Neonatal jaundice: study of its associated factors and treatment outcomes among pediatric in Baquba city

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Abstract

Introduction: Neonatal jaundice affecting up to 50–60% of full-term and 80% of preterm newborns within their first week of life. While usually harmless. The newborn's skin, mucous membranes, and eyes turn yellow due to elevated levels of bilirubin in the blood, leading to its accumulation on the skin and mucous membranes. Bilirubin is a byproduct of the breakdown of old red blood cells during the early neonatal period.

Materials and methods: This is a prospective randomized study to evaluate the cause and the possible risk factors that contribute to with treatment outcome of jaundice among neonate. The study was evaluated between December/ 2023 and January 2024 in AL-Batoul Hospital for Obstetrics and Gynecology in Baquba/ Diyala/ Iraq. Data from (75) neonate (42) male and (33) female who attempted AL-Batoul hospital suffering from jaundice were selected for the study.

Results: our study and it show that 42(56%) of them were male and 33(44%) were female, most of them were living in urban places 44(58.6%) and the rest of

them 31(41.4%) in rural places. Most of the neonate were admitted to the hospital after 2-7 days from their life 33(44%), 26(34.6%) admitted within their first 24hrs of life and about 16(21.4%) admitted after 7 days from their lives. About 52(69%) of them born in the hospital and 23(31%) were out born. The study show that most of the neonate born with weight over 2.5kg 47(63%) and 28(37%) born with weight less than 2.5kg and its show also that about 53(71%) born after 37 weeks and 22(29%) born before they complete 37 weeks. 72(96%) improved from jaundice after been treated with phototherapy and only 3(4%) had no improvement from the disease.

Conclusion: Neonatal jaundice is one of the most common disease between newborn babies as it appear during the first few days of the baby life, phototherapy is the treatment of choice for jaundice and most of the cases show improvement in our study it show that most of the neonate show improvement from phototherapy and that maybe due to early admission due to higher knowledge of the mother and there was little ABO and Rh incompatibility between the mother and fetus.

Introduction

Jaundice is defined as yellowing of the skin, mucous membranes, and sclera due to the deposition of yellow-orange bile pigment. H. bilirubin (Muhammad *et al.,* 2016).

The term jaundice derives from the French word "jaune," which means yellow. It is the most commonly encountered medical problem in the first two weeks of life and a common cause of readmission to the hospital after birth (Gale R *et al.,* 2001).

Approximately 60% of term and 80% of preterm newborns develop clinical jaundice in the first week after birth. In most cases, it is a mild, transient, and self-limiting condition and resolves without treatment referred to as "physiological jaundice." However, it is imperative to distinguish this from a more severe form called "pathological jaundice." Failure to identify and treat this entity may result in bilirubin encephalopathy and associated neurological sequelae (Mitra S and Rennie J, 2017).

Jaundice is the most common physical abnormality in the first week of life. Her 25–50% of all term newborns and a higher proportion of preterm infants develop clinical jaundice (Dayama *et al.*, 2015; Obeagu, 2019).

Enzyme immaturity and limited substrate availability are temporary and normalize in the first few days of life. In breastfed infants, prolonged unconjugated hyperbilirubinemia beyond the third week of life in healthy neonates is a normal and regularly occurring extension of physiologic jaundice. This is called breast milk jaundice. Human breast milk factors that may be associated with the etiology of breast milk jaundice include pregnane-3α, 20β-diol, interleukin IL1β, β-glucuronidase, epidermal growth factor, and α-fetoprotein (Stephanie B *et al.,* 2021).

Inadequate caloric intake due to maternal and/or infant breastfeeding problems can also increase serum levels of unconjugated bilirubin.

A newborn has a bilirubin formation rate two to three times higher than that of an adult, largely due to the high hematocrit and short life span of the newborn's red blood cells. Decreased bilirubin excretion is due to impaired ability of the neonatal liver to conjugate bilirubin and increased enterohepatic recirculation. Jaundice can result from an increase in either unconjugated (indirect) or conjugated (direct) bilirubin (Willy, 2021).

Unconjugated hyperbilirubinemia (UHB) is the cause of clinical jaundice in most neonates, but some infants with jaundice have conjugated hyperbilirubinemia (CHB), which is always pathological and signifies an underlying medical or surgical cause. The etiology of pathological UHB and CHB is vast and varied. Preterm infants and those born with congenital enzyme deficiencies are particularly prone to the harmful effects of unconjugated bilirubin on the central nervous system (Kaplan M *et al.,*2007: Moncrieff MW and Dunn J, 2006).

Severe hyperbilirubinemia can cause bilirubin-induced neurological dysfunction (BIND) and, if not treated adequately, may lead to acute and chronic bilirubin encephalopathy (Bhutani VK and Wong R, 2015).

Phototherapy and exchange transfusions are the mainstay of treatment of UHB, and a subset of patients also respond to intravenous immunoglobulin (IVIG). Treatment of CHB is more complex and depends mainly on the etiology. Despite advances in care and management of hyperbilirubinemia, it remains a significant cause of morbidity and mortality (Ip S *et al.,* 2004).

Aim of the study

The objective of this study was to determine the causes, extent and influences linked to the treatment outcomes of neonatal jaundice

Chapter One
Literature review

1.1. Types of jaundice

1.1.1. Physiological jaundice

Physiological jaundice is the most common type of jaundice in neonates. It typically occurs within the first few days after birth and resolves on its own within two weeks (Dennery *et al.,* 2011). This type of jaundice is usually benign and does not lead to serious complications. However, in rare cases where bilirubin levels become dangerously high, there is a risk of neurodevelopmental abnormalities, including intellectual deficits, athetosis, and hearing loss. Physiological jaundice is characterized by predominantly unconjugated bilirubin, with serum levels typically not exceeding 15 mg/dl. Recent guidelines have suggested that even higher bilirubin levels, up to 17 or 18 mg/dl, may still be considered normal and physiological in otherwise healthy full-term neonates (Clarkson *et al.,* 2013)

1.1.2. Breast feeding/milk jaundice

Breast feeding/milk jaundice is another type of jaundice that can affect neonates and infants who are exclusively breastfed. Similar to physiological jaundice, breastfeeding jaundice typically appears within the first few days after birth, peaking at around one week of age. However, it can persist longer than physiological jaundice, often not resolving completely until the third or fourth week of life. Infants with breastfeeding jaundice may have higher levels of bilirubin compared to physiological jaundice, and in some cases, the jaundice may recur as long as breastfeeding continues (Gartner LM, Lee KS, 2014).

Although it is rare for breastfeeding jaundice to lead to toxic levels of bilirubin, in severe cases, it can result in serious cerebral lesions known as nuclear jaundice. This condition may manifest with mental retardation, behavioral disorders, and hearing loss (Schneider AP , 2012).

It is estimated that up to 30% of breastfed infants may develop mild jaundice within the first three weeks of life, and in some cases, the jaundice may persist for up to three months. However, reducing the frequency of breastfeeding can increase the risk and severity of physiological jaundice. Therefore, the recommended management for breastfeeding jaundice in an otherwise healthy full-term baby is to encourage mothers to continue breastfeeding at least ten times daily (Schneider AP , 2012).

The composition of the mother's breast milk can also influence the occurrence of hyperbilirubinemia in neonates. Approximately 4% of exclusively breastfed infants may develop jaundice within the first three weeks of life, with bilirubin levels exceeding 10 mg/dl. If jaundice persists for an extended period, it should be managed as prolonged jaundice. In cases of breast milk jaundice, bilirubin is typically unconjugated, which may require careful differentiation from other causes of jaundice. It is important to advise mothers to increase breastfeeding frequency until bilirubin levels normalize. However, if bilirubin levels exceed 20 mg/dl, discontinuation of breastfeeding is recommended to prevent potential permanent neurological complications (Gartner LM, Lee KS, 2014).

1.1.3. Hemolytic jaundice

1. Rh factor hemolytic disease

In cases where alloimmunization of maternal RBCS, Rhesus hemolytic disease of the newborns (RHDN) occurs. In these cases, the mother's body produces antibodies that attack specific antigens on the RBCs of the fetus, most likely, the Rh antigens. This is most likely to occur when an Rh negative mother has an Rh positive fetus. In these cases, the mother produces antibodies against the Rh antigen, and these antibodies can cross the placenta and enter the circulation of the fetus. This will cause the fetus to develop a clinical picture that ranges from mild hemolytic anemia, to severe hemolytic anemia followed by fetal hydrops. Infants who have a risk of developing Rhesus hemolytic disease

of the newborns should be early investigated and treated. Investigations for these infants include packed cell volume, blood group, Rh typing, serum bilirubin, and reticulocytes count. Immediately following birth, these patients should be initiated on phototherapy, which should continue until the level of bilirubin decreases significantly (Stockman JA, 2011).

2. ABO incompatibility

It is estimated that ABO incompatibility between the fetus and the mother can occur in up to 20% of pregnancies, and results from an O mother and who has an A or B fetus. Therefore, it is important to closely monitor mothers who have an O blood group for at least three days after birth. However, it is not generally recommended to perform routine screening of cord blood in their infants. ABO incompatibility jaundice usually starts to appear at the age of one day. If it appears earlier, or it becomes severe, further investigations must be done to rule out more severe etiologies. Intensive phototherapy is indicated in these cases (Murray NA, 2007).

3. G6PD deficiency

The management of spherocytosis, G6PD deficiency, and similar diseases is similar to the management of ABO incompatibility. Of these, the most common one is G6PD deficiency. It causes significant dysfunction of the hexose monophosphate pathway within the RBCs leading to hemolysis. It should be suspected in any neonate who has a family history with hemolytic jaundice, or who originates from are where G6PD is prevalent (Kaplan M, Hammerman C, 2010).

1.1.4. Pathological jaundice

Pathological jaundice is characterized by elevated bilirubin levels beyond the normal range, necessitating medical intervention. It typically manifests as jaundice appearing within 24 hours after birth, with serum bilirubin increasing by more than 5 mg/dl per day. Additionally, peak bilirubin levels surpass the

expected normal range, and clinical jaundice persists for over two weeks. Presence of conjugated bilirubin, evident through dark urine staining the clothes, further categorizes the jaundice as pathological (Boyd S, 2014).

1.2. Etiology of jundaice

There are two distinct types of Neonatal hyperbilirubinemia:

1.2.1. Unconjugated hyperbilirbinemia (UHB) or indirect hyperbilirbinemia

Bilirubin is formed from the catabolism of heme. About 75% of bilirubin is derived from the breakdown of hemoglobin from aged red blood cells. The remainder results from ineffective erythropoiesis and the breakdown of heme proteins such as cytochromes, myoglobin, nitric oxide synthase, glutathione peroxidase, and catalase. There are two types of neonatal hyperbilirubinemia.

Unconjugated hyperbilirubinemia is the more common type and can be physiological or pathological. Physiological jaundice accounts for 75% of neonatal hyperbilirubinemia and results from physiological alterations in neonatal bilirubin metabolism. Healthy adults have normal total serum bilirubin (TSB) levels below 1 mg/dL, in contrast to neonates, where TSB levels are physiologically high. Healthy full-term neonates also have an increased bilirubin load due to increased red blood cell (RBC) mass and shortened RBC lifespan. Bilirubin clearance is also affected by impaired activity of uridine diphosphate glucuronosyltransferase (UGT), an enzyme required for bilirubin conjugation. UGT enzymes have activity in neonates that is approximately 1% of adult levels. In addition, these infants also have increased enterohepatic circulation, further contributing to elevated TSB levels. Physiological jaundice usually develops 24 hours after birth, peaks at approximately 48–96 hours, and in term infants he resolves in 2–3 weeks (Lawrence, 2002).

Jaundice is considered pathological if it presents on the first day of life, TSB is more than the 95th centile for age based on age-specific bilirubin

nomograms, levels rise by more than 5 mg/dL/day or more than 0.2 mg/dL/hour, or jaundice persists beyond 2 to 3 weeks in full-term infants (Lawrence M and Gartner M.D, 2002).

Based on the mechanism of bilirubin elevation, the etiology of unconjugated hyperbilirubinemia can be subdivided into the following three categories:

1.2.1.1. Increased Bilirubin Production

Immune-mediated hemolysis - Includes blood group incompatibilities such as ABO and Rhesus incompatibility. Non-immune mediated hemolysis - includes RBC membrane defects like hereditary spherocytosis and elliptocytosis; RBC enzyme defects like glucose-6-phosphate dehydrogenase (G6PD) deficiency; pyruvate kinase deficiency; sequestration like cephalohematoma, subgaleal hemorrhage, Intracranial hemorrhage; polycythemia, and sepsis.

1.2.1.2. Decreased Bilirubin Clearance

Crigler-Najjar type I & II, and Gilbert syndrome.

1.2.1.3. Miscellaneous Causes

Other miscellaneous etiologies include the infant of a mother with diabetes, congenital hypothyroidism, drugs like sulfa drugs, ceftriaxone, and penicillins, Intestinal obstruction, pyloric stenosis, breast milk jaundice, breastfeeding jaundice.

Exaggerated hemolysis, either immune or non-immune mediated, is the most common cause of pathological hyperbilirubinemia in newborns. Immune-mediated hemolysis is seen with blood group incompatibility such as ABO/RH incompatibility and leads to hemolytic disease of newborns (HDN). In HDN, due to ABO incompatibility, preformed maternal anti-A and anti-B antibodies of immunoglobulin (Ig) G subclass cross the placenta and cause hemolysis and UHB in newborns with blood type A, B, or AB. Although the direct Coombs

test is used to aid diagnosis, the sensitivity and positive predictive value for predicting severe UHB are low (Shahid R and Graba S,2012).

ABO incompatibility between mother and fetus exists in about 15% of pregnancies, but HDN due to ABO incompatibility is seen only in 4% of newborns with ABO incompatibility (Desjardins L *et al.*, 2009).

In Rhesus (Rh) incompatibility, an Rh-negative mother who has been previously exposed to Rh-positive RBCs usually from a previous pregnancy or miscarriage, becomes sensitized and develops antibodies against Rh antigen. Initially, sensitization produces IgM antibodies that cannot cross the placenta. However, during subsequent pregnancies, the antibody class switch produces IgG antibodies which can cross the placenta, causing RBC hemolysis in the fetus with Rh-positive blood. The Rh antigen is very immunogenic, and the resultant HDN is usually severe, often leading to hydrops in fetuses or severe UHB in newborns. The American College of Obstetricians and Gynecologists (ACOG) has recommended that all Rh-negative pregnant women receive anti-D immune globulin at 28 weeks of gestation and again following delivery if the infant is Rh-positive/unknown (ACOG practice bulletin, 1999).

Breast milk jaundice and breastfeeding jaundice are two other common etiologies of UHB in newborns. Breastfeeding jaundice, also known as breastfeeding failure jaundice, occurs in the first week of life and is due to inadequate intake of breast milk leading to dehydration and sometimes hypernatremia (Leung AK and Sauve RS, 2009).

Breastfeeding failure leads to decreased intestinal motility and decreases the elimination of bilirubin in the stool or meconium. Breast milk jaundice occurs late in the first week, peaks in the second, and usually resolves by two weeks of age. It is thought to be mainly due to inhibition of the UGT enzyme by pregnanediol and deconjugation of conjugated bilirubin in the intestines by beta-glucuronidase present in breast milk (Preer GL and Philipp BL, 2011).

1.2.2. Conjugated Hyperbilirubinemia (CHB) or Direct Hyperbilirubinemia

Conjugated hyperbilirubinemia, also known as neonatal cholestasis, manifests with elevated serum conjugated (direct) bilirubin levels (> 1.0 mg/dL) and results from impaired hepatobiliary function. Differentiating CHB from unconjugated hyperbilirubinemia is crucial due to the pathological nature of cholestatic jaundice/CHB, necessitating prompt evaluation and intervention (Fawaz *et al.*, 2017).

The causes of neonatal cholestasis/CHB encompass a wide range of etiologies, categorized as follows (Fawaz et al, 2017):

1. Obstruction of Biliary Flow

- Biliary atresia
- Choledochal cysts
- Neonatal sclerosing cholangitis
- Neonatal cholelithiasis

2. Infections

- Cytomegalovirus (CMV)
- Human immunodeficiency virus (HIV)
- Rubella virus
- Herpes virus
- Syphilis
- Toxoplasmosis
- Urinary tract infection (UTI)
- Septicemia

3. Genetic Causes

- Alagille syndrome
- Alpha-1 antitrypsin deficiency
- Galactosemia

- Fructosemia
- Tyrosinemia type 1
- Cystic fibrosis
- Progressive familial intrahepatic cholestasis (PFIC)
- Aagenaes syndrome
- Dubin-Johnson syndrome
- Bile acid synthesis disorders (BASD)

4. Miscellaneous

- Idiopathic neonatal hepatitis
- Parenteral nutrition-induced cholestasis
- Gestational alloimmune liver disease/neonatal hemochromatosis
- Hypotension

Biliary atresia emerges as the most prevalent cause of conjugated hyperbilirubinemia in infants. Its incidence varies across regions, with reported frequencies ranging from 1 in 6,000 to 1 in 12,000 live births. Early diagnosis, often facilitated by ultrasonography, is critical for optimizing outcomes with interventions such as the Kasai operation. Choledochal cysts, neonatal sclerosing cholangitis, and neonatal cholelithiasis represent other notable etiologies of CHB (Pan DH, Rivas Y, 2017).

Infectious causes, including CMV, syphilis, and UTI, underscore the importance of thorough evaluation and appropriate serological testing in neonates presenting with cholestasis. Genetic disorders such as Alagille syndrome, alpha-1 antitrypsin deficiency, and metabolic disorders like galactosemia and tyrosinemia type 1 further contribute to the spectrum of CHB etiologies (Plosa et al, 2012).

Progressive familial intrahepatic cholestasis (PFIC) encompasses a group of genetic disorders characterized by cholestasis, while parenteral nutrition-associated cholestasis (PNAC) underscores the iatrogenic implications of

prolonged parenteral nutrition in preterm infants. Gestational alloimmune liver disease (GALD) represents a fulminant alloimmune disorder associated with significant morbidity and mortality (Jesina D, 2017).

The term idiopathic neonatal hepatitis is reserved for cases where the underlying cause of cholestasis remains elusive despite extensive diagnostic workup. However, advancements in diagnostic modalities continue to elucidate previously unidentified causes of neonatal cholestasis, reducing the prevalence of idiopathic cases (Pan *et al.,* 2010).

1.3. Diagnosis of jaundice

Diagnosis of jaundice typically involves a combination of medical history, physical examination, and laboratory tests:

1.3.1. Medical history

The evaluation of neonates with jaundice begins with a comprehensive history, encompassing birth details, family history, onset of jaundice, and maternal serologies. Observation of stool color and urine presence, along with assessment for pruritus, can offer insights into the type of jaundice present. The American Academy recommends universal screening of all newborns for jaundice, identifying risk factors for severe hyperbilirubinemia. Major risk factors include pre-discharge bilirubin in the high-risk zone, jaundice within the first 24 hours, blood group incompatibility, gestational age of 35 to 36 weeks, previous sibling with phototherapy, cephalhematoma, exclusive breastfeeding, and East Asian race. Prematurity is also a known risk factor (Maisels et al, 2009).

To assess jaundice, newborns should ideally be examined in daylight. However, reliance solely on clinical assessment may be unreliable, particularly in cases of phototherapy or dark skin. Therefore, clinically significant jaundice should be confirmed with a total serum bilirubin or transcutaneous bilirubin measurement. A focused physical examination should aim to identify the cause of pathological jaundice, including evaluation for pallor, petechiae,

cephalhematoma, bruising, hepatosplenomegaly, weight loss, and signs of dehydration (Dennery *et al.*, 2011). Infants with jaundice should also be assessed for signs of bilirubin encephalopathy, such as poor feeding, lethargy, altered sleep, abnormal tone, or seizures. It's important to note that up to 15% of neonates with kernicterus may be clinically asymptomatic. Certain etiologies of neonatal cholestasis may involve multiple systems, and signs of such involvement should be sought during physical examination to aid in diagnosis and guide specific work-up (Johnson L, Bhutani VK, 2010).

1.3.2. Physical examination

During a physical examination, neonatal jaundice typically becomes noticeable first in the face and forehead, with the color becoming evident upon applying pressure to the skin, revealing the underlying hue. Gradually, jaundice spreads to the trunk and extremities, a progression described even in medical texts dating back to the 19th century. The disappearance of jaundice follows the opposite pattern. While the exact explanation for this phenomenon remains unclear, proposed factors include changes in bilirubin-albumin binding related to pH and variances in skin temperature and blood flow. This progression is considered clinically useful, as visible jaundice in the lower extremities often indicates the need for bilirubin level assessment, either via serum analysis or noninvasive transcutaneous bilirubinometry (Knudsen A, 2010)

However, recent research from the author's group was unable to confirm this purported cephalocaudal progression of jaundice. Measurements of dermal jaundice on the forehead, sternum, and symphysis did not reveal any discernible cephalocaudal trend.

In most cases, the primary physical finding is a yellow discoloration of the skin. More severe jaundice may be accompanied by drowsiness. Brainstem auditory-evoked potentials may show abnormalities, such as prolonged latencies or decreased amplitudes (Purcell N, Beeby PJ, 2009).

Signs of neurological involvement, such as changes in muscle tone, seizures, or alterations in cry characteristics, in a markedly jaundiced infant are concerning and necessitate immediate attention to prevent kernicterus. In such cases, prompt initiation of phototherapy is recommended, regardless of pending laboratory results. Hepatosplenomegaly, petechiae, and microcephaly may indicate underlying conditions such as hemolytic anemia, sepsis, or congenital infections, warranting further diagnostic evaluation. These conditions may exacerbate neonatal jaundice and require appropriate management (Bhutani *et al.,* 2004).

1.3.3. Laboratory investigations

Laboratory investigations are critical for assessing and managing neonatal jaundice. Below are essential laboratory tests commonly utilized (Moyer *et al.,* 2004):

1. Total Serum Bilirubin (TSB) Levels

TSB levels provide a quantitative measure of bilirubin concentration in the blood, serving as a jaundice indicator. Typically, spectrophotometry or other colorimetric techniques determine these levels (Moyer *et al.,* 2004).

2. Direct (Conjugated) Bilirubin

Direct bilirubin quantifies the conjugated bilirubin portion, aiding in differentiating jaundice types. Elevated direct bilirubin levels may indicate cholestasis or hepatic dysfunction (Moyer *et al.,* 2004).

3. Indirect (Unconjugated) Bilirubin

Indirect bilirubin measurement outlines the unconjugated fraction, facilitating jaundice etiology diagnosis (Moyer *et al.,* 2004).

4. Complete Blood Count (CBC)

CBC analysis may unveil hemolysis or anemia signs, contributing to elevated bilirubin levels. Supplementary diagnostic insights come from

parameters like reticulocyte count and red blood cell morphology (Moyer *et al.*, 2004).

5. Blood Group and Rh Typing

Identifying the neonate's blood group and Rh type is crucial, especially in ABO or Rh incompatibility scenarios (Moyer *et al.*, 2004).

6. Coombs Test

The Coombs test identifies antibodies presence on red blood cell surfaces, indicative of hemolytic disease in newborns (Moyer et al, 2004).

7. Liver Function Tests (LFTs)

LFTs assess liver enzyme concentrations, including ALT and AST, and hepatic function markers like albumin and alkaline phosphatase. Abnormal LFT results may suggest hepatic dysfunction or cholestasis pathology (Moyer *et al.*, 2004).

8. Urinalysis

Urinalysis is an analysis of the urine and is a very useful test in the diagnosis of screening many diseases (Moyer *et al.*, 2004).

1.4. Imaging Studies

1. Ultrasound

Using sound waves, ultrasound is a non-invasive imaging technique to assess the liver, gallbladder, and pancreas. It excels in detecting gallstones and dilated bile ducts, and can also reveal liver and pancreatic abnormalities (SUMMERSKILL WH, JONES FA, 2007).

2. Computerized Tomography (CT) Scan

Similar to X-rays, CT scans offer detailed images of abdominal organs. While not as effective as ultrasound for gallstone detection, CT scans can identify various liver, pancreas, and abdominal abnormalities (SUMMERSKILL WH, JONES FA, 2007).

3. Cholescintigraphy (HIDA Scan)

This imaging study utilizes a radioactive substance to evaluate the gallbladder and bile ducts (SUMMERSKILL WH, JONES FA, 2007).

4. Magnetic Resonance Imaging (MRI)

MRI employs a magnetic field to examine abdominal organs, providing detailed imaging of the bile ducts (SUMMERSKILL WH, JONES FA, 2007).

5. Endoscopic Retrograde Cholangiopancreatography (ERCP)

ERCP involves inserting an endoscope with a camera through the mouth into the small intestine. Dye is injected into the bile ducts while X-rays are taken, aiding in identifying stones, tumors, or bile duct narrowing (SUMMERSKILL WH, JONES FA, 2007).

1.5. Liver Biopsy

A minimally invasive procedure, liver biopsy involves inserting a needle into the liver under local anesthesia. Ultrasound may guide needle placement. The obtained liver tissue sample is examined by a pathologist to diagnose conditions such as liver inflammation, cirrhosis, and cancer (SUMMERSKILL WH, JONES FA, 2007).

1.6. Risk factor

Risk factors associated with neonatal jaundice include

1. Prematurity

Premature infants are at higher risk due to their underdeveloped liver function, which may result in inadequate bilirubin processing (Keren *et al.*, 2005).

2. Blood type incompatibility

Rh or ABO incompatibility between the mother and baby's blood types can lead to increased breakdown of red blood cells and subsequent jaundice (Keren *et al.*, 2005).

3. Exclusive breastfeeding

Breastfeeding jaundice can occur in newborns who are exclusively breastfed, possibly due to inadequate milk intake or delayed passage of meconium (Keren *et al.*, 2005).

4. East Asian ethnicity

Infants of East Asian descent have an increased risk of neonatal jaundice (Keren *et al.*, 2005).

5. Sibling history

Having a sibling who experienced jaundice requiring treatment increases the likelihood of neonatal jaundice in subsequent siblings (Keren *et al.*, 2005).

6. Cephalohematoma or bruising during birth

Trauma during delivery can lead to increased breakdown of red blood cells and subsequent jaundice (Keren *et al.*, 2005).

7. Maternal diabetes

Infants born to mothers with diabetes, especially if poorly controlled, are at increased risk of neonatal jaundice (Mohammad Beigi *et al.*, 2007).

8. Polycythemia

Excessive red blood cell production can lead to increased bilirubin levels and jaundice (Steiner LA, Gallagher PG, 2007).

9. Male gender

Male infants have a slightly higher risk of developing jaundice compared to females.

10. Certain medications

Some medications taken by the mother during pregnancy or administered to the newborn after birth may increase the risk of jaundice (Steiner LA, Gallagher PG, 2007).

1.7. Treatment / Management

1.7.1. Treatment of Unconjugated Hyperbilirubinemia

Phototherapy and exchange transfusion are the primary approaches for managing unconjugated hyperbilirubinemia.

1.7.1.1. Phototherapy

Phototherapy is the initial treatment choice for pathological unconjugated hyperbilirubinemia. It effectively reduces total serum bilirubin (TSB) levels, mitigating the risk of bilirubin toxicity and obviating the need for exchange transfusion (AAPS, 2004). The efficacy of phototherapy depends on factors such as light dose, wavelength, and the extent of infant's body surface exposed to light. Phototherapy units emitting light in the blue-green spectrum (460 to 490 nm) facilitate bilirubin photoisomerization, promoting its conversion into lumirubin, a precursor for excretion. Measures to optimize phototherapy include shielding the infant's eyes, ensuring adequate hydration, and maximizing skin exposure to light. Although generally safe, phototherapy may lead to adverse effects such as rash, dehydration, and retinal damage (Maisels *et al.*, 2012).

1.7.1.2. Exchange Transfusion

Exchange transfusion is the secondary intervention for severe unconjugated hyperbilirubinemia unresponsive to phototherapy or when initial TSB levels indicate the need. This procedure involves replacing a portion of the neonate's blood with cross-matched donor blood, effectively removing bilirubin and hemolytic antibodies from circulation (Patra *et al.*, 2004). Close monitoring of vital signs and laboratory parameters is essential during exchange transfusion to detect and manage potential complications like electrolyte imbalances and cardiac arrhythmias. Complications may also include blood-borne infections and thrombocytopenia. Phototherapy should be resumed post-exchange transfusion until bilirubin levels reach a safe threshold for discontinuation (Patra *et al.*, 2004).

1.7.1.3. Intravenous Immunoglobulin (IVIG)

IVIG administration is reserved for cases of immune-mediated hemolysis contributing to unconjugated hyperbilirubinemia. IVIG coats Fc receptors on red blood cells, preventing their hemolysis. Its use is considered when TSB levels remain close to the exchange threshold despite intensive phototherapy. However, the efficacy of IVIG in reducing the need for exchange transfusion is uncertain (Gottstein R, Cooke RW, 2003).

1.7.2. Treatment of Conjugated Hyperbilirubinemia

The management of conjugated hyperbilirubinemia varies depending on the underlying cause (Serinet *et al.*, 2009):

1. Biliary Atresia: Kasai operation (hepatic portoenterostomy) is the preferred treatment within the first two months of life to establish an alternative biliary drainage pathway.
2. Infectious Causes: Specific antimicrobial therapy is indicated.
3. Bile Acid Synthetic Disorders (BASDs): Treatment with cholic acid and chenodeoxycholic acid is often effective.
4. Genetic Abnormalities of Liver Enzymes (GALD): IVIG and exchange transfusion may be beneficial.
5. Liver Transplant: Curative but technically challenging in infants.
6. Parenteral Nutrition-Induced Cholestasis: Managed by cyclic parenteral nutrition, minimizing exposure duration, and early initiation of enteral feeds with reduced manganese and copper content (Serinet *et al.*, 2009).

Chapter Two
Materials and methods

2.1. Study design

This is a prospective randomized study to evaluate the cause and the possible risk factors that contribute to with treatment outcome of jaundice among neonate. The study was evaluated between December/ 2023 and January 2024 in AL-Batoul Hospital for Obstetrics and Gynecology in Baquba/ Diyala/ Iraq.

2.2. Materials and Methods

Data from (75) neonate (42) male and (33) female who attempted AL-Batoul hospital suffering from jaundice were selected for the study.

Detailed informations involved, sex, gestational age, weight at birth, place of birth, Post-natal age at admission, type of feeding, neonate blood type, hospital stay along with maternal information involved age, blood type and mood of delivery. Lab data involved total serum bilirubin were collected and information about phototherapy outcome was also collected. All these information were obtained using special designed data sheet (appendix 1).

2.3. Statistical analysis

The data was analyzed by using spss (version 24) to calculate the frequency and percentage of the data.

Chapter Three
Results

3.1. Neonate socio-demographic characteristics

Table (3,1) represent the socio-demographic characteristics of the (75) neonate involved in our study and it show that 42(56%) of them were male and 33(44%) were female, most of them were living in urban places 44(58.6%) and the rest of them 31(41.4%) in rural places. Most of the neonate were admitted to the hospital after 2-7 days from their life 33(44%), 26(34.6%) admitted within their first 24hrs of life and about 16(21.4%) admitted after 7 days from their lives. About 52(69%) of them born in the hospital and 23(31%) were out born. In order to see the time they spent in the hospital before getting better the study show that 43(57%) of the neonate spent more than 7 days in the hospital and 32(43%) spent less than 7 days in the hospital.

Table (3,1): Socio-demographic characteristics of neonates

Characteristics		**Frequency**	**Percentage%**
Sex	Male	42	56%
	Female	33	44%
Residence	Rural	31	41.4%
	urban	44	58.6%
Post-natal age at admission	Within 24 hrs	26	34.6%
	2-7 days	33	44%
	>7 days	16	21.4%
Origin of admission	In born	52	69%
	Out born	23	31%
Length of hospital stay	<7 days	32	43%
	>7days	43	57%

3.2. Maternal characteristic

In order to study the effect of maternal characteristic on the cause of the disease for then neonate, our result show that 38(51%) of the mothers were between 20-34 years old, 28(37%) were under 20 years and only 9 (12%) were older than 35 years old. The study show a small variation between their education level 29(39%) had college degree, 22(29%) had a high school degree and 24 (32%) had primary school degree. Most of the women deliver their child through vaginal delivery 45(60%) and 30(40%) had CS. 54(72%) of them deliver their child in hospital and 21(28%) deliver at home.

Table (3,2): Maternal characteristics

Characteristics		**Frequency**	**Percentage%**
Maternal age	<20yrs	28	37%
	20-34yrs	38	51%
	≥35yrs	9	12%
Education level	Primary	24	32%
	Secondary	22	29%
	College	29	39%
Mode of delivery	Vaginal delivery	45	60%
	CS	30	40%
Placed of delivery	Home	21	28%
	Hospital	54	72%

3.3. Neonatal characteristics for neonate involved in the study

In an attempt to see the effect of the neonate characteristic on having the disease the study show that most of the neonate born with weight over 2.5kg

47(63%) and 28(37%) born with weight less than 2.5kg and its show also that about 53(71%) born after 37 weeks and 22(29%) born before they complete 37 weeks. We attempt to see if the Rh incompatibility has an effect on the neonate in having jaundice and in our result 50(67%) had no Rh incompatibility and 25(33%) had Rh incompatibility. Total serum bilirubin is the detector of the disease and in our study about 43(57%) of the neonate had TSB under 20mg/dl and 32(43%) their TSB were over 20mg/dl. In our study 46(62%) of the neonate is breast feeding and 25(33%) had bottle feeding and only 4(5%) had mixed feeding.

Table (3,3): Neonate characteristics among neonates treated at AL-Batoul hospital

Characteristics		**Frequency**	**Percentage%**
Birth weight	< 2.5kg	28	37%
	≥2.5kg	47	63%
Gestational age	< 37 weeks	22	29%
	≥37 weeks	53	71%
Abo incompatibility	Yes	32	43%
	No	43	57%
Rh incompatibility	Yes	25	33%
	No	50	67%
Total serum bilirubin	<20mg/dl	43	57%
	≥20mg/dl	32	43%
Infant feeding	Breast milk	46	62%
	Bottle feeding	25	33%
	Mixed feeding	4	5%

3.4. Treatment outcome with phototherapy

Jaundice treated with phototherapy and in order to see the outcome of the treatment the results show that 72(96%) improved from jaundice after been treated with phototherapy and only 3(4%) had no improvement from the disease.

Table (3,4): Treatment outcome with phototherapy

Treatment outcome	Frequency	Percentage %
Improved	72	96%
Dead	3	4%

Chapter Four
Discussion

4.1. Discussion

One of the most common diseases among newborns is jaundice, which can affect more than half of them (50 to 60%). This disease is not considered dangerous and is very normal among premature babies, but it must be treated in a quick and correct way to ensure the safety of the baby and avoid death.

Through our study it was found that the majority of those infected with it were male (56%) and percentage of female was (44%) and this is due to deficiency of enzyme system maturation or secondary effects resulting from higher acuity of illness in newborn males may influence the generation, metabolism and elimination of serum bilirubin in the male, these result agree with a study done by Bulbul A et al., 2014, in turkey to evaluate the risk factor for developing hyperbilirubinemia in newborn and it show that increase serum bilirubin was more common in male than female (Bulbul A et al., 2014).

In order to study the possible risk factors that may contribute to the jaundice in neonate, the study show that residency is one of these factors that significantly influence the treatment outcome of jaundice in neonate and it show that babies who come from rural places was less likely to improved compaired to urban places (58.6% urban, 41.4% rural), this maybe due to the fact that rural mother have less knowledge about the disease and it's severity and the right treatment. This study finding agree with a study done in Nepal by Sharma S in 2016, Research revealed that mothers residing in rural areas often lack awareness about neonatal jaundice, potentially leading to delayed treatment. Limited access to nearby healthcare facilities could be a contributing factor to this delay in seeking medical assistance for their children (Sharma S, 2016).

Early admission of the neonate to the hospital is one of the factors that increase the improvement and healing from the disease and that may contribute why most of our study neonate improved as most of them admitted within the

first 24 hrs. of their life or after 2 or 5 days, also born in the hospital may also increase the improvement rate and treatment outcome. In our study inborn baby were 69% and out-born baby were 31% and this discrepancy may arise because out-born babies often present with more severe illness and higher total serum bilirubin levels compared to in-born babies. Additionally, they tend to present later due to being referred from farther distances, resulting in the detection of jaundice at a more advanced stage. In contrast, in-born babies benefit from earlier diagnosis and treatment facilitated by the availability of equipment and healthcare professionals in hospitals, leading to less severe illness and a higher likelihood of improvement and that agree with a study done in South East Nigeria by Onyearugha C et al., in 2011(Onyearugha C et al., 2011).

Maternal characteristic may contribute to the neonate in having the disease and also may have an influence on treatment outcome, Rh incompatibility and ABO incompatibility between the child and mother may cause development of jaundice in neonate after birth, It is estimated that ABO incompatibility between the fetus and the mother can occur in up to 20% of pregnancies, and results from an O mother and who has an A or B fetus. ABO incompatibility jaundice usually starts to appear at the age of one day and in our study there was ABO incompatibility in only (43%) of the neonate.

Breast feeding is one of the reason for developing jaundice in neonate during their first weeks of life and our study show that (62%) of the neonates were breast feeding and (33%) were bottle feeding, so most of our study neonate may developed jaundice due to breast feeding and that because inhibition of the UGT enzyme by pregnanediol and deconjugation of conjugated bilirubin in the intestines by beta-glucuronidase present in breast milk.

Gestational age is one of the contributed factor for developing jaundice in newborn and child who born before 37 weeks were less likely to improved compared to those who born after 37 weeks (71%≥ 37 weeks, 21%<37 weeks). This phenomenon could be attributed to the vulnerability of preterm neonates to

severe neurotoxic effects of free bilirubin, stemming from an immature blood-brain barrier and liver compared to mature neonates. Consequently, they exhibit a reduced response to treatment and are less likely to show improvement compared to mature neonates. The finding of our study agree with a study done in India by Rao AK et al., in 2017, which show that premature babies were less responsive to treatment and less likely to improve than mature babies (Rao AK et al., 2017).

Total serum bilirubin is the investigation tool for jaundice and our study show that (57%) of the neonate admitted with TSB less than 20 mg/dl and (43%) admitted with TSB more than 20 mg/dl. So having less TSB level mean the chance for improvement from the disease is higher and that maybe due to the fact that unconjugated bilirubin is neurotoxic at a high level that can lead to ABE and eventually death. This finding agree with a study done in china by Zhang R et al., 2022 (Zhang R et al., 2022).

Phototherapy is the treatment of choice for neonatal jaundice and most of them show improvement and that was seen in our study as most of the neonate around (96%) show improvement and only (4%) dead and this agree with a study done in Bangladesh by Zabeen B et al., 2017 (Zabeen B et al., 2017).

4.2. Conclusion

Neonatal jaundice is one of the most common disease between newborn babies as it appear during the first few days of the baby life due to many reasons like breast feeding, low birth weight, ABO and Rh incompatibility between the mother and fetus etc.., phototherapy is the treatment of choice for jaundice and most of the cases show improvement in our study we tried to evaluate the possible causes and risk factors for developing the disease and its effect on the treatment outcome and it show that most of the neonate show improvement from phototherapy and that maybe due to early admission due to higher knowledge of the mother and there was little ABO and Rh incompatibility between the mother and fetus.

4.3. Recommendation

1. More study need to be done in this topic in order to get better knowledge of the disease and it’s risk factor.
2. Increase awareness of the disease specially for pregnant women to help them in seeking medical help more quickly as that help in the treatment outcome for the baby.
3. Special care needs to be given to low-gestational-age babies with jaundice.
4. Priority needs to be given to those babies who come from rural areas and who have elevated serum bilirubin levels.