INTRODUCTION

Hemolytic disease of the newborn (also called erythroblastosis fetalis) is a condition in which the fetal red cells cross the placenta and the mother is immunized with a fetal red cell antigen that is not present in her red cells. The resulting immune response triggers the production of IgG antibodies, often in high titres and with high affinity, that are then transferred to the fetus and cause hemolysis of fetal red cells. This occurs in case of Rhesus and other blood group incompatibilities ***(Vaughan et al., 1998)***.

Exchange transfusion and phototherapy have traditionally been used to treat this condition and avoid the associated neurological complication. Exchange transfusion is however not without risk ***(Lakatose, 2004)***.

Intravenous immunoglobulin has been used widely for the treatment of immunodeficiency syndromes and several autoimmune diseases. Intravenous immunoglobulin has also been administered directly to the fetus both in combination with or without intrauterine intravascular transfusion for severe RhD hemolytic disease. As a progression from its use for the treatment of erythroblastosis fetalis, high dose intravenous immunoglobulin is now used in hemolytic disease of the

newborn as an alternative therapy to reduce the need for exchange transfusion ***(Gottstein and Cooke, 2003)***.

AIM OF THE WORK

The aim of the work is to assess the effectiveness of high dose intravenous immunoglobulin in reducing the need for exchange transfusion and duration of phototherapy and hospital stay in neonates with proven hemolytic disease due to Rh or ABO incompatibilities.

NEONATAL HYPERBILIRUBINEMIA

Jaundice is a visible manifestation in skin and sclera of elevated serum concentration of bilirubin; it may not appear until serum bilirubin concentration exceeds 5 to 7mg/dL ***(MacMahon, 1998)***.

Neonatal jaundice affects 60% of full-term infant and 80% of preterm in the first 3 days afterbirth ***(Britton, 1994)***.

Pathophysiology:

Neonatal hyperbilirubinemia results from a predisposition to the production of bilirubin in newborn infants and their limited ability to excrete it. Infants, especially preterm infants, have higher rates of bilirubin production than adults because they have red cells with a higher turnover and a shorter life span ***(Phyllis, 2001)***.

Metabolic pathway and formation of bilirubin:

The predominant source of bilirubin is the breakdown of hemoglobin in hemolyzed red cells. Heme is degraded by heme oxygenase, resulting in the release of iron and the formation of carbon monoxide and biliverdin (Figure 1).

Heme released from the hemoglobin of red cells or from other hemoproteins is degraded by an enzymatic process involving heme oxygenase, the first and rate-limiting enzyme in a two-step reaction requiring NADPH and oxygen, and resulting in the release of iron and the formation of carbon monoxide and biliverdin. Metalloporphyrins (synthetic heme analogues) can competitively inhibit heme oxygenase activity (indicated by the X). Biliverdin is further reduced to bilirubin by the enzyme biliverdin reductase. Carbon monoxide can avtivate Guanylyl Cyclase (GC) and lead to the formation of cyclic Guanosine Monophosphate (cGMP). It can also displace oxygen from oxyhemoglobin or be exhaled. The bilirubin that is formed is taken up by the liver and conjugated with glucuronides to form bilirubin monoglucuronide or diglucuronide (BMG and BDG respectively), in reactions catalyzed by uridine diphosphate and monophosphate glucuronosyl-transferase. The bilirubin glucuronides are then excreted into the intestinal lumen but can be deconjugated by bacteria so that the bilirubin is reabsorbed into the circulation ***(Verman, 2000)***.

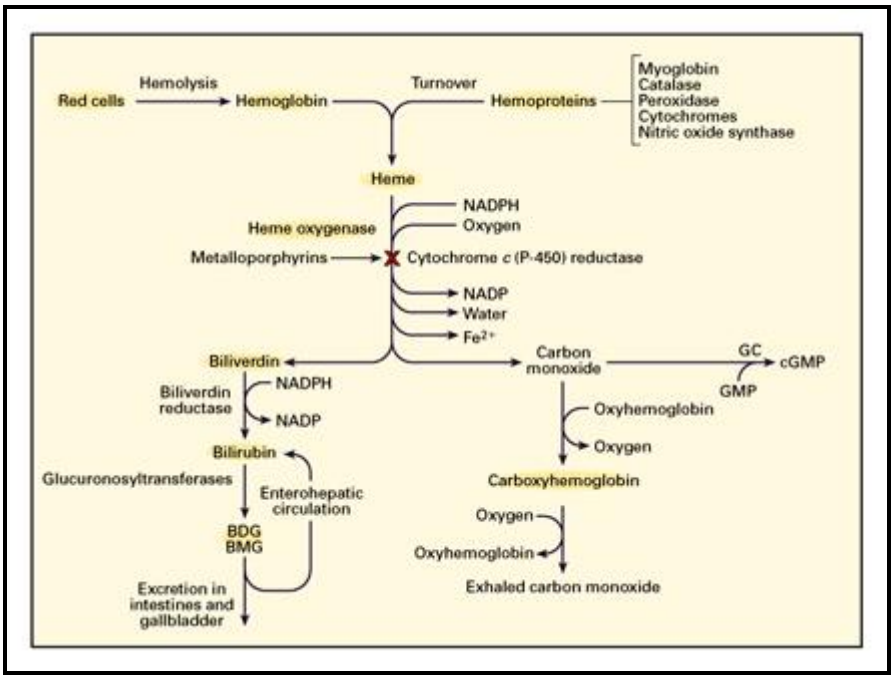

Fig. (1): Metabolic pathway of the degradation of heme and the formation of bilirubin ***(Adapted from Vreman, 2000)***.

Classification:

Jaundice can be classified as physiologic or nonphysiologic according to post-delivery timing of onset, clinical course, resolution, rate of bilirubin increases, and total serum bilirubin levels.

Physiological jaundice:

In newborn infants, unconjugated bilirubin is not readily excreted, and the ability to conjugate bilirubin is limited. Together, these limitation lead to physiologic jaundice—that is, high serum bilirubin concentrations in

the first days of life in full-term infants (and up to the first week in preterm infants and in some full-term Asian infants), followed by decline during the next several weeks to the values commonly found in adults. The average full-term newborn infant has a peak serum bilirubin concentration of 5 to 6mg per deciliter (86 to 103μmol per liter). Serum bilirubin concentration higher than 17mg per deciliter in full-term infants are no longer considered physiologic, and a cause of pathologic jaundice can usually be identified in such infants ***(Halamek, 1997)***.

Pathologic jaundice:

Table (1): Factor suggesting pathological causes and risk factors

Factors suggesting pathologic cause of jaundice	Risk factors for jaundice
• Jaundice in first 24 hours of life.	• Sibling with jaundice in newborn period.
• Total serum bilirubin rising more than 5mg/dl/24h.	• Prematurity, perinatal depression-decreased Apgar score at 5 minutes.
• Total serum bilirubin >15mg/dl in full-term infant.	• Inadequate or in-effective breastfeeding.
• Jaundice persisting after first week of life.	• Significant weight loss after birth.
• Direct reacting bilirubin >1mg/dl at any time.	• Maternal diabetes.
• Family history of hemolytic disease.	• Altitude.
• Pallor, hepatomegaly, splenomegaly.	• Polycythemia.
• Failure of phototherapy to lower bilirubin.	• Blood group incompa-tibility, known hemolytic disease G6PD deficiency.
• Excessive weight loss.	• Male gender.
	• Brusing, cephalohematoma.
	• Delayed stooling.
	• Trisomy 21.
	• Early discharge with inadequate follow up and poor feeding.
	• Jaundice observed within first 24 hours of life.

(American Academy of Pediatrics, 2004)

Hemolytic Disease Of The Newborn (HDN)

Definition:

Hemolytic disease of the newborn (also called erythroblastosis fetalis) is a condition in which the fetal red cell cross the placenta and the mother is immunized with a fetal red cell antigen that is not present in her red cells. The resulting immune response triggers the production of IgG antibodies, often in high titres and with high affinity, that are then transferred to the fetus and cause hemolysis of fetal red cells ***(Vaughan et al., 1994)***.

Causes:

A. Common causes:

1. Rh system antibodies.
2. ABO system antibodies.

B. Uncommon causes:

1. Kell system antibodies.

C. Rare causes:

1. Duffy system antibodies.
2. MNS and S system antibodies.

(Bowman, 1994)

1. Rhesus hemolytic disease:

The identification of the cause of the hemolysis had to await the discovery of the Rh system in 1940 and the determination soon thereafter that hemolytic disease of the fetus occurred in an RhD-positive fetus carried by an RhD-negative woman who had been immunized by transplacental passage of RhD-positive red cells during a prior pregnancy ***(John-Bowman, 1998)***.

Structures and inheritance:

Rh factor is a protein found only in the red cell membrane. Highly antigenic and capable of causing sever isoimmunization with high risk of fetal hydrops and death ***(Widness, 1996)***.

According to the Fisher and Race theory of inheritance:

- The Rh alleles (D, Cc, Ee) are inherited as a complex of three loci. One allele from each parent.
- A person is Rh-positive if they possess the D allele and Rh negative if it is absent.

There are more than forty antigens in the Rh system including weak D (formerly called D^u variant). Mothers typed as weak D appear to be Rh negative on blood screening ***(Flegel, 2002)***.

Table (2): Incidence of Rh negative blood group in various population

Population	Incidence
Chinese and Japanese	1%
North American	1-2%
Indo-Eurasian	2%
African American	4-8%
Caucasian	15-16%
Basque	30-35%

(John Bowman, 1992)

While large amount of bilirubin are produced in the uterus, erythroblastic infants are nor ictric at birth since serum bilirubin concentration are kept below 5mg/dl through the transfer of unconjugated bilirubin by the placenta and jaundice may appear within 30 minutes after delivery. In those neonates who had received intrauterine transfusion, there is moderate to marked conjugated hyperbilirubinemia which has been seen in cord blood or during the first days of life ***(Stoll and Kliegman, 2000)***.

Pathogenesis:

Blood production in the fetus begins at about 3 weeks' and Rh antigen has been identified in the red cell membrane as early as 38 days after conception ***(John Bowman, 1998)***.

- The initial response to D antigen is slow sometimes taking as long as months to develop.
- Re-exposure to the antigen produces a rapid immunological response usually measured in days ***(Bergstrom et al., 1967)***.
- The sensitized mother produces IgG anti-D (antibody) that crosses the placenta and coats D-positive fetal red cell which are then destroyed in the fetal spleen.
- Mild to moderate hymolysis (red cell destruction) manifests as increased indirect bilirubin (red cell pigment) ***(John Bowmann, 1992)***.
- Severe hemolysis leads to red blood cell production by the spleen and liver followed by:
    - Hepatic circulatory obstruction (portal hypertension with placental edema interferes with placental perfusion and ascites develops ***(Pierce, 2004)***.
    - Hepatomagely, increased placental thickness, and polyhydramnios often precede the

development of hydrops (fetal heart failure) ***(Stedman, 2004)***.

- As liver damage progresses decreased albumin production results in the development of anasarca, and effusions ***(Stockman, 2001)***.

- Overall, 16% of Rh-negative women will become sensitized after their first pregnancy if not given anti-D ***(Stoll and Kliegman, 2000)***.
- ABO incompatibility reduces this risk to 4-5%. The reduced risk of Rh sensitization with ABO incompatibility may result from the rapid clearance of incompatible red cells thus reducing the overall exposure to D antigen ***(John Bowman, 1992)***.

Screening:

Initial blood type and screening for antibodies is part of routine prenatal care. The evaluation of a positive antibody screen should include identification of the antibody and its titre.

Identification of antibodies:

- There are several classes of antibodies. The two of interest are IgM and IgG. If the antibody can be identified as an IgM then it does not cross the placenta and there is no risk of hemolysis to the fetus.
    - "Naturally occurring" IgM antibodies may result from antigenic stimulus such as bacteria, which have antigens on their surface chemically similar to blood group antigens. Anti-M antibodies are usually IgM, but IgG Anti-M does occur and is capable of causing hemolytic disease ***(Harkness, 2004)***.
    - Anti-K, anti-D, anti-E, anti-Fya, anti-Jka, and antibodies directed against Rh antigens comprise the majority of antibodies responsible for hemolytic disease of the newborn ***(John Bowman, 1992)***.

Table (3): Antibodies not associated with Hemolytic Disease of the Newborn (HDN)

• Lewis: Le^a, Le^b • Lutheran: Lu^a, Lu^b • I • Duffy: Fy^b • P • Jk^b	Vw, Mure, Hil, Hut, Batty, Becker, Berrens Evans, Gonzales, Hunt Jobbins, Rm, Ven, $Weight^b$, Yt^b, Ge, Jr^a, Co^{a-b}, Xg^a.

(Michael, 1998)

Table (4): Antibodies associated with HDN

• Rh: D, E, c, C, C^w, e • Kell: K_1, KP^a, k, Js^a, Js^b, • Duffy: Fy^a • MNS: M, S, s, N • Kidd: JK^a	Di^a, Di^b, PP_1P^k, Far, Good, Lan, LW, Mta, U, Wr^a, Zd

(Michael, 1998)