual period to estimate gestational age may have resulted in larger numbers of births being classified as preterm. Changes in the definitions of fetal loss, stillbirth and early neonatal death may also have contributed to the substantial increases in

preterm birth rates recorded in developed countries in the past two decades **(Stanton et al ., 2006)**

Number of Preterm Births	**Preterm Birth Rates (%)**	
World Total	12,870,000	9.6%
Africa	4,047,000	11.9%
North America	480,000	10.6%
Asia	6,907,000	9.1%
LA & the Caribbean	933,000	8.1%
Oceania Australia & New Zealand	20,000	6.4%
Europe	466,000	6.2%

Table (1): The estimated worldwide incidence of preterm birth in 2005, shown in the table, represent the data reported by the World Health Organisation (WHO) in a systematic review aiming to understand the global extent of this specific public health problem. Note these figures were only based on singleton births so are likely to underestimate the actual number of preterm births globally.

Etiology of preterm birth:

As the cause of labor still remains elusive, the exact cause of preterm birth is also unresolved. Infact, the cause of 50% of preterm birth is never determined **(Simhan et al., 2007).** Four different pathways have been identified that can result in preterm birth and have considerable evidence: precocious fetal endocrine activation, uterine over distension, decidual bleeding and intrauterine inflammation/infection. Activation of one or more of these pathways may happen over weeks even months **(Simhan et al., 2007).**

the lower the socioeconomic standard, the more the risk for preterm labor , smoking whether active or passive is associated with preterm labor , threatened or induced abortion, unwanted pregnancy, psychological trauma and surgical intervention during current pregnancy are associated with preterm labor . History of preterm labor is associated with the present condition. Anemia, hypertension, body weight less than 70 kgm are associated with preterm labor **(Fahim et al., 1992)** .

Assessment of fetal growth and maturity:

Fetal growth can be assessed clinically by determining the fundal height through bimanual examination of the gravid

uterus and ultrasonographic measurements of the fetal biparietal diameter, femur length and abdominal circumference **(Kliegman, 2000).**

Neonatal problems associated premature infants:

Preterm infants usually show physical signs of prematurity in reverse proportion to the gestational age **(Eichenwald and Stark, 2008)** as a result of anatomical and functional immaturity of their different body systems **(Faranoff et al., 2007).** So they are at risk for numerous medical problems affecting them.

A) Nervous disorders:

Neurodevelopmental problems include apnea of prematurity **(Batton, 2009)** , retinopathy of prematurity **(Heller et al., 2007)** , developmental disabilities, cerebral palsy **(Marlow et al., 2005)** and intraventricular hemorrhage. The latter affecting 25 percent of babies born usually before 32 weeks of pregnancy **(March of Dimes, 2009),** mild brain bleeds usually leave no few lasting complications, but severe bleeds often result in brain damage or even death **(March of Dimes, 2009 and Shankaran, 1997).** Also hypoxic ischemic encephalopathy, periventricular leukomalacia, seizures,

hypotonia, deafness, congenital malformations and kernicterus (bilirubin encephalopathy) **(Stephens and Vohr ., 2010).** Retinopathy of prematurity **(Hakeem et al.,2012).**

B) Cardiovascular disorders:

Failure of the ductus arteriosus to close after birth (patent ductus arteriosus), hypotension, hypertension, bradycardia (with apnea), congenital malformations are the main cardiovascular complications in preterm infants **(Faranroff et al., 2007).**

C) Respiratory disorders:

They are common specifically the respiratory distress syndrome (previously called hyaline membrane disease) **(Ventolini et al., 2006**), brochchopulmonary dysplasia (BPD), also, pneumothorax, interstitial emphysema, congenital pneumonia, pulmonary hypoplasia and pulmonary hemorrhage **(Jobe and Bancalari, 2001).**

D) Hematological disorders:

Anemia of prematurity (**Bishara et al., 2008)**, hyperbilirubinemia –indirect or direct **(Maisels et al., 2012)**,

dissiminated intravascular coagulopathy **(Veldman et al., 2010).**

E) Gastrointestinal disorders:

The ability to suck, swallow and breath in a coordinated fashion is not in place until 34-36 weeks of gestation, so entral feeding must be provided by gavage. Furthermore, preterm infants frequently have gastro osophagel reflux **(Golski et al., 2010)** and immature gag reflex, which increases the risk of aspiration of feeding. Poor gastrointestinal function-poor motility **(Zangen et al., 2003),** necrotizing enterocolitis **(Duro et al., 2010).**

F) Metabolic-endocrine disorders:

Hypocalcemia , hypoglycemia and hyperglycemia **(Hovi et al., 2007).**

G) Renal disorders:

Immature renal function (including both filteration and tubular function), and electrolyte disturbance leading to hyponatremia, hypernatremia, hyperkalemia, renal tubular acidosis, renal glycosuria and edema (**Kleigman et al., 2000).**The diseased preterm neonates showed worse renal

function and structure with minimal improvement regardless of the underlying sickness. **(Awad et al.,2002)**

H) Others:

Increased susceptibility to infection (congenital, prenatal, nosocromial: bacterial, viral, fungal and protozoal **(Stoll et al., 2004)**.

❖ ***Preterm Brain injury:***

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).**

New born brain injury occurs as often as 1 in 4000 live births. Greater than 95% of infants who survive a brain injury survive until adulthood, but many suffer motor and cognitive disabilities **(Nelson and Lynch, 2004).** Therefore, it is important to examine the brain complications of preterm infants whose susceptibility for brain injury is higher than that of term infants. Neonatal brain injury is difficult to detect in VLBW infants due to the absence of some common signs of brain injury, including lethargy, hyper-excitability, and stupor **(Mercuri et al., 2003).**

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).**

The most common brain injury in preterm infants is periventricular white-matter injury. Periventricular white matter injury is the primary cause of chronic neurological morbidity **(Deng et al., 2008).**

White-matter damage is accompanied by neuronal loss and impaired neuronal guidance. Some preterm infant complications result from reduced connectivity between areas of the brain needed for integrating information **(Kadhim et al., 2003).**

The neonatal brain is vulnerable to oxidative damage because of its high concentrations of unsaturated fatty acids, high rates of oxygen consumption, low concentrations of antioxidants, and availability of redox-active iron **(Halliwell, 1992).** In the immature brain, oligodendrocyte progenitor cells are susceptible to the depletion of antioxidants and exposure to free radicals, while mature oligodendrocytes are extremely resistant to this stress **(Baud et al., 2004).** This vulnerability gives reason to white matter injury occurring more often in preterm infants. Oxidative stress can lead to ischemic damage to the neonatal brain. Ischemia is a decrease in the blood supply caused by constriction or obstruction of blood vessels. This leads to tissue damage because of a lack of oxygen and nutrients **(Kanold et al., 2003).**

Excitotoxicity is also a factor in ischemic damage to the preterm brain. Excitotoxicity is the excessive activation of glutamanergic neurotransmitters leading to cell death **(Olney, 2003).** This cell death in the neonate brain may be triggered by