# REVIEW OF PATIENTS WITH ABO INCOMPATIBILTY IN HEALTHY NEONATAL JAUNDICE IN KIRKUK

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SUMMERY:

Prospective study involved 63 patient admitted to kirkuk pediatric hospital from 15/5/2008 to 15/7/2008 collectively patients submitted to all required investigations TSB level , complete blood picture, reticulocyte count direct coombs test via two methods antihuman globulin test and old standard technique of o cell technique ,the most common cause of neonatal jaundice among them was physiological one and ABO incompatibility being the next common one male patients were the commonest among these patients ,blood group of most of patients was Followed by b ,being the mothers blood group o was the predominant one in this study, this disease was mostly seen in low birth patients (<3 kg )in our study ,higher levels of total serum bilirubin(>200mmole/liter) noticed among these patient

We concluded that ABO incompatibility is a well documented cause of neonatal morbidity in this city finally we recommend performing reticulocyte count , complete blood picture ,total serum bilirubin and direct coombs test in every patient with blood group A or B and mother blood group o sine a lot of complication can be prevented by diagnosing this serious illness.

Keywords: ABO incompatibilty, neonate, Kirkuk, jaundice

## Aims of this study:

Reviewing of ABO incompatibility in healthy neonates with jaundice in daily practice in pediatric hospital in kirkuk government.

## Introduction

*jaundice,*from the old French jaundice, a ward rooted in the Latin ***galbinus,*** meaning greenish yellow ,from ***galbus(1)***
Jaundice is the most common condition that requires medical attention in newborns (1-2 ). The yellow coloration of the skin and sclera in newborns with jaundice is the result of accumulation of unconjugated bilirubin. In most infants, unconjugated hyperbilirubinemia reflects a normal transitional phenomenon. However, in some infants, serum bilirubin levels may excessively rise, which can be a cause for concern because unconjugated bilirubin is neurotoxic and can cause death in newborns and lifelong neurological sequel in infants who survive (kernicterus). For these reasons, the presence of neonatal jaundice frequently results in diagnostic evaluation (1, 2).

Neonatal jaundice may have first been described in a Chinese textbook 1000 years ago. Medical theses, essays, and textbooks from the 18$^{th}$ and 19$^{th}$ centuries contain discussions about the causes and treatment of neonatal jaundice. Several of these texts also describe a lethal course in infants who probably had Rh isoimmunization. In 1875, Orth first described yellow staining of the brain, in a pattern later referred to as kernicterus . **(1-3)**

## Pathophysiology

Neonatal physiologic jaundice results from simultaneous occurrence of the following 2 phenomena:

- Bilirubin production is elevated because of increased breakdown of fetal erythrocytes. This is the result of the shortened lifespan of fetal erythrocytes and the higher erythrocyte mass in neonates.
- Hepatic excretory capacity is low both because of low concentrations of the binding protein ligandin in the hepatocytes and because of low activity of glucuronyl transferase, the enzyme responsible for binding bilirubin to glucuronic acid, thus making bilirubin water soluble (conjugation) .**(2,3)**

Bilirubin is produced in the reticuloendothelial system as the end product of heme catabolism and is formed through oxidation-reduction reactions. Approximately 75% of bilirubin is derived from hemoglobin, but degradation of myoglobin, cytochromes, and catalase also contributes. In the first oxidation step, biliverdin is formed from heme through the action of heme oxygenase, the rate-limiting step in the process, releasing iron and carbon monoxide. The iron is conserved for reuse, whereas carbon monoxide is excreted through the lungs and can be measured in the patient's breath to quantify bilirubin production.**(2,3)**

Next, water-soluble biliverdin is reduced to bilirubin, which, because of the intramolecular hydrogen bonds, is almost insoluble in water in its most common isomeric form (bilirubin IXá Z, Z). Because of its hydrophobic nature, unconjugated bilirubin is transported in the plasma tightly bound to albumin. Binding to other proteins and erythrocytes also occurs, but the physiologic role is probably limited. Binding of bilirubin to albumin increases postnatally with age and is reduced in infants who are ill. **(3, 4)**

The presence of endogenous and exogenous binding competitors, such as certain drugs, also decreases the binding affinity of albumin for bilirubin. A minute fraction of unconjugated bilirubin in serum is not bound to albumin. This free bilirubin is able to cross lipid-containing membranes, including the blood-brain barrier, leading to neurotoxicity. In fetal life, free bilirubin crosses the placenta, apparently by passive diffusion, and excretion of bilirubin from the fetus occurs primarily through the maternal organism. **(3, 4)**

Albumin is bound to a receptor on the cell surface when the bilirubin-albumin complex reaches the hepatocyte, and bilirubin is transported into the cell, where it binds to ligandin. Uptake of bilirubin into hepatocytes increases with increasing ligandin concentrations. Ligandin concentrations are low at birth but rapidly increase over the first few weeks of life. Ligandin concentrations may be increased by the administration of pharmacologic agents such as Phenobarbita **(4)**.

Bilirubin is bound to glucuronic acid (conjugated) in the hepatocyte endoplasmic reticulum in a reaction catalyzed by uridine diphosphoglucuronyltransferase (UDPGT). Monoconjugates are formed first and predominate in the newborn. Diconjugates appear to be formed at the cell membrane and may require the presence of the UDPGT tetramer. **(4, 5)**

Bilirubin conjugation is biologically critical because it transforms a water-insoluble bilirubin molecule into a water-soluble molecule. Water-solubility allows conjugated bilirubin to be excreted into bile. UDPGT activity is low at birth but increases to adult values by age 4-8 weeks. In addition, certain drugs (phenobarbital, dexamethasone, clofibrate) can be administered to increase UDPGT activity. **(5)**

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 increased risk of significant hyperbilirubinemia. Interactions between the Gilbert genotype and hemolytic anemias such as glucose-6-phosphatase dehydrogenase (G-6-PD) deficiency, hereditary spherocytosis, or ABO hemolytic disease also appear to increase the risk of severe neonatal jaundice. **(2-5)**

Once excreted into bile and transferred to the intestines, bilirubin is eventually reduced to colorless tetrapyrroles by microbes in the colon. However, some unconjugation occurs in the proximal small intestine through the action of B-glucuronidases located in the brush border. This unconjugated bilirubin can be reabsorbed into the circulation, increasing the total plasma bilirubin pool. This cycle of uptake, conjugation, excretion, unconjugation, and reabsorption is termed the enterohepatic circulation. The process may be extensive in the neonate, partly because nutrient intake is limited in the first days of life, prolonging the intestinal transit time. **(5, 6)**

Certain factors present in the breast milk of some mothers may also contribute to increased enterohepatic circulation of bilirubin (breast milk

jaundice). Data suggest that the risk of breast milk jaundice is significantly increased in infants who have genetic polymorphisms in the coding sequences of the *UDPGT1A1* or *OATP2* genes. Although the mechanism that causes this phenomenon is not yet agreed upon, evidence suggests that supplementation with certain breast milk substitutes may reduce the degree of breast milk jaundice

- Neonatal jaundice, although a normal transitional phenomenon in most infants, can occasionally become more pronounced. Blood group incompatibilities (e.g., R5: recurrence of jaundice
-

h, ABO) may increase bilirubin production through increased hemolysis. Historically, Rh isoimmunization was an important cause of severe jaundice, often resulting in the development of kernicterus. Although this condition has become relatively rare in industrialized countries following the use of Rh prophylaxis in Rh-negative women, Rh isoimmunization remains common in developing countries.

Nonimmune hemolytic disorders (spherocytosis, G-6-PD deficiency) may also cause increased jaundice, although increased hemolysis appears to have been present in some of the infants reported to have developed kernicterus in the United States in the last 10-15 years. **(5, 6)**

## . Causes of indirect hyperbilirubinemia **( 6,7)**

**A**: .Hemolysis disorders
1. feto-maternal blood incompatibility
2. Gentic causes of hemolysis
A: Hereditary spherocytosis
B: Enzymatic defect (G6PD), py5ruvaate kinase
C: Haemoglobinopathy (thallasemia)
D: Galgectocaemia

3: Drug induced haemolysis (vit k)

**B**: extra vascular blood (petechie), hematoma,pulmonary and cerebral swallowed blood hemorrhage

**C:** Polycythemia
1 chronic fetal hypoxia
2 materno-fetal or feto-fetal transfusions
3 placental transfusions (cord striping)

**D:** Exaggerated enterohepaticcirculation
1 mechanical obstruction
A atresia and stenosis
B hurschprung disease
C meconium ileus
D me conium plug syndrom
2 reduced perstalisis
A fasting
B drugs
C pyloric stenosis
**E:** Reduced hepatic uptake of bilirubin
1 persistence of ductusc venosus shunt
F: decreased bilirubinconjugation]
1 congenital reducto glucourenyl transferase
A familial non hemolytic jaundice
B Gilbert disease
2 enzyme inhibitor galagctoscaemia

# Differentiation between physiological and pathological jaundice (7, 8)

## Physiological :

1: Visible at 2-3 days
Of birth and mostly
At 4-6 days after birth
2: absent after 2, 3-4weeks
For full term and preterm infant
Respectively
3: TSB<12mg/dl (205mmole.liter)
<15mg/dl, 257mmole/ Liter
4: no disorder were found

## Pathological:

1: clinical jaundice in first 24 hr of life
2: total serum bilirubin >>12-15mg/dl or increase by 5 mg/dl a day
3: direct serum bilirubin>>1.5-2mg/dl
4: prolonged jaundice

5: recurrence of jaundice

| Clinical features | RH DISEASE | ABO INCOMPATIBILITY |
|---|---|---|
| **Frequency** | Unusual | Common |
| Pallor | Marked | Minimal |
| Jaundice | Marked | Min-moderate |
| Hydrops | Common | Rare |
| hepatosplenomegally | Marked | Rare |
| Lab features | | |
| Blood group | | |
| Mother | Rh negative | O+ |
| Infant | Rh positive | A+, B+, AB+ |
| Anaemia | Marked | MINIMAL |
| Direct coombs test | Positive | Frequently negative |
| Indirect coombs test | Positive | Usually positive |
| Hyperbilirubinemia | Marked | Variable |
| RBC morphology | Nucleated RBC | Spherocyte |

## Clinical and lab features of immune haemolysis due to Rh disease and ABO- incompatibility (8, 9)

# Hemolytic disease of the newborn (ABO)

In ABO hemolytic disease of the newborn (also known as ABO HDN) maternal IgG antibodies with specificity for the ABO blood group system pass through the placenta to the fetal circulation where they can cause hemolysis of fetal red blood cells which can lead to fetal anemia and HDN. In contrast to Rh disease, about half of the cases of ABO HDN occur in a firstborn baby and ABO HDN does not become more severe after further pregnancies. **(9-10)**

The ABO blood group system is the best known surface antigen system, expressed on a wide variety of human cells. For Caucasian populations about one fifth of all pregnancies have ABO incompatibility between the fetus and the mother, but only a tiny minority develops symptomatic ABO HDN [1]. The latter only occurs in mothers of blood group O because they can produce enough IgG antibodies to cause hemolysis. (**10**)

# Causes:

- Environmental exposure

Anti-A and anti-B antibodies are usually IgM and do not pass through the placenta, but some mothers "naturally" have IgG anti-A or IgG anti-B antibodies, which can pass through the placenta. Exposure to A-antigens and B-antigens, which are both widespread in nature, usually leads to the production of IgM anti-A and IgM anti-B antibodies but occasionally IgG antibodies are produced. **(10, 11)**

- Fetal-maternal transfusion

Some mothers may be sensitized by fetal-maternal transfusion of ABO incompatible red blood and produce immune IgG antibodies against the antigen they do not have and their baby does. For example, when a mother of genotype OO (blood group O) carries a fetus of genotype AO (blood group A) she may produce IgG anti-A antibodies . **(10, 11)**

The father will either have blood group A, with genotype AA or AO, or more rarely, have blood group AB, with genotype AB.

- Blood transfusion

It would be very very rare for ABO sensitization to be caused by therapeutic blood transfusion as a great deal of effort and checking is done to ensure that blood is ABO compatible between the recipient and the donor. **(10, 11)**

**Moderating factors**

In about a third of all ABO incompatible pregnancies maternal IgG anti-A or IgG anti-B antibodies pass through the placenta to the fetal circulation leading to a weakly positive direct Coombs test for the neonate's blood. However, ABO HDN is generally mild and short-lived and only occasionally severe because:

IgG anti-A (or IgG anti-B) antibodies that enter the fetal circulation from the mother find A (or B) antigens on many different fetal cell types, leaving fewer antibodies available for binding onto fetal red blood cells.

Fetal RBC surface A and B antigens are not fully developed during gestation and so there are a smaller number of antigenic sites on fetal RBCs.

# Diagnosis

Routine antenatal antibody screening blood tests (indirect Coombs test) do not screen for ABO HDN. If IgG anti-A or IgG anti-B antibodies are found in the pregnant woman's blood, they are not reported with the test results, because they do not correlate well with ABO HDN. Diagnosis is usually made by investigation of a newborn baby who has developed jaundice during the first day of life.

# PATIENTS AND METHODS

This is prospective study conducted in Kirkuk pediatric general hospital from 15/5/2008 to 15/7/2008 involving all healthy neonates with jaundice admitted to the hospital or referred for evaluation for their jaundice, the total number of patients is 63.

A predesigned format was made and distributed to all residents in the hospital in order not to miss any patient.
After a thorough history and physical examination 5 cc of blood aspirated and sent for total serum bilirubin and fractionation and blood group of baby and complete blood picture including morphology and retics count and finally direct combs test done by adding 50 micromill human anti-globulin to 50 micromill of patient's serum incubating them at 37 degree centigrade for 24 hours if agglutination found the test conceded to be positive.
In order to confirm the positive results we also used the old standard method by o cell take blood group o and wash it 3 times by normal saline
2-3 drop of o cell+normal saline=red color
Serum of patient +0 cell (khon tube)
2:1
Or 4:1
Wait for 45 minute and see agglutination
Then titering
Blood group of the mother was also tested and recorded in the format.
Weight of the patient and his order was also included in the format.
Diagnosis was made upon the followings **(12)**
1: elevated serum indirect bilirubin with normal reticulcyte count and negative coombs test is associated with physiological, breast milk jaundice. **(12)**

2: elevated serum indirect bilirubin with increase of retics count is indication of increase hemolysis seen with ABO Rh incompatibility **(12)**

3: elevation of both direct and indirect bilirubin with negative coombs test and normal retics count is indication of pathological process. **(12)**

Statistical analysis was done based on SPSS (PROPABILTY TEST) program from the internet and it was done by specialist in medical statistics.

# Results

Total number of neonates involved in this prospective study is 63, of these patients 17(26.9%) had physiological jaundice, 5(7.9%) pathological, 14(22.2%) Rh incompatibility, 18(28.5%) got ABO incompatibility, 5(7.95%) haemolysis and those with breast feeding got 4 (6.3%).

**Table (1)**
**Causes of neonatal jaundice**

| Total No. | Physiological | Pathological | Rh incompatibility | ABO incompatibility | Hemolysis | Breast feeding | P value |
|---|---|---|---|---|---|---|---|
| 63 | 33(26.9 %) | 3(7.9%) | 4 (%) | 18 (28.5%) | 2(7.9%) | 3(6.3%) | 0. 02 |

Those with ABO incompatibility account for 28.5 % of total patients (18 patients) sex distribution among these patients was not equal 60- 40%. (Table 2).

**Table (2)**
**Sex distribution among ABO incompatibility cases**

| Total No. | Male patients | Female patients | P value |
|---|---|---|---|
| 18 | 10 (60%) | 8 (40%) | 0.04 |

Regarding the association between the blood groups of neonates and their mothers the results were significant p value <0.04 when mother blood group was o and the neonates A or B groups table (3).

**Table (3)**

**Association between Mother and child blood groups in ABO incompatibility patient**

| Mother blood groups Total No. 18 | | Child blood groups | | |
|---|---|---|---|---|
| | | A +ve | B +ve | P value |
| | O +ve 16 (88.8%) | 10 (62.5 %) | 6(37.5 %) | 0.0 2 |
| | A +ve 2(11.1%) | 0 (0%) | 2 (100%) | 0.1 |

Weight is an important determinate in management of neonatal jaundice in our study 2.5 kilograms was the standard weight those above and below 2.5 kg were equally distributed 50-50 % table (4).

**Table (4)**
**Association between weight and children born with ABO incompatibility**

| Total No | Wt < 2.5 Kg | Wt > 2.5 kg | P value |
|---|---|---|---|
| **18** | **12(66.6%)** | **6(33.4 %)** | **0.0 5** |

Another very important determinant of the management is total serum bilirubin level as it is shown in following table (5).

**Table (5)**

**Level of TSB with children born with ABO incompatibility**

| Total No. | TSB> 200 | TSB< 200 | P value |
|---|---|---|---|
| **18** | **14 (77.7%)** | **4 (22.2%)** | **0.0 4** |

**TSB= total serum billirubin**
**P value < 0.05= significant value**
**P Value > 0.05 = non significant value**

Type of the jaundice

Indirect hyperbilirubinemia was countered in 60 while direct one seen in 3 patents only.

Table (6)

| Number of the patients | Indirect hyperbiliruinmia | Direct hyperbilirubinemia |
|---|---|---|
| 63 | 60 | 3 |
| | | |

# Discussion

In this study we are trying to delineate common causes of neonatal jaundice in Kirkuk region mainly concentrating on ABO -incompatibility as a cause of neonatal jaundice in otherwise healthy neonate

Starting with the first table in our study physiological jaundice was the most common cause encountered among patients followed by ABO-incompatibility, Rh- incompatibility then breast fed and pathological jaundice (direct hyperbilirubinemia) finally other hemolytic disease as comparing with a local study conducted in medical city in Baghdad (Almansor teaching hospital) in 2001 physiological jaundice was the most common cause of neonatal jaundice **(10-13).**

While the Rh was the second common and ABO-incompatibility is the third one this change in the pattern and reduction of Rh- incompatibility is most probably attributed to the use of anti d antibody in all Rh –ve mothers born +ve babies **( 10,13 ).**

In comparing with other study in India by lalita bahl et al **(13)** still the physiological jaundice and ABO is the second one in order and breast milk and other hemolytic disease is third one and Rh- incompatibility is fourth one . The two results were not statistically different.

Michael Srgo et al … in their study conducted in Canada searching for major causes of severe hyper bilirubinmia they found that the cause was ABO– incompatibility followed by G6PD deficiency which supports our opinion about importance of this subject in neonatology. **(1, 13).**

Regarding association of sex with development of neonatal jaundice Male patient with a bit higher level 60% in our study which in comparison with local study **(10) was** done in Baghdad,

male patients were Just the same 59% also another study in Canada **(1)** more afflicted by this disease process the most likely explanation of this phenomenon is:

Male disadvantage theory (Y chromosome effect)
Higher metabolic rates in male patients may be another contributing factor. This theory is enforced by the fact that XY blastocysts and embryos grow at an accelerated rate when compared with XX chromosome bearers an inverse relationship between lifespan and metabolic rate has been established and may reflect significant differences in associated physiological mechanisms. **(14)**

Regarding the incidence of associated blood groups we found that babies with blood group A are most predominate than those with group B and the difference was statistically significant this can be explained on the basis that that blood group A are more common than blood group B **(14,15)**

In this study we found a small group of patient s whose mother were group A their blood group was B since maternal antibody may be formed against b cells if the mother is type A or against A cell if the mother is of type B **(16).**

Body weight was always considered to be one of major determinant of the therapy of neonatal jaundice since those who are underweight or premature patients are more prone to complication of neonatal jaundice hence they need a quicker intervention than those with normal body weight **(17 )**

Most LBW infants develop clinically significant hyperbilirubinemia (jaundice) requiring treatment **(17).**

Hyperbilirubinemia develops as a result of increased red blood cell turnover and destruction in the context of an immature liver that has physiologically impaired conjugation and elimination of bilirubin **(17, 18)**

In addition, most preterm infants have reduced bowel motility due to inadequate oral intake, which delays elimination of bilirubin-containing meconium, coupled with increased enterohepatic circulation of conjugated bilirubin that enters the intestinal tract. **(17, 18)**

These complications of prematurity, in addition to typical conditions that cause jaundice (e.g., ABO incompatibility, Rh disease, sepsis, inherited diseases), is thought to place these infants at higher risk for kernicterus at levels of bilirubin far below those in more mature infants, although specific serum bilirubin levels that are safe versus toxic have never been elucidated **(18,19 )**

Coming into most important determinant of therapy in patients with jaundice due to ABO incompatibility which is the level of total serum bilirubin **( 19,20** ) and its fractionation in our results we found that level of TSB is more than 200 moles/liter in our patients was much higher than those with below 200mmole /liter indicating that ABO – incompatibility is one of major causes of sever jaundice in a study conducted in India**(13)** the TSB level in ABO- incompatibility was more than in any cause of jaundice**(18),** and in the study it signify ABO- incompatibity as a major cause significant jaundice **.(21-25)**

## CONCLUSIONS :

With regarding total jaundice patients, ABO-incompatibility is a major cause of morbidity in Kirkuk region

It should be suspected in every baby with blood group **A** or **B** with blood group o mothers since these children are more risk for hyperbilirubinemia requiring treatment.

## RECOMINDATIONS:

Newborn with blood group A are to kept in consideration being the most vulnerable to develop ABO- incompatibility.

Blood grouping to be done in all patients and mothers referred to the hospital for neonatal jaundice management.

The study is self-funded
There is no conflict of interest between the authors

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