INTRODUCTION

Necrotizing enterocolitis (NEC) is one of the most serious and life threatening conditions in the neonatal period. NEC is considered a major cause of high morbidity and mortality especially in premature infants ***(Kafetzis, 2003).***

It is defined as an inflammatory disease of the neonatal bowel ***(Thompson, 2008).*** Till now, the pathogenesis of NEC is definitely unknown. However, It is believed to be multi factorial in nature ***(Lin and stoll, 2006).*** Ischaemia and exaggerated inflammatory response of the intestinal villi to hypoxia, early enteral feeding with artificial milk formula in addition to abnormal bacterial colonization of the neonatal GIT are believed to play the main role in development of the disease. The most important risk factor at all is prematurity ***(Crissinger, 2008, Pietz et al., 2007, Lin and stoll, 2006 and Claud and Walker, 2008).***

Preterm infant's bowel has defective blood supply, immature motility and digestion. As well as, cell mediated and humoral immunity and local host defense mechanisms of the preterm infants are not well developed so that they are more liable to several intestinal diseases especially necrotizing enterocolitis ***(Lin and Stoll, 2006).***

Necrotizing enterocolitis is classified into three stages according to the severity of symptoms and signs. Stage I: includes patients with the mildest symptoms and signs as lethargy, temperature instability, apnea and bradycardia. Poor activity and feeding, vomiting with increasing gastric residuals, and mild abdominal distension may be the first signs to be seen. Stage II have the previous signs but more relevant with persistent frank or occult blood in the stool. X-ray may show fixed dilated bowel loops, pneumatosis intestinalis, and or portal venous gases. Stage III includes the previous signs with septic shock and more deterioration of the patients vital signs and may have marked GIT bleeding ***(Katherine et al., 2011).***

As NEC may have a rapidly progressive course with catastrophic endings, its diagnosis at the earliest point is life saving issue ***(Gordon, 2007).*** Many researches all over the world were done to obtain a predictive marker for early detection of NEC as plasma arginine, glutamine, and citrulline level ***(Wu et al., 2009).***

According to the biophysiology of the intestine, glutamine is supplied from arterial blood and intestinal lumen. Both enter the enterocytes to be converted to glutamate. Then glutamate is reduced to pyrroline 5 carboxylate [P5C] via an enzyme called pyroline -5 -carboxylate synthase [P5CS]. This enzyme is exclusively present in the small intestine enterocytes.

P5C is then converted to ornithine which in turn is converted to citrulline ***(Malvika et al., 2014).***

Citrulline is a natural non-essential amino acid. It is believed to be an intermediate of urea cycle. Most of the plasma citrulline is derived from glutamine conversion in the enterocytes as previously described. A small amount of citrulline is synthesized in the liver but its catabolism occurs in situ ***(Crenn et al., 2000).***

Human enterocytes are responsible for digestion and absorption of most nutrients, water and electrolytes required for normal metabolism. This important function of the GIT depends on the viability of the enterocytes along with the length of the absorptive surface of the intestine. Many studies done on infants with short bowel syndrome have shown significant correlations between plasma citrulline level and the mass of functioning enterocytes. This correlation side by side with the unique metabolism of citrulline have increased suggestions that plasma citrulline level could be a reliable marker of gut function ***(Bailly et al., 2009)***.

AIM OF THE WORK

The aim of this study is to evaluate the efficacy of plasma citrulline level as a predictor of enterocytes function in preterm neonates with NEC.

Chapter 1

PREMATURITY

Definition:

Prematurity is the delivery of an infant before 37weeks of gestation. Prematurity has different degrees according to gestational age**(Mathews and MacDorman, 2007).**

Assessment of preterm infant:

Clinical assessment of gestational age post natally can be achieved by the use of new Ballard Score ***(Sunjoh et al., 2004)*****.** It can estimate the gestational age via physical criteria.

Incidence:

The incidence of preterm labor varies from 2-3 % in some developed countries to 25-35% in developing countries ***(Shalj et al., 2003)***.

In USA, 12% of neonates are premature and 2% are < 32 weeks gestational age ***(William, 2004)***.

Causes of preterm labor

1- Fetal causes:

i. Fetal distress. ii. Multiple gestations.

iii. Erythroblastosis fetalis and non immune hydrops.

2- MATERNAL

i. Preeclampsia.
ii. Chronic medical illness (e.g, cyanotic heart disease, renal disease).
iii. Infections as UTI, TORSH, bacterial vaginosis and Chorioamnionitis.
iv. Drug abuse.
v. Placental problems as placental insufficiency, Placenta previa and Abruptio placenta.
vi. Uterine problems as bicornucate uterus or incompetent cervix.
vii. Polyhydramnios and premature rupture of membranes.
viii. Trauma. (***Fanaroff et al., 2007)***

Complications of prematurity

Preterm infants are susceptible to various complications . The risk of developing such complications increases with increasing the degree of prematurity.***(Fanaroff et al., 2007)***.

1. Hypothermia.
2. Respiratory disorders as RDS, bronchopulmonary dysplasia or apnea of prematurity.
3. Cardiovascular problems as PDA or hypotension.

4. Neurological problems as hypoxic ischaemic encephalopathy[HIE], kernicterus or intracranial hemorrhage.
5. Hyper or hypoglycemia.
6. Infections.
7. Hematological disorders as anemia or DIC.
8. Retinopathy of prematurity.
9. GIT disorders.

1- Hypothermia:

Preterm neonates bodies have relative large surface area in comparison with full term babies in addition to decreased heat production. This makes them more liable to excessive heat loss ***(Knobel et al., 2005)***.

2- Respiratory disorders:

i- Respiratory distress syndrome [RDS]

Surfactant deficiency in preterm neonates is the cause of RDS. The severity of RDS increases with increasing the degree of prematurity **(Mandy, 2009).**

ii- Bronchopulmonary dysplasia[BPD]

It is oxygen dependency in newborn infants. Its more common in preterm infants**(Mandy, 2009).**

iii- Apnea of prematurity:

Apnea of prematurity occurs in 25% of preterm neonates and its incidence increases with decreasing post conceptional age ***(Mandy, 2009)***

3- <u>Cardiovascular problems</u>

i- Patent ductus arteriosus

30 % of VLBW neonates may have symptomatic PDA. Blood shunts from the aorta to the pulmonary artery resulting in pulmonary hypertension with decreased systemic circulation. The presentation of PDA depends on its size and the response of CVS and lungs ***(Fanaroff et al., 2007).***

ii- Systemic hypotension; Hypotension in neonatal period is associated with increased mortality and significant morbidity ***(Miletin and Dempsey, 2008)***.

4- <u>Neurological disorders:</u>

Kernicterus, hypoxic ischemic encephalopathy and intracranial hemorrhage are common complications of prematurity**(*Bolisetty et al. ,2014).***The incidence of IVH and periventricular leucomalacia are inversely proportional with gestational age***(*Ward and Beachy, 2003).*** Hydrocephalous occurs in 25 - 33% of neonates with IVH **(*Bolisetty et al. ,2014).***

5- <u>Hyper or hypoglycemia:</u>

Preterm neonates are liable to hypoglycemia or hyperglycemia***(Mandy, 2009).***

6- **Infection:**

Sepsis is very common among preterm neonates ***(Stoll and Kleigman, 2004)***.

7- **Hematologic disorders:** Anemia, DIC, hyper bilirubinemia.

8- **Retinopathy of prematurity[ROP]:**

ROP occurs due to incomplete vascularization of the retina of preterm neonates. ROP incidence and severity is inversely proportional with birth weight and gestational age ***(Mandy, 2009)***.

9- **GIT problems:**

Disturbed motor functions of the intestinal wall appears to play a major role in feeding intolerance in preterm neonates. Co-ordination of swallowing with suckling does not usually develop till 34 weeks gestational age. Esophageal tone and gastric emptying are limited in preterm babies especially those less than 30 weeks gestational age. **(Josef Neu, 2007)** Defective motility along with immature defense mechanisms render the intestine of preterm baby more liable to pathogenic bacterial colonization. This makes preterm infants more liable to feeding intolerance and enteropathies of prematurity **(Moore and Wilson, 2011)**. There are many types of enteropathies that affect preterm gut as:

i- Allergic colitis: It is an inflammatory disease of the colon and rectum presented with bleeding per rectum following enteral feeding**. (Sicherer, 2005)**

ii- Microvillous inclusion disease: A rare autosomal recessive disease manifested by chronic intractable diarrhea. Diagnosis is by biopsy and treatment is by total parenteral nutrition **(Salvatore et al., 2007).**

iii- Necrotizing enterocolitis: It the most common and most serious catastrophic disorder of neonatal GIT.

Chapter 2

NECROTIZING ENTEROCOLITIS

Necrotizing enterocolitis (NEC) is one of the most serious life threatening disorders of the neonatal gastro intestinal tract. It is a syndrome of acute intestinal necrosis of non specific etiology ***(Karen, 2004)***.

Epidemiology:

Necrotizing enterocolitis is an inflammatory bowel disease of neonates. Its incidence rate ranges from 1% to 5% of all neonates admitted to NICU increases to 7 - 14% of VLBW infants. It can be considered as a disease of prematurity in which preterm infants account for about 90% of cases of NEC, while full term neonates account for 10% ***(Schnabl et al., 2008).***

NEC has a high mortality rate of about (9-28%) regardless any medical management or surgical intervention, and increases up to 45*%* of neonates weighing less than 1.5 kg ***(Karen, 2004)***. The mortality rate obviously decreases with the use of standardized therapeutic protocols with early prediction for the disease and definite criteria for medical management or surgical intervention***(Eichenwald, 2008).***

Risk Factors:

It is believed that NEC is multi factorial in origin in which many risk factors have been identified as a predisposing factors for the development of NEC. The most important factors are as follows:

1- Prematurity.
2- Low birth weight.
3- Infantile disorders as: a-Respiratory distress syndrome, b-congenital heart diseases, c-Hypoxia, d- Polycythemia, e-Umbilical catheterization and infection.
4- Drugs as indomethacin, ibuprofen, vitamin E, H2 blocker and theophylline.
5- Maternal conditions as multiple gestations and pregnancy induced hypertension.
6- Feeding.
7- Surgical procedures.

1-Prematurity:

Prematurity is thought to be the major risk factor for NEC. 90% of cases of NEC are premature ***(Ewer, 2002).*** Premature infants have immature digestion, motility and circulation of the bowel. Preterm infants have impaired humoral and cell mediated immunity. Also the local host defense

mechanisms of the preterm infants GIT are under developed, so that they are more liable to intestinal diseases ***(Linet al., 2008).*** The degree of prematurity is the dominant risk factor for developing NEC ***(Alen and Richard, 2001).***

2- Low birth weight:

Low birth weight is an important risk factor in developing NEC***(Guthrie et al., 2003).*** Full term and near term neonates can be considered in a high risk of NEC ***(Ruangtrakool et al., 2001)***.

3-Infantile disorders:

A. Respiratory Distress Syndrome (RDS):

It is thought that hyaline membrane disease (HMD) increases the risk of developing NEC. Intestinal ischaemia caused by prolonged hypoxia plays an important role in NEC ***(Crissinger 2008).*** Also the introduction of artificial surfactant to extreme premature neonates has improved the survival to develop NEC later ***(Luig and lui, (2005).***

B. Congenital Heart Diseases (CHD):

Infants with congenital heart diseases has an incidence of NEC of about 3.3 -6.8%***(Giannone et al., 2008).*** Truncus