INTRODUCTION

Neonatal jaundice is a common physiological problem affecting over half of all full term and most preterm infants ***(Chen et al., 2011).***

Breast-fed newborns have a higher incidence of hyperbilirubinemia and exhibit earlier onset and often longer duration of this condition than formula fed newborns ***(Gulcan et al., 2007).***

There is a strong association between breast-feeding and jaundice in healthy newborns during the first weak of life and the incidence of hyperbilirubinemia in breast-fed newborns was significantly higher than that in formula-fed newborns ***(Adams et al., 2007)***.

Increased absorption of breast milk compared to formula and consequent increased entero-hepatic circulation of bilirubin are through to explain this high incidence of hyperbilirubinemia in breast-fed newborns ***(Maisels, 2006)***.

Phototherapy is effective and widely used for treating neonatal unconjugated hyperbilirubinemia and breast-fed newborns respond well ***(Gulcan et al., 2007)***.

Evidence exists supporting the benefits of baby massage to increase neonatal physical and mental development and elimination and reduction of colic and wind ***(Field et al., 2010).***

Baby massage would promote early-stage defecation of neonates, which may accelerate bilirubin excretion with the possibility of reducing neonatal jaundice ***(Chen et al., 2011)***.

AIM OF THE WORK

1) Is to asses the efficacy of phototherapy for non hemolytic hyperbilirubinemia and rebound bilirubin in breast-fed newborns as compared with mixed-fed (breast milk& formula) newborns.

2) To asses the effect of neonatal massage on phototherapy response.

Chapter (1)

NEONATAL JAUNDICE

Definition:

Hyperbilirubinemia is one of the most common problems encountered in term newborns. Jaundice describes the yellow orange hue of the skin caused by excessive circulating levels of bilirubin that accumulate in the skin, It is defined as a serum unconjugated bilirubin concentration of greater than 1.3 to 1.5 mg/dL (22.2 to 25.7 μmol/L) or conjugated bilirubin concentration of higher than 1.5 mg/dL (22.2 μmol/L) ***(De Almeida and Draque, 2007).***

Jaundice is a common, temporary and usually harmless condition in newborn infants. It affects both full-term and premature babies, usually appearing during the first week of the baby's life and it's commonly lasts for one to two weeks. It manifests clinically when bilirubin level of more than 85 umol/l (5 mg/dL). In newborns jaundice is detected by blanching the skin with digital pressure so that it reveals underlying skin and subcutaneous tissue. It is first noted in the face and as the bilirubin level rises proceeds caudal to the trunk and then to the extremities ***(Parks et al., 2000).***

Incidence:

This condition is common in newborns affecting over half (50 - 60%) of term and 80% of preterm babies in the first

week of life and it is considered as the most common reason for readmission of a newborn to the hospital in the first 2 weeks of life ***(Escobar et al., 2005).***

Neonatal jaundice can be best understood as a balance between the production and elimination of bilirubin, with magnitude of factors and conditions affecting each of these processes. When an imbalance results because of an increase in circulating bilirubin to significantly high levels (severe hyperbilirubinemia) ***(Cohen et al., 2010).***

Significant jaundice (value > 15 mg⁄dl) is present in 4-6 percent of neonates. Over the years, it has been documented that there is an increase in this incidence to around 10-14%. The increase of number of cases could be due to more awareness and better laboratory methods ***(Dennery et al., 2001).***

In most cases it is benign and no intervention is required approximately 5-10% of them have clinical significant hyperbilirubinemia mandating the use of phototherapy ***(Maisels et al., 1988)***.

Bilirubin metabolism:

Bilirubin is the potentially toxic catabolic product of heme metabolism (fig.1). There are elaborated physiologic mechanisms for its detoxification and disposition. Understanding these mechanisms is necessary for interpretation

of the clinical significance of high serum bilirubin concentrations ***(Sandeep et al., 2010).***

Humans continuously form bilirubin, and newborn infants produce relatively more bilirubin than any other age group. The typical bilirubin load of the newborn is quite high, 2 to 3 times that of an adult. Red blood cells (RBCs) only live for 70-90 days in the newborn period unlike the older child whose cells live 120 days ***(Berkowitz, 2000).***

Although bilirubin production is elevated in newborns, conjugation and clearance of bilirubin can be slow. Immaturity of hepatic glucuronosyl transferase and inadequate milk intake can cause delayed clearance of bilirubin ***(Moerschel et al., 2008).***

Bilirubin is a product of the normal destruction of circulating erythrocytes (which have a shortened life span in the newborn infant) and increased turnover of cytochromes **(**fig. 2) ***(Wong et al., 2006).***

Some infants have excessive bilirubin production, and a correspondingly elevated load of unconjugated bilirubin. Unconjugated bilirubin (UCB) is lipid-soluble and must be transported to the liver in the plasma, bound reversibly to albumin ***(Maisels, 2005).***

In the liver, bilirubin is transported across hepatic cell membranes, where it binds to ligandin for conjugation. A liver

enzyme, uridine diphosphoglucuronate transferase (UDPGT) conjugates bilirubin, converting it to water-soluble bilirubin pigments that can be excreted into the bile and exit the body via the intestines or, to a lesser degree, filtered through the kidneys. Bilirubin pigments in the gut that are not eliminated can be reabsorbed into the circulation as UCB, essentially recycling the bilirubin load, a process called enterohepatic recirculation. Breast milk increases bilirubin reabsorption through this enterohepatic absorption ***(Gowen, 2006)***.

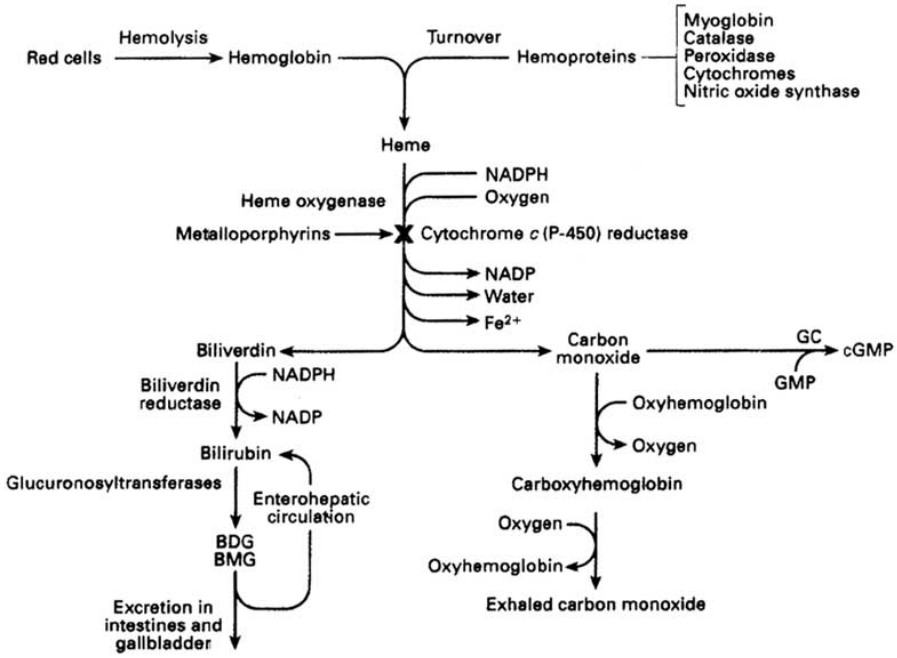

Fig. (1): Degradation of heme, formation of bilirubin, the conjugation of bilirubin in the liver, and its excretion from the body ***(From Dennery et al., 2001).***

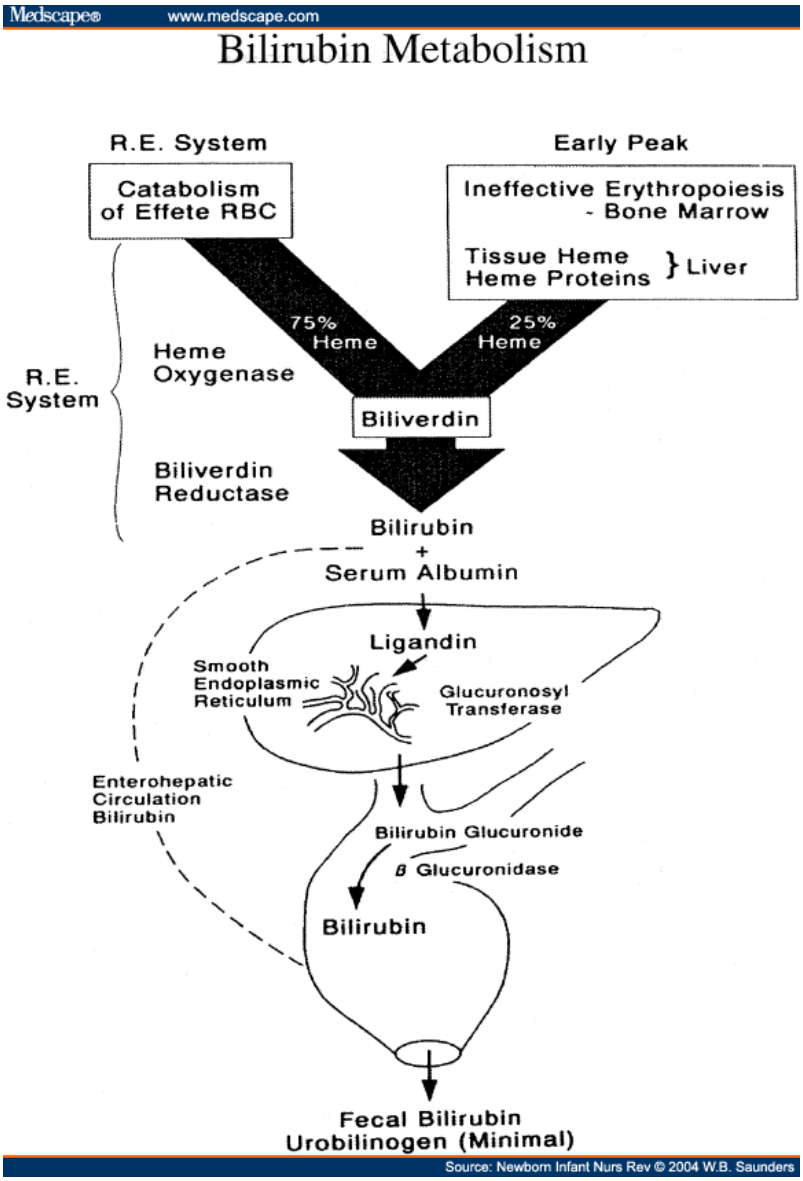

Fig. (2): Neonatal bile pigment metabolism.

Deficiency of bilirubin-UGT leads to ineffective esterification of bilirubin, which in turn results in an unconjugated hyperbilirubinemia. Reduced bilirubin conjugation as a result of a decreased or absent UD P-

glucuronosyltransferase activity is found in several acquired conditions and inherited diseases, such as Crigler-Najjar syndrome (types I and II) and Gilbert syndrome. Bilirubin conjugating activity is also very low in the neonatal liver ***(Sandeep et al., 2010).***

Bilirubin glucuronidation can also be inhibited by certain antibiotics (eg, novobiocin or gentamicin at serum concentrations exceeding therapeutic levels) and by chronic hepatitis, advanced cirrhosis, and Wilson disease ***(Saeki et al., 2007 and Saito et al., 2009).***

Causes of neonatal hyperbilirubinemia:

(1) Genetic and familial causes.

(2) Maternal causes.

(3) Neonatal causes.

(4) Metabolic diseases.

1. Genetic and familial causes:

● **Crigler-Najjar syndrome**:

It is a rare congenital non hemolytic autosomal recessive (AR) condition associated with high serum levels of unconjugated bilirubin. If left untreated, it may lead to bilirubin encephalopathy and death ***(Bosma, 2003).***

Crigler-Najjar syndrome is a familial disorder of bilirubin metabolism caused by deficiency or complete absence of hepatic microsomal bilirubin uridine diphosphate glucuronyltransferase 1 family, polypeptide A1 (UGT1A1) activity ***(Lucey et al., 2000).***

The absence of UGT1A1 leads to Crigler-Najjar type I syndrome which is a very rare disease (estimated at 0.6 -1.0 per million live births) and consanguinity increases the risk of this condition. Intense jaundice appears in the first days of life and persists thereafter ***(Toietta et al., 2005).***

Serum bilirubin levels may be very high (>20.0 mg/dL) and, if untreated by phototherapy it may result in kernicterus with permanent neurologic damage or death. Serum bilirubin concentrations in type 1 Crigler-Najjar syndrome are un-responsive to phenobarbital therapy ***(Kalpan and Hammerman, 2005).***

Crigler-Najjar type II syndrome results from decreased levels of UGT1A1. It is a more mild form of the disease. Serum bilirubin concentrations are usually lower, and may decrease by 30-80% in response to phenobarbital treatment. Kernicterus usually does not develop in this disease; therefore, the long-term prognosis is better ***(Sugatani et al., 2003).***

● **Gilbert syndrome** (GS):

Gilbert syndrome is a common, benign autosomal dominant disorder frequently encountered in healthy adults. Is the most common hereditary cause of increased bilirubin, and is found in up to 5% of the population ***(Radu and Atsmon, 2001).***

The main symptom of GS is otherwise harmless jaundice which does not require treatment, it is caused by elevated levels of unconjugated bilirubin in the blood stream. Gilbert syndrome is caused by approximately 70%-80% reduced glucuronidation activity of the enzyme UGT1A1 but normally this has no serious consequence ***(Raijmakers et al., 2000)***.

Mild jaundice may appear under conditions of exertion, stress, fasting and infections, it has been reported that GS may contribute to an accelerated onset of neonatal jaundice but the condition is otherwise usually asymptomatic. The long-term prognosis is good ***(Kasper et al., 2005& Boon et al., 2006).***

Certain drugs as phenobarbital, dexamethasone and clofibrate can be administered to increase UDPGT activity. Infants who have Gilbert syndrome or who are compound heterozygotes for the Gilbert promoter and structural mutations of the UDPGT1A1 coding region are at an increase risk of significant hyperbilirubinemia ***(Trevett et al., 2005).***

Interactions between the Gilbert genotype and hemolytic anemias such as Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency or ABO hemolytic disease also appear to increase the risk of severe neonatal jaundice ***(Kalpan et al., 2002).***

- **Glucose**-6-**phosphate dehydrogenase deficiency:**

Glucose 6-phosphate dehydrogenase is the first enzyme of pentose phosphate pathway, where 5-carbon sugar, ribose and NADPH were synthesized by coupled oxidation/reduction reactions. The function of the normal G6PD enzyme is critical to human survival since G6PD is the only enzyme producing NADPH required for antioxidative repair systems in circulating erythrocytes ***(Minareci et al., 2006).***

It is X liked recessive (XL-R) disease that is associated with severe rapidly rising jaundice following one of documented triggers e.g. Fava beans ***(Luzzatto et al., 2001).***

G6PD deficiency occurs in 11 to 13 percent of African Americans, and G6PD was the cause of kernicterus in 26 out of 125 patients (21 percent), according to the kernicterus registry. G6PD testing is part of the newborn screening programs in Pennsylvania and the District of Columbia. Screening the parents for G6PD deficiency is also helpful in making the diagnosis. Infants who had G6PD deficiency and were discharged early have been reported with severe

hyperbilirubinemia and significant sequelae ***(Bhutani, et al., 2004)***.

2. Maternal causes:

- Diabetes: The main cause may be due to polycythemia (occur in about 30%in infants of diabetic mothers) and due to large amount of B-glucuronidase enzyme which present in breast milk of diabetic mothers that stimulates intestinal reabsorption of bilirubin ***(Hintz et al., 2001).***
- Anaesthesia
- Breast milk jaundice
- Breast feeding jaundice
- Drugs**.**

Certain drugs may affect the metabolism of bilirubin and result in hyperbilirubinemia or displacement of bilirubin from albumin. They are listed in (tab.1).

Table (1): Drugs that cause significant displacement of bilirubin from albumin in vitro.

- Sulfonamides
- Moxalactam
- Fusidic acid
- Radiographic contrast media for cholangiography (sodium iodipamide, sodium ipodate, iopanoic acid, meglumine loglycamate)
- Aspirin
- Apazone
- Tolbutamide
- Rapid infusions of albumin preservatives (sodium caprylate and N-acetyltryptophan)
- Rapid infusions of ampicillin
- Ceftriaxone
- Long-chain free fatty acids (FFAs) at high molar ratios of FFA:albumin

(Moerschel et al., 2008)

3- Neonatal causes:

- **Blood group (ABO) incompatibility:**

Hemolysis from ABO incompatibility has become the commonest cause of isoimmune hemolytic disease in newborns. In about 15% of pregnancies, an infant who has blood type A or B is carried by a mother who is type O. Of these infants, only 20% develop a peak of total serum bilirubin (TSB) of more than 12.8 mg/dl. Severe jaundice (TSB>20 mg/dl) in these infants is uncommon. Nevertheless, ABO hemolytic disease can cause severe hyperbilirubinemia and kernictrus ***(Maisels, 2006).***

It is limited to type O mothers with fetuses who have type A or B blood. In mothers with type A or B blood, naturally occurring antibodies are of immunoglobulin M (IgM) class, which do not cross the placenta, whereas in type O mothers, the antibodies are predominantly immunoglobulin G (IgG) in nature. Because A and B antigens are widely expressed in a variety of tissues besides RBCs, only small portion of antibodies crossing the placenta is available to bind to fetal RBCs. In addition, fetal RBCs appear to have less surface expression of A or B antigen, resulting in few reactive sites-hence the low incidence of significant hemolysis in affected neonates ***(Opekes et al., 2004).***

- **Rhesus factor (Rh) incompatibility:**

The most common cause of Rh incompatibility is exposure of Rh-negative pregnant mother to Rh-positive fetal RBCs secondary to feto-maternal hemorrhage during the course of pregnancy from spontaneous or induced abortion or trauma, once produced, maternal Rh (IgG) antibodies may cross freely from the placenta to the fetal circulation, where they form antigen-antibody complexes with Rh-positive fetal erythrocytes and eventually are destroyed, resulting in a fetal alloimmune-induced hemolytic anemia. Although the Rh blood group systems consist of several antigens (eg, D, C, c, E, e) the D antigen is the most immunogenic; therefore, it most commonly is involved in Rh incompatibility ***(Thorp, 2008).***