PREDICTION OF SIGNIFICANT HYPERBILIRUBINEMIA IN LATE PRETERM AND TERM BABIES USING FIRST DAY SERUM BILIRUBIN LEVEL – A PROSPECTIVE STUDY

BY

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Dissertation Submitted To

BLDE University, Vijayapur, Karnataka

In partial fulfilment of the requirements for the degree of

MD

IN

PEDIATRICS

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VIJAYAPUR, KARNATAKA.

2017

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ACKNOWLEDGMENT

Words would not be sufficient to express my deepest gratitude and indebtedness to my honorable and esteemed teacher and guide **Dr. S. S. KALYANSHETTAR** $_{MD}$, Professor , Department of Pediatrics, an outstanding and revered teacher for his avid interest, unremitting encouragement and invaluable guidance throughout the course of my study. Indeed it's an honor for getting the opportunity to express my most sincere gratitude to him for his valuable suggestions given at all the steps of the study. Not only has he provided me with the analytical and conceptual tools to complete my study but he has also had a profound influence on both my personal growth and professional pursuits.

I am also extremely fortunate to have a caring, approachable and supportive department, who have advised and mentored me and made it conceivable for me to expedite this dissertation. I am thankful to Prof & HOD, **Dr.S.V. Patil,** Prof, **Dr. Bhavana. B**, Prof, **Dr.R.H.Gobbur**, Prof, **Dr.A.S.Akki**, and Assoc Prof, **Dr.M.M.Patil** for their congenial supervision, assiduous concern and positive feedback at all steps of this work.

My sincere thanks to all my batchmates, seniors and juniors who have helped and encouraged me during my work. I am very grateful to all the non teaching staff of Department of Pediatrics, who has helped me during this work.

I am deeply indebted to my **parents, Dr. Baby Mathew & Dr. Sara Mathew, my husband, Dr. Ciju K. George** and all my **family members** for their help, constant encouragement and moral support that led me to successfully complete this dissertation work. Last but not the least**,** my sincere gratitude to all my study subjects whose cooperation has contributed to this study.

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LIST OF ABBREVIATIONS

AAP	-	American Academy of Pediatrics
ATP	-	Adenosine Triphosphate
BIND	-	Bilirubin Induced Neurological Dysfunction
DCT	-	Direct Coomb's Test
LSCS	-	Lower Segment Cesarean Section
NVR	-	Normal Vaginal Route
NICU	-	Neonatal Intensive Care Unit
PRIMI	-	Primi gravida
TSB	-	Total Serum Bilirubin
TSB1	-	Total Serum Bilirubin on 1st day of life
TSB3	-	Total serum bilirubin on 3rd day of life
TSB5	-	Total serum bilirubin on 5th day of life
UDP	-	Uridine Diphosphate
UGT	-	Uridine Glucuronyl Transferase
B/A	-	bilirubin/albumin complex

ABSTRACT

Title : Prediction of significant hyperbilirubinemia in late preterm and term babies using first day serum bilirubin - A Prospective Study.

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Background & Objectives

Jaundice occurs in most newborns. Most jaundice is benign, but because of the potential toxicity of bilirubin, newborn infants must be monitored to identify those who go for severe hyperbilirubinemia and in rare cases, acute bilirubin encephalopathy / kernicterus. With increasing trend on early discharge of term and late preterm newborns, the study aim was to predict significant hyperbilirubinemia using first day serum bilirubin.

Study hypothesis was that serum bilirubin level on first day of life is a good predictor of its own peak achieved later in the week (by day 3 of life).

Methods

The study was conducted on a prospective cohort of 170 babies (late preterm and term) born at a tertiary level hospital in North Karnataka. The main outcome measured was significant hyperbilirubinemia on day 3 of life.

Serum bilirubin was estimated within 24 hours of life. Exclusion criteria were Rh incompatibility, ABO incompatibility, life threatening congenital malformations, birth asphyxia, sepsis and hypothyroidism.

Daily clinical examination of the babies were done and then, on day 3 of life, serum bilirubin was estimated. If the value of TSB falls in high/intermediate risk zone, phototherapy was started. Those babies who didn't develop significant hyperbilirubinemia, are subjected to daily clinical examination till day 5 of life and TSB is estimated on the day 5.

Results

Total of 170 newborns were included in the study. Out of these, 33 newborns developed significant hyperbilirubinemia. This includes 27 term (18%) and 6 late preterm (27%) newborns.

TSB on day 1 of life with more than 3.3mg/dl for the 6 late preterms was 18% and more than 4.2mg/dl for the 27 term newborns was 81%.

Conclusion

TSB more than 3.3mg/dl on day 1 of life for late preterm and more than 4.2mg/dl for term newborns was predictive of significant hyperbilirubinemia.

Keywords : Neonatal Jaundice ; Prediction ; Hyperbilirubinemia ; Kernicterus.

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INTRODUCTION

Hyperbilirubinemia is a common and in most cases, benign problem in neonates. Jaundice is observed during the first week of life in approximately 60% term infants and 80% preterm infants. The yellow colour usually results from the accumulation of unconjugated, non-polar, lipid soluble bilirubin pigment in the skin. This unconjugated bilirubin is an end product of heme-protein catabolism from a series of enzymatic reactions by heme oxygenase and biliverdin reductase & non-enzymatic reducing agents in the reticuloendothelial cells [1].

Neonatal hyperbilirubinemia remains a public health concern as documented by recent reports of kernicterus in otherwise healthy term and near term newborns. Kernicterus in such newborns is preventable, provided excessive hyperbilirubinemia for age is promptly identified and treated. With the intent to facilitate such identification and treatment, universal screening for severity of hyperbilirubinemia before hospital discharge may predict the neonatal population that is at risk for excessive hyperbilirubinemia during the first week after birth [2].

Jaundice is physiologic when the total serum bilirubin falls within the normal range. Defining this normal range is problematic. Upper limit (95th percentile) of normal TSB has been shown to vary from 12.9 mg/dl to 17.5 mg/dl. If left untreated, however the bilirubin levels within the physiological range in premature infants are potentially hazardous and are treated with phototherapy[3,4].

Jaundice should be considered non-physiologic or pathologic, if it occurs less than 24hours after birth, if bilirubin levels rise at a rate more than 0.5mg/dl per hour or 5mg/dl per day, if total bilirubin level exceeds 15mg/dl in full term infant or 10mg/dl

in preterm infant, if there is evidence of hemolysis or if hyperbilirubinemia persists beyond 10days in full term and 21days in preterm infants[5].

The term "bilirubin induced neurologic dysfunction" has been coined to describe the changes assosciated with acute bilirubin encephalopathy.

Acute bilirubin encephalopathy, an uncommon disorder which may frequently evolve into kernicterus and is characterised by a tetrad of choreoathetoid cerebral palsy, high frequency central neural hearing loss, palsy of vertical gaze, dental enamel hypoplasia[6]. Kernicterus has been more recently reported in apparently healthy term and late preterm gestation breastfed infants without documented hemolysis [7].

Quantifying the level of jaundice has been the foundation for satisfactory management of hyperbilirubinemia. But observer variability and skin colour has influenced the clinical evaluation of hyperbilirubinemia by "Kramer Index" [8]. So measurement of total serum bilirubin has become the gold standard for diagnosing and treating hyperbilirubinemia in newborns [9].

Interpretation of bilirubin level in a neonate is based on the postnatal age. Hour specific bilirubin nomogram developed by Bhutani et al [4] has demonstrated that measurement of TSB before discharge from hospital can help to identify those neonates at risk of having higher percentile values of TSB during follow up.

The AAP (American Academy of Pediatrics) recommends that newborns discharged before or within 48 hours should have a follow up visit after 2-3 days to detect significant jaundice and other problems. However this is not possible in our country due to limited follow up facilities. The present study is to predict significant hyperbilirubinemia in term and late preterm neonates using first day TSB.

AIM AND OBJECTIVE

To determine the predictive ability of 1st day total serum bilirubin level for subsequent significant hyperbilirubinemia in term and late preterm newborns which require treatment.

REVIEW OF LITERATURE

Synthesis of bilirubin :-

Bilirubin is produced by the breakdown of heme containing proteins. In newborns, 75% of all bilirubin comes from catabolism of erythrocyte hemoglobin [9]. The remaining 25% of bilirubin is produced from breakdown of other proteins like myoglobin, cytochromes, catalase and peroxidases. Bilirubin synthesis starts with lysis of senescent red blood cells (RBC) in the reticuloendothelial cell. When the RBCs are degraded, heme is released from hemoglobin. Heme oxygenase, an enzyme found in most cells of the body except anucleated RBCs, catalyzes the first step in breakdown of heme, yielding equimolar parts of biliverdin, iron and carbon monoxide. Heme oxygenase is the rate limiting step for bilirubin production and carbon monoxide production is linked to bilirubin synthesis and if measured, can serve as a proxy for the extent of hemolysis. Biliverdin, a water soluble, non-toxic, blue-green pigment is then rapidly converted by a second enzyme, biliverdin reductase, to unconjugated bilirubin. This bilirubin isomer is orange-yellow, fat soluble and not readily excreted in the bile or urine. Each gram of hemoglobin yields 35mg of bilirubin [9].

Transport and Hepatic Uptake:

When released from the reticuloendothelial system, unconjugated bilirubin binds reversibly with albumin for its journey to liver. In the liver, conjugation occurs. The circulating bilirubin which is not bound to albumin is called "free bilirubin" and it is this bilirubin that can enter the brain and cause neuronal injury. The bilirubin-albumin complex is vulnerable to seperation by factors including metabolic

derangements, such as acidosis and hyoxia, hypothermia, infections. Drugs which decrease B/A binding include salicylates, sulfonamides, sodium benzoate and indomethacin.

Conjugation:

When the B/A complex reaches the plasma membrane of the hepatocyte, bilirubin detaches from albumin and enters the liver cell. Inside the hepatocyte, bilirubin binds with other carrier proteins to be carried into the endoplasmic reticulum for conjugation. Protein Y is the primary carrier and protein Z is used during the times of increased bilirubin load to liver. Conjugation occurs inside the smooth endoplasmic reticulum, where each molecule of bilirubin combines with 1 or 2 molecules of glucuronic acid to produce bilirubin monoglucoronide and diglucoronide pigments. Conjugated bilirubin is water soluble and can be excreted into the bile and eventually eliminated from the body. Uridine diphosphoglucuronate glucoronosyl transferase (UGT) is the liver enzyme responsible for conjugation and formation of glucuronides.

Excretion:

After conjugation, bilirubin is readily excreted by the hepatocyte into the bile canaliculi as bilirubin mono or diglucuronide. This water soluble conjugated bilirubin is then emptied into small intestine via the common bile duct. Conjugated bilirubin is not absorbed in the small intestine. The mono and diglucuronides are relatively unstable molecules and can be converted into unconjugated bilirubin and absorbed by the intestine. The enteric mucosal enzyme beta glucuronidase helps the conjugated bilirubin to hydrolyse back t the lipid soluble unconjugated form which is easily absorbed from the small intestine into the portal circulation. Enterohepatic circulation describes this route of circulation from intestines to liver.

Once conjugated bilirubin reaches the colon, it is catabolised by colonic flora to urobilinogen, some of which is oxidised to stercobilin, which is excreted in stool. Stercobilin is what gives the stool its brown colour. The remaining urobilinogen is reabsorbed and excreted in the urine as urobilin. The yellow colour of urine is due to urobilin.

Fetal Bilirubin Metabolism

Bilirubin can be detected in amniotic fluid after 12weeks of gestation but disappears by 36-37 weeks of gestation. The fetus has a limited ability to conjugate bilirubin. Circulating unconjugated fetal bilirubin readily crosses the placenta to maternal circulation, where it is excreted by maternal liver. Because fetal bilirubin is effectively excreted by the mother, newborns are rarely born jaundiced. Jaundice at birth usually indicates hemolysis, intestinal obstruction or obstruction of bile ducts.

PHYSIOLOGIC JAUNDICE

The jaundice which occurs in most of the newborns in the first few days of life has been termed "physiologic jaundice" and represents a phenomenon that occurs as a result of normal maturational limitations of newborn. This term has been also applied to newborns whose TSB falls within the normal range. Defining this normal range is problematic. The upper limit (95th percentile) of normal TSB has been shown to vary from 12.9 mg/dl to 17.5mg/dl, depending upon the population studied. If left untreated, however, bilirubin levels within the physiologic range in premature infants are potentially hazardous and are treated with phototherapy[10].

ASSESSMENT OF SEVERITY OF JAUNDICE

Visual assessment of TSB levels relies on cephalocaudal progression of jaundice with a rising TSB level (head and neck:4-8mg/dl, upper trunk:5-12mg/dl, lower trunk and thigh: 8-16mg/dl, palm and soles: >15mg/dl)[8]. This is called Kramer Index. Cephalocaudal progression of jaundice is apparently related to the relative thickness of skin at various parts, skin being the thinnest on the face and extremely thick over the palms and soles. The cephalocaudal colour difference may be related to the difference in blood flow or lipid content of skin due to conformational changes in the newly formed bilirubin-albumin complexes.

The severity of jaundice should be assessed in natural day light by observing cephalocaudal progression.

Kramer Index -

Areas of Body	Range of bilirubin (mg)
Face	4-8
Upper trunk	5-12
Lower trunk and thighs	8-16
Arms and lower legs	11-18
Palms and soles	>15

VARIOUS MODALITIES TO ASSESS JAUNDICE

- Icterometer - matching skin colour with the colour codes depicted on plastic strip

- Transcutaneous bilimeter - works on the principle of computerised spectrophotometry

- Conventional Van den Bergh test [11] - It is a quantitative method for bilirubin assay and is based on the coupling of diazotized sulfanilic acid (Ehrlich's diazoreagent) and bilirubin to produce a reddish-purple azo compound. Direct and indirect reactions - bilirubin is as such insoluble in water while the conjugated bilirubin is soluble. Van den Bergh reagent reacts with conjugated bilirubin and gives purple colour (within 30seconds). Addition of methanol dissolves the unconjugated bilirubin which then gives the Van den Bergh reaction (within 30minutes). The form of bilirubin which reacts without addition of methanol is called "direct bilirubin"; to that form of bilirubin which is measured only after the addition of methanol is called "indirect bilirubin".

- End tidal carbon monoxide levels ($ETCO_c$) - it is an index of the rate of bilirubin production. Breakdown of heme by the rate limiting enzyme heme oxygenase leads to the formation of equimolar amounts of carbon monoxide and biliverdin, with biliverdin immediately reduced to bilirubin ; the measurement of carbon monoxide in the exhaled breath of newborn can be used as an index of heme degradation and bilirubin production.

HISTORY OF BILIRUBINEMIA

TSB levels in cord blood ranges from 1.4 - 1.9mg/dl [10]. At birth, cord TSB levels are relatively normal because fetal bilirubin is cleared by the mother. After birth,the newborn has to assume responsibility for the process of conjugation and excretion. Because of maturational limiations in bilirubin conjugation and excretion, all newborns experience a rise and then fall of TSB after birth. The rates of increase and decline in TSB and peak TSB level are affected by many factors, including gestational age, race and breastfeeding. The advent of exchange transfusion and phototherapy adds to the difficulty of getting a true picture of the natural history of neonatal bilirubinemia because many infants with rising TSB are treated within 72-96 hours.

Bilirubin levels in normal term infants increase from birth, reaching peak levels of 5 to 7mg/dl around days 3 to 5 of life and then decline by days 7 to 10 [8].

Gartner and coworkers [13] divided the clinical course of physiological jaundice into two phases :

- phase 1 - it includes the first 5 days of life in term newborns and is characterised by a rapid increase in TSB for 3-4days, afterwhich the level begins to decline
- Phase 2 - it is characterised by stable, but elevated TSB levels lasting for 2weeks.

  A rise in TSB upto 12mg/dl is in physiological range. In premature newborns, the peak maybe 10-12mg/dl on day5, possibly rising over 15mg/dl without any specific abnormality of bilirubin metabolism.

BREAST FEEDING AND JAUNDICE

Breastfed infants are three times as likely to develop TSB levels higher than 12mg/dl and six times as likely to develop TSB levels higher than 15mg/dl as bottle-fed infants. Although two phenomena assosciating breast milk and jaundice have been described - breastfeeding jaundice and breast milk jaundice - there is considerable overlap between the two entities and they maybe indistinguishable from one another in some infants [9]. Breast feeding jaundice usually begins within 2-4 days of life and peaks between 3-6 days of life. Approximately, 10% of breastfed infants develop breastfeeding jaundice. Dehydration, poor caloric intake, increased enterohepatic circulation are implicated in the development of breastfeeding jaundice. Breastfed infants take in fewer calories than bottle-fed infants, so pass less stool by weight and excrete significantly less bilirubin in their stools in the first 3days of life[16]. Breastfeeding jaundice is managed not by limiting breastfeeding but by encouraging breastfeeding. De Carvalho and assosciates found that lower bilirubin levels for infants nursed more than 8 times a day compared with infants who nursed fewer than 8 times a day. Improving milk intake by increasing feeding results in increased caloric intake, increased weight gain, increased meconium passage and lower bilirubin levels and is strongly encouraged by the AAP. [17]

Breast milk jaundice usually appears by days 4 to 7 of life and peaks between days 5 to 15 of life. It is believed that the ingredients in breast milk are the primary basis for breast milk jaundice. The most likely mechanism is thought to be related to increased intestinal absorption of bilirubin into the enterohepatic circulation. Beta - glucuronidase activity is higher in breast milk and plays a role in breast milk jaundice. Bile salt - stimulated lipase, found in human milk, increases fat absorption, which is believed to be assosciated with an increased absorption of intestinal bilirubin.

Decreased formation of urobilinogen in breast fed infants play a role in breast-milk jaundice. Infants fed breast milk excrete urobilin in their stools later than formula fed infants. [9]

CAUSES OF UNCONJUGATED HYPERBILIRUBINEMIA[9]

1) **Increased production or bilirubin load on the liver**

   Hemolytic disease - immune mediated, Rh isoimmunisation, ABO or other blood group incompatibilities

2) **Heritability**

   Red cell membrane defects

   Hereditary spherocytosis, elliptocytosis, pyropoikilocytosis, stomatocytosis Red cell enzyme defects G6PD deficiency, pyruvate kinase deficiency, other erythrocyte enzyme deficiency

3) **Hemoglobinopathies**

   alpha and beta thalassemia

4) **Unstable Hemoglobin Level**

   Congenital Heinz body hemolytic anaemia

5) **Other causes**

   sepsis, DIC

   extravassation of blood , hematomas, and pulmonary, abdominal, cerebral or other occult hemorrhage, polycythemia, macrosomic infants of diabetic mother

6) **Increased enterohepatic circulation**

Breast milk jaundice

Pyloric stenosis

Small or large bowel obstruction or ileus

7) **Decreased clearance**

Prematurity, G6PD deficiency, pyruvate kinase deficiency

8) **Inborne Errors of Metabolism**

Crigler Najjar syndromes 1 and 2, Gilbert syndrome, Galactosemia, Tyrosinemia, Hypothyoidism

INCREASED BILIRUBIN PRODUCTION OR LOAD ON THE LIVER

The most frequently identified pathologic cause leading to hyperbilirubinemia is hemolytic disease of newborn[18]. Fetal and newborn RBC destruction most commonly results from Rh and ABO incompatibility. Rh isoimmunisation requires requires an Rh negative mother who has developed antibodies to the Rh antigen in a Rh positive baby. This formation of antibodies to the Rh antigen takes place after exposure to Rh positive blood, which can occur from an improperly matched blood transfusion or fetal-maternal blood transfusion during pregnancy, abortion, amniocentesis or delivery. The IgG antibodies cross the placenta and destroy the fetal Rh positive RBCs. The antenatal administration of anti-D immunoglobulin to Rh negative women has significantly decreased the incidence of Rh disesase. Unlike Rh disease, ABO incompatibility does not require previous exposure to a different blood type. ABO incompatibility is seen in mothers who are O type and infants who are type A or B. Individuals with blood group O have naturally occuring IgG antibodies to groups A

and B, which can cross the placenta and destroy the fetal RBCs. Naturally occuring antibodies found in mothers with type A or type B blood are mostly IgM antibodies, which do not cross the placenta. ABO blood group incompatibility is the most frequent cause of hemolytic disease in newborns, however the disease is milder than Rh disease. Minor blood group incompatibilities account for a small proportion of infnats with hemolytic disease.

Of the inherited disease causing hemolytic disease in newborns, glucose-6-phosphate dehydrogenase deficiency is an important cause for neonatal hyperbilirubinemia.[19] G6PD is an enzyme found in all cells of the body, and it plays a significant role in protecting cells, especially RBCs, from oxidative damage. In the absence of G6PD, cells become vulnerable to oxidation resulting in cellular death. Hemolysis and hyperbilirubinemia in G6PD deficiency can be triggered by oxidative stresses like sepsis and exposure to several agents like naphthalene, agents used for umbilical cord antisepsis, breast milk of mothers who have eaten fava beans and household cleaning agents. G6PD deficiency is an X-linked disorder and an important cause of neonatal hyperbilirubinemia and kernicterus.

DECREASED BILIRUBIN CLEARANCE

Conjugation of bilirubin inside the hepatocyte depends on a single form of the uridine diphosphoglucuronate glucoronosyltransferase (UGT) enzyme. Three inherited defects of UGT deficiency are noted to cause neonatal hyperbilirubinemia : Crigler-Najjar syndrome types 1 and 2 , Gilbert syndrome.

Criggler - Najjar syndromes 1 and 2

Caused by one or more mutations of the 5 exons of UGT1A1 gene, the gene that determines the structure of UGT, or mutations in the noncoding region of the gene. Infants with Criggler-Najjar syndrome type 1 have no functioning UGT and are unable to conjugate bilirubin. Severe, prolonged unconjuagted hyperbilirubinemia begins in the first few days of life and persists throughout life. Bilirubin levels are usually 20-45mg/dl or higher. These infants often require exchange transfusion in the first week of life. Currently, the only definite therapy for type 1 is liver transplantation. Human hepatocyte transplantation and administration of tin-protoporphyrin, tin-mesoporphyrin, and calcium phosphate have been used with limited success to reduce TSB levels. Infants with Crigler-Najjar syndrome type 2 are able to synthesise small amounts of UGT and usually have less severe hyperbilirubinemia. Peak levels are 6-20mg/dl, but they maybe higher in newborns and kernicterus has been reported.[9] These infants generally respond to phenobarbital therapy.

Gilbert syndrome

It occurs in 6-9% of population and involves a mutation in UGT1A1 gene promoter or misense mutations in the coding region.[9] Both autosomal dominant and recessive patterns of inheritance have been noted. These individuals have reduced activity of UGT. Gilbert syndrome is most commonly diagnosed in young adults. When Gilbert syndrome occurs in combination with other conditions that exacerbate bilirubinemia, such as breastfeeding, G6PD deficiency and blood group incompatibility, the risk of hyperbilirubinemia increases. [9]

CONJUGATED HYPERBILIRUBINEMIA

Elevated serum levels of conjugated bilirubin are a less frequent but significant cause of hyperbilirubinemia in neonates. Conjugated hyperbilirubinemia is the primary manifestation of neonatal cholestasis and should be differentiated from unconjugated hyperbilirubinemia. Any infant who is jaundiced beyond 3 weeks of life should have a measurement of total and direct bilirubin levels and be evaluated for neonatal cholestasis.

Neonatal Cholestasis :

It is defined as decreased canalicular bile flow and is a term used to describe various disorders assosciated with conjugated hyperbilirubinemia. Subsequently, biliary substances such as bilirubin, bile acids, and cholesterol accumulate in the blood and extrahepatic tissues. [18]

Etiologic factors can be classified based on the anatomic location of the pathology into extrahepatic and intrahepatic causes. [20]

Common extrahepatic causes are biliary atresia and choledochal cyst.

Intrahepatic causes include idiopathic neonatal hepatitis, infections, alpha-1 antitrypsin deficiency and metabolic disorders like galactosemia, tyrosinemia and glycogen storage disease type 4.

Biliary atresia and idiopathic neonatal hepatitis are the most common causes of neonatal cholestasis.

Since several disorders that cause neonatal cholestasis require immediate intervention for optimal survival, early recognition of cholestasis and prompt intervention are

imperative. McKiernan suggested a systematic and structured approach to determining the cause, beginning first with evaluating the infant for conditions that require immediate intervention, such as sepsis, and metabolic disturbances like galactosemia and glycogen storage disorder. Once these causes have been ruled out, the next step is to rule out biliary atresia.

If diagnosis of biliary atresia is made, Kasai portoenterostomy must be performed before the infant is 60days old. If biliary atresia is ruled out, then further evaluation to identify the cause ensues.

Idiopathic neonatal hepatitis occurs in approximately 15% to 30% of cases and is diagnosed when no specific cause can be found.

KERNICTERUS

The term "kernicterus" was first used more than a century ago to describe the yellow staining of the brain in the nuclear region. It is used to describe the acute and chronic effects of hyperbilirubinemia.

Also, the terms "kernicterus" and "bilirubin encephalopathy have been used interchangeably. The AAP suggests that the term "acute bilirubin encephalopathy" be used to describe the acute manifestations of bilirubin toxicity seen in the first few weeks of life and that the term "kernicterus" be reserved for describing the chronic and permanent clinical sequelae of bilirubin toxicity.[21]

Recently the term "bilirubin-induced neurologic dysfunction" has been coined to describe the changes assosciated with acute bilirubin encephalopathy along with a scoring system to quantify the severity of symptoms.[22]

Pathophysiology

Areas of brain most commonly affected by bilirubin staining are the basal ganglia, particularly the globus pallidus and subthalamic nucleus, hippocampus, substantia niagra, cranial nerve nuclei, especially the occulomotor, vestibular, cochlear and facial nerve nuclei and other brain stem nuclei, and the anterior horn cells of spinal cord. These areas of neuronal injury help to explain the clinical manifestations of bilirubin encephalopathy.

Various theories exist to support bilirubin transport across an intact blood-brain barrier.

Entry across an intact blood-brain barrier likely occurs by bilirubin binding with phospholipids of capillary endothelial cells which then easily move into the brain.

Anything that overwhelms the ability of bilirubin to bind with albumin, such as increased synthesis of bilirubin, decreased albumin levels, or competition for binding sites, can lead to increased amounts of free bilirubin and so enhances the movement of bilirubin into the brain.

Bilirubin tends to take up hydrogen ions, forming aggregates of toxic bilirubin acid that may damage the capillary endothelial cell and may advance further uptake of bilirubin by the brain. This occurrence may explain why acidosis plays a role in bilirubin encephalopathy since bilirubin is enhanced in acidotic environment.

Evidence also exists for bilirubin to cross damaged blood-brain barrier. Bilirubin needs to dissosciate from albumin to cause neuronal toxicity. Hyperosmolar solutions,

hypercarbia, asphyxia, intracranial infection and increase in blood pressure play a role in bilirubin encephalopathy.

It is likely that injury to cellular membranes play a significant role.

Volpe proposed that free bilirubin enters intracellular organelles, such as mitochondria, endoplasmic reticulum and nucleus in a similar way that free bilirubin gained access to the brain by binding to membrane phospholipids. In the brain, susceptibility to injury varies by cell type, brain maturity and brain metabolism.

Traditionally, a peak serum bilirubin level of more that 20mg/dl has been used to predict a poor outcome in infants with Rh hemolytic disease.[23] In otherwise healthy neonates (without hemolytic disease), serum bilirubin levels which do not exceed 25mg/dl are unlikely to place the infants at risk of adverse neurodevelopmental outcome. [24]

SIGNS AND SYMPTOMS

Acute encephalopathy usually progresses through three phases, each of increasing severity. The first phase occurs in the first few days and is characterised by slight stupor (lethargy, sleepiness, slight hypotonia, decreased movement and poor sucking). Infants who are not managed effectively at this phase show a significant deterioration in prognosis.

After a week, the cardinal signs of the second phase appear, including marked stupor, often with irriability, increased tone, fever, and a high-pitched cry. The increased tone is demonstrated by backward arching of the neck (retrocollis) and trunk (opisthotonus), rigid extension of all 4 extremities, tight-fisted posturing of the arms and crossed extension of the legs.

Subsequently, phase three is characterised by deep stupor or coma, increased tone, pronounced retrocollis and opisthotonus, no feeding and a shrill cry.

Chronic bilirubin encephalopathy is demonstrated , kernicterus, is demonstrated by a tetrad consisting of extrapyramidal, auditory abnormalities, gaze palsies and dental dysplasia[9]. These manifestations may not become apparent until after 6months to 1 year of age.

Extrapyramidal movement abnormalities are the most remarkable feature of the tetrad and may not be well developed for several years.

The most prominent motor movement is athetosis of all limbs, although arms are more affected than legs. Other movements include chorea, ballismus, tremor.

The predominant gaze abnormality seen in kernicterus is an upward gaze. The most common auditory disturbances noted is high-frequency hearing loss.

BILIRUBIN-INDUCED NEURONAL INJURY IN PREMATURE INFANTS

Premature infants are considered to be at greater risk for developing kernicterus than full-term infants. Although kernicterus is considered as a rare event in the neonatal intensive care unit, reviews of the recent kernicterus cases have identified the late preterm gestation as a significant risk factor for the development of severe hyperbilirubinemia.[19] Unlike very low birth weight infants who are cared for in normal newborn nurseries, where caretakers may treat them as full-term infants. Late preterm infants deserve the same vigilance in regards to assessment and management of hyperbilirubinemia as all preterm infants.

UNIVERSAL BILIRUBIN SCREENING

It is to target early post discharge follow up and serum bilirubin measurement to those newborns at highest risk while minimizing or eliminating repeat bilirubin measurements in newborns at lower risk has been proposed.[25,26]

The purpose of predictive bilirubin monogram is to provide a practical, readily available guide for monitoring severity of jaundice so as to allow both timely institution of simple preventive measures such as counseling about feeding and care, use of formula or expressed breast milk supplements or phototherapy.

AAP Practice Parameter for management of hyperbilirubinemia in healthy term newborns

Age in hours	**Consider phototherapy****	**Phototherapy**	**ET**	**ET and IP**
<24	...	...	...	...
25-48	> 12	>15	>20	>25
49-72	>15	>18	>25	>30
>72	>17	>20	>25	>30

ET - Exchange transfusion if phototherapy fails

IP - Intensive phototherapy

** Phototherapy at these TSB level is a clinical option meaning that intervention is available and may be used on the basis of individual clinical judgement.

Intensive phototherapy should produce a decline of TSB of 1-2mg/dl within 4-6 hours and the TSB level should continue to fall and remain below the threshold level for exchange transfusion.

Term neonates who are clinically jaundiced at less than 24 hours, are not considered healthy and require further evaluation.

The practice parameter for the management of hyperbilirubinemia in the healthy newborns published in 1994 by the AAP recommended that a serum bilirubin to be done on any neonate noted to be jaundiced by visual assessment in the first 24hours after birth.

It also states that follow up by a health care professional should be scheduled within 2-3days for all neonates discharged within 48 hours after birth. The need for measurement of serum bilirubin at follow up is left to the judgement of the professional providing care based on his/her visual estimation of the severity of jaundice.

Phototherapy is recommended if the TSB is rising at the rate of 6mg/dl or more in 24hours, when the TSB reaches 18mg/dl by the age of 49-72hours, 20mg/dl after the age of 72hours or if for any reason the newborn is not well.

Unless the visual estimate of severity of jaundice is fairly accurate and there is concern about its intensity, especially as related to neonate age in hours, the bilirubin levels can rise to dangerous levels before being diagnosed as excessive and treated.

RISK PREDICTION FOR HYPERBILIRUBINEMIA

Before discharge, every newborn should be assessed for the risk of developing severe hyperbilirubinemia. [21] Risk assessment is performed using two methods, used individually or in combination. The best method of assessing risk of subsequent hyperbilirubinemia is done by measuring TSB and the TcB level and plotting the value on an hour specific normogram which identifies the risk levels.

Alternatively, or in combination, the clinician can evaluate the infant for the presence of risk factors [21].

These risk factors are categorised into Major Risk Factors, Minor Risk Factors and Decreased Risk.

MAJOR RISK FACTORS

- Predischarge TSB or TcB level in the high risk zone
- Jaundice observed in the first 24hours
- Blood group incompatibility, with positive direct antiglobulin test, other known hemolytic disease (G6PD deficiency), elevated $ETCO_c$
- Gestational age 35-36 weeks
- Previous sibling having recieved phototherapy
- Cephalohematoma or significant bruising
- Exclusive breastfeeding, particularly if nursing is not going well and weight losss is exesssive

MINOR RISK FACTORS

- Predischarge TSB or TcB level in the high intermediate risk zone
- Gestational age 37-38weeks
- Jaundice observed before discharge
- Previous sibling with jaundice
- Macrosomic infant of a mother who has diabetes
- Maternal age more than 25 years
- Male gender

DECREASED RISK

- TSB or TcB level in the low-risk zone
- Gestational age more than 41weeks
- Exclusive bottle feeding
- Discharge from hospital after 72 hours

ROLE OF HOUR SPECIFIC BILIRUBIN VALUE

The clinical practice of reporting bilirubin on the basis of age in days was misleading. It should be remembered that bilirubin rises by the "hours" of life and hence the time of sampling must be as "hours of life" and not "day of life". [27] It is more accurate to report bilirubin level according to age in hours. [28] This allows placement of the level in a predictive percentile tract for hour specific bilirubin values. [29]

Bhutani et al [29] was the first to report the predictive value of hour specific bilirubin.

In this study, TSB levels were obtained at the time of routine screening in all term and near term newborns. Postnatal age (hours) at the time of TSB measurement was recorded. A percentile based bilirubin nomogram for the first week was constructed from hour specific pre and post discharge TSB values of newborns.

The nomogram has following zones :

High risk zone - > 95th centile

Intermediate risk zone -

upper intermediate (76th-95th centile) and lower intermediate (40th-75th centile)

Low risk zone - <40th centile

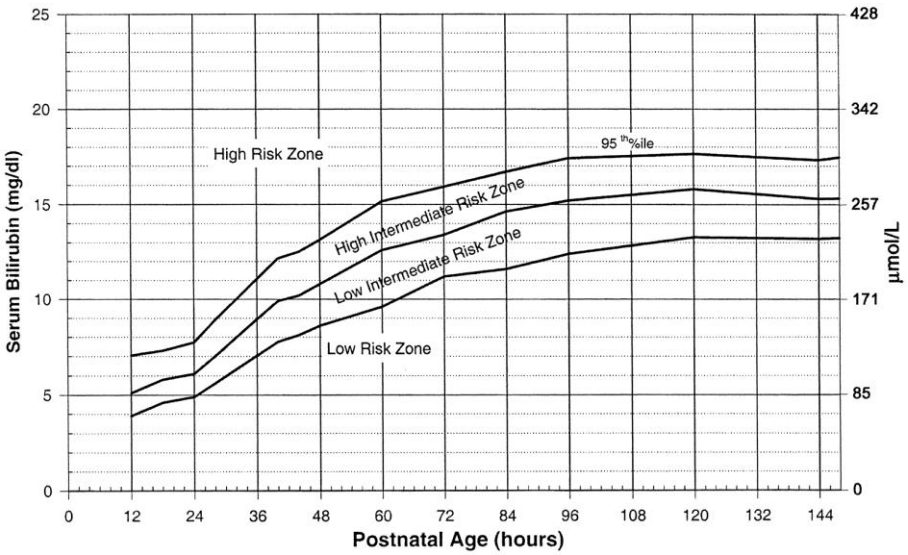


Photo 1 : Bhutani's Nomogram

Based on their data, the probability of subsequent hyperbilirubinemia as whole was expressed as a ratio of 1:22 for diseaese/no disease. The overall risk is none in low risk zone, nearly halved (1:45) in lower intermediate zone, tripled in upper intermediate zone (1:7) and increased 14 fold in the high risk zone (2:3).

The appeal of nomogram lies in its simplicity, availability and cost effectiveness.

Awasthi and Rehman [30] in a cohort of 275 healthy term neonates found that by using TSB 18-24 hours as the prediction test approximately two third of neonates were test negative and had about one in ten chances of readmission for treatment of hyperbilirubinemia.

Alpay et al [31] in a cohort of 500 healthy term newborns found that a serum bilirubin measurement and the critical bilirubin level of 6mg/dl in the first 24 hours of life will predict nearly all of the term newborns who will have significant hyperbilirubinemia.

Agarwal et al [32] in a prospective study of neonates with gestation > 35weeks showed that TSB level of <6mg/dl at 24 +/- 6 hours of life predicts absence of subsequent hyperbilirubinemia.

Early discharge and risk of Hyperbilirubinemia

If babies leave the hospital before they are 36hours old, the peak bilirubin level will occur after they are discharged. Thus jaundice has become a large OPD problem and to ensure that we do not miss any baby who develops high bilirubin level, we need to reconsider our approach.

All evaluation and interpretation of serum bilirubin must be done with reference to baby's age in hours and not days.

The data of Bhutani et al show that bilirubin of 8mg/dl at 24hours is the 95th centile and requires an evaluation for the presence of hemolysis and close follow up.

A level of 8mg/dl at 30hours is at 80th centile and requires no investigations, but baby should be folllowed because subsequent course is not entirely predictable.

This same level at 48 hours in otherwise healthy neonate is at 50th centile and requires no further intervention.

HISTORICAL OVERVIEW

Orth, (1875) was the first to observe and describe the relation between clinical encephalopathy and the gross pathological changes seen as yellow staining of specific areas of central nervous system

Beneke, (19077) was the first to suggest that septicemia might play an important role in icterus gravis neonatorum

Van den Bergh & Muller, (1916) observed that serum from patients with hemolytic jaundice could be differentiated from serum of patients with obstructive jaundice on the basis of chemical reactions.

They also termed these reactions as "indirect" and "direct" which have come to be recognised as conjugated and unconjugated.

Hart, (1925) reported the first successful exchange transfusion.

Land Steiner & Weiner, (1940) identified the Rh system of antigens

Criggler & Najjar, (1952) found kernicterus as a process related more to elevated unconjugated bilirubin levels than to specific blood group incompatibilities or even hemolysis

Cremer et al, (1958) first proposed phototherapy for neonatal hyperbilirubinemia

Kramer, (1969) suggested visual assessment of STB levels which relies on the cephalocaudal progression of jaundice wih a rising STB level.

Seidman et al, (1991) revealed an assosciation between severe hyperbilirubinemia and low intelligence quotient (IQ) in boys

Gartner, (1994) suggested breast feeding need not be rountinely interrupted solely for the purpose of establishing a diagnosis of breastmilk or breastfeeding jaundice.

Bhutani et al, (1999) found the practice of reporting the STB level on basis of age in days rather than hours to be misleading and ineffective at accurate prediction of infants at risk for severe hyperbilirubinemia.

Bhutani et al, (1999) generated the percentile based bilirubin nomogram using hour specific pre-discharge STB levels

Dennery et al, (2001) showed conventional phototherapy involves exposing a maximal area of skin to an irradiance of 6-12 $\mu W/cm^2/nm$

Stevenson et al, (2001) showed that $ETCO_c$ measurement at 30 ± 6 hours in combination of an STB measurement did not improve the predictive ability of the hours specific TSB.

MATERIALS AND METHODS

STUDY SETTING

The study was conducted in the post natal ward in the tertiary care hospital.

STUDY DESIGN

This was a hospital based prospective observational study. All neonates born in the tertiary care hospital, after fulfilling inclusion criteria and with parental consent were included in the study. Goal of our study was to predict significant hyperbilirubinemia in term and late preterm neonates using first day serum bilirubin.

STUDY DURATION

The study was conducted during the period November 2014 to June 2016.

SAMPLE SIZE

Prevalence of significant hyperbilirubinemia in term and late preterm neonates is 12%[33] at 95% confidence interval and 5% allowable error , the sample size is 170.

- $n= Z^2 p (1-p) / d^2$

Where Z – 1.96 (normal statistical value)

p – prevalence (0.12)

d – precision (5%)

alpha error – 5%

So, sample size (n) = 170

INCLUSION CRITERIA:

- Neonates born in the tertiary care hospital during the study period
- All late preterm (34weeks – 36weeks 6days) and term neonates (37-42weeks of gestation)

EXCLUSION CRITERIA:

- Rh incompatibility
- ABO incompatibility
- Newborns with obvious life threatening congenital malformation
- Newborns with moderate to severe birth asphyxia
- Sepsis
- Hypothyroidism

STUDY METHOD

All babies of late preterm / term gestation borne in tertiary care hospital , fulfilling inclusion criteria and after having obtained informed parental consent were included in the study.

These babies admitted in postnatal ward were examined daily and following which feeds were ensured to be commenced within few hours of life. Visual assessment was done by Kramer Index on daily basis, on days 1-5 of life.

Total serum bilirubin level and unconjugated bilirubin level was measured on days 1 and 3 of life.

Serum bilirubin level was assessed using venous blood and the site from which blood drawn was variable.The first sample of blood was drawn within the first 24 hours of life.

It was ascertained that first sample was taken within first day / 24hours of life. Following sampling, it was sent to the biochemistry lab for analyisis within half an hour of collection.

The sample was analysed by "Fujifilm Dri-chem 7000i ", which is an innovative, high performance biochemical express analyser and is reported within 5-10minutes.

This was helpful for those babies who get discharged on 1st day of life and so that attenders can return on day 3 of life if the value on day 1 is predicitve of significant hyperbilirubinemia.

Those babies who got shifted to intensive care unit on day 2 for lethargy / feed refusal were excluded.

Then, on day 3 of life, total serum bilirubin and unconjugated bilirubin were analysed again.

If the value of TSB comes under the intermediate / high risk zone according to Bhutani normogram at 72 hours of age, then that baby is admitted to intensive care for phototherapy. Thereafter, the cause for hyperbilirubinemia is evaluated.

If the value of TSB comes under the low risk zone, then baby doesn't require any phototherapy.

Babies who don't develop significant hyperbilirubinemia by day 3 of life are subjected to clinical examination on days 4 and 5 of life.

Serum bilirubin level was also sent for babies who appeared icteric even on day 5 of life.

The primary outcome was defined as the presence of hyperbilirubinemia on day 3 of life which requires intervention (Significant hyperbilirubinemia). So, at 72hours of life, a TSB more than 13mg/dl was considered significant.

This is based on the 3 risk zones in the study done by Bhutani et al.[29]

- High risk zone - bilirubin level above 95th centile.
- Intermediate risk zone - bilirubin level between 40th to 95th centile.
- Low risk zone - bilirubin level less than 40th centile.

    - Blood group and DCT was done in children of O positive mothers
    - Neonates who developed direct hyperbilirubinemia, features suggestive of sepsis, respiratory distress were excluded from the study.

STATISTICAL ANALYSIS

Maternal and neonatal data were collected in predesigned and pretested proforma.

All characteristics were summarized descriptively. For continuous variables, the summary statistics of N, mean, standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries. Chi-square (χ^2)/Fisher exact test was employed to determine the significance of differences between groups for categorical data. The difference of the means of analysis variables was tested with the unpaired t-test. If the p-value was < 0.05, then the results will be considered to be significant. Data were analyzed using SPSS software v.23.0.

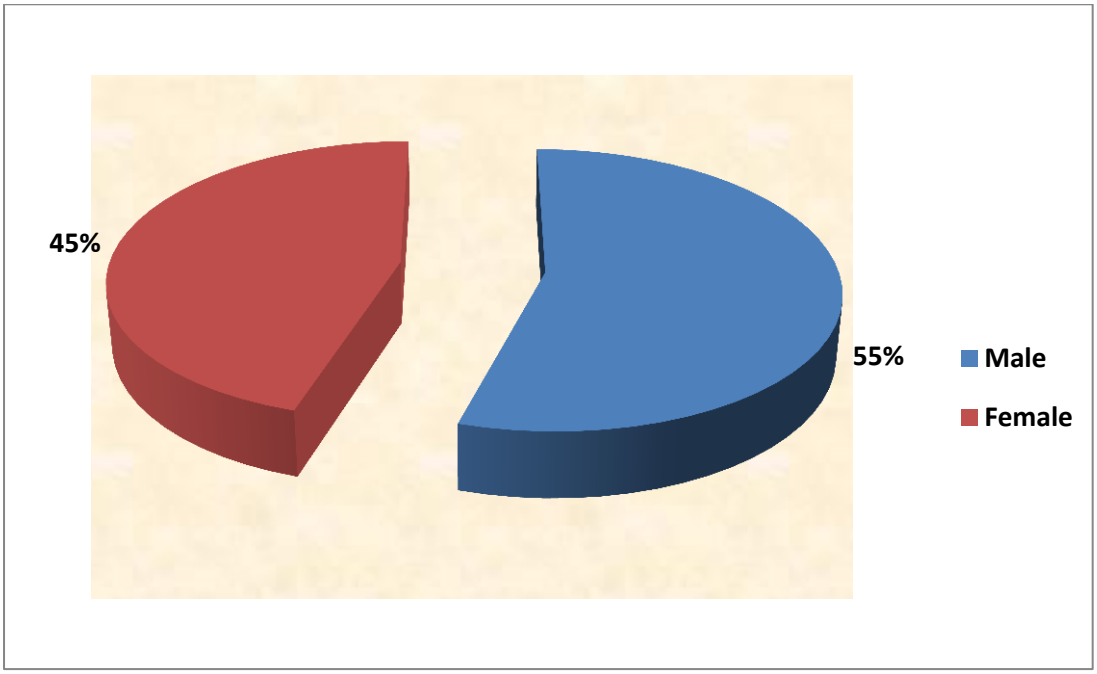
RESULTS

SEX DISTRIBUTION AMONG NEONATES

TABLE 1

Sex of neonate	Number	Percent
Males	93	55%
Females	77	45%
Total	170	100 %

GRAPH 1



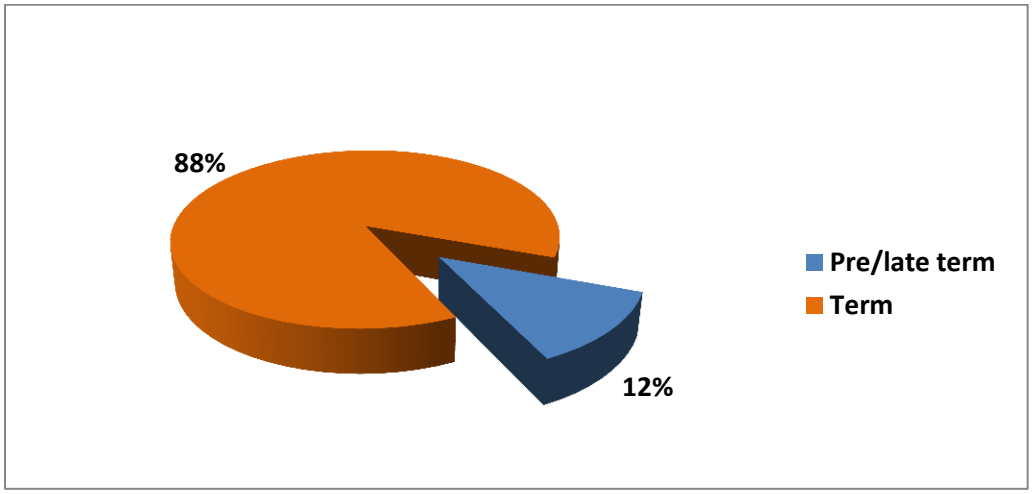
Among the 170 neonates included in the study, majority were males (93 or 55%) and females were 77in number (45%).

GESTATION PERIOD AMONG NEONATES

TABLE 2

Gestation period	Number	Percent
Term	149	88%
Late preterm	21	12%
Total	170	100%

GRAPH 2



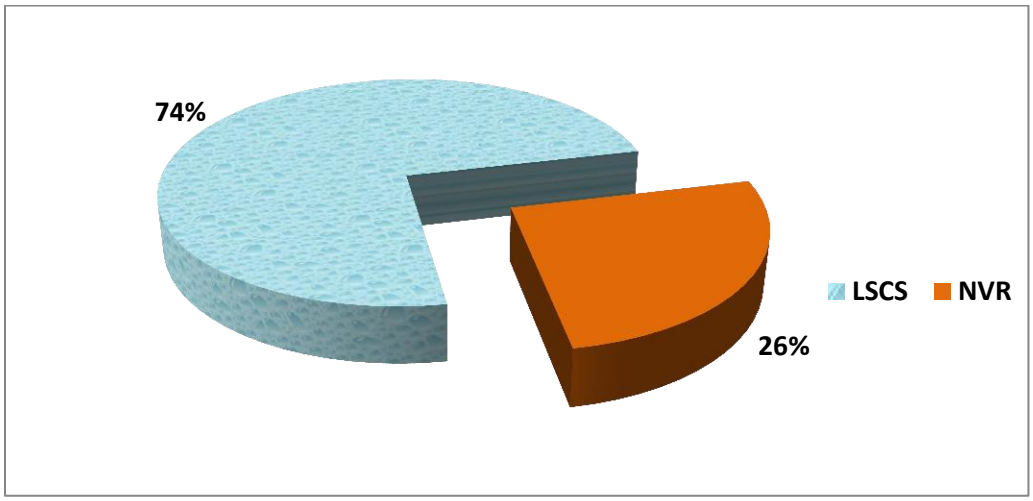
In this study, 88% of neonates were term and only 12% were late preterm.

ROUTE OF DELIVERY

TABLE 3

Route of delivery	Number	Percent
LSCS	126	74%
NVR	44	26%

GRAPH 3



74% of the neonates were borne by LSCS and 26% of them were borne by NVR.

SIGNIFICANT HYPERBILIRUBINEMIA

Out of the 170 neonates, 33 neonates developed significant hyperbilirubinemia (19%)

TABLE 4

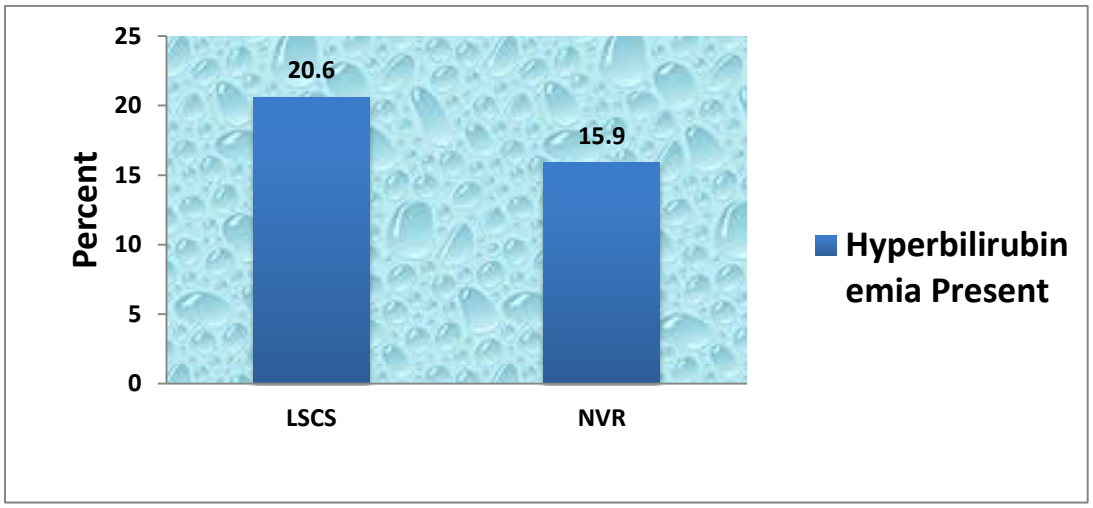
Hyperbilirubinemia	**Number**	**Percent**
Significant Hyperbilirubinemia	33	19%
No hyperbilirubinemia	137	81%
Total	170	100 %

ROUTE OF DELIVERY AND HYPERBILIRUBINEMIA

TABLE 5

Hyperbilirubinemia	LSCS		NVR	
	Number	Percent	Number	Percent
Yes	26	20.6%	7	15.9%
No	100	79.4%	37	84.1%

GRAPH 5



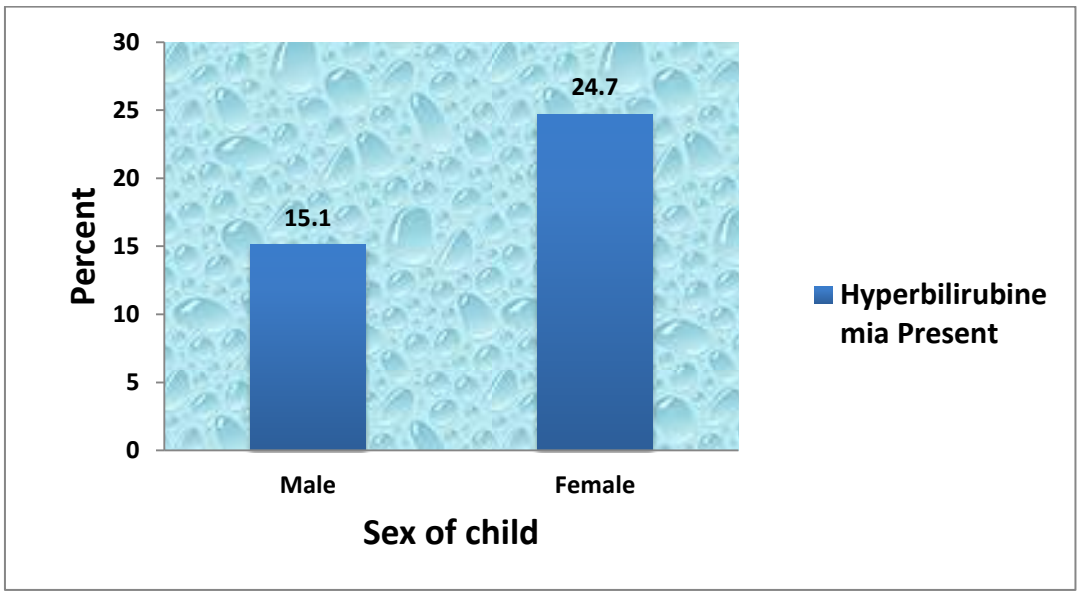
Among the neonates who developed significant hyperbilirubinemia (33), 20% of them were borne by LSCS and 15% were borne by NVR.

SEX OF NEONATE AND HYPERBILIRUBINEMIA

TABLE 6

Hyperbilirubinemia	MALES		FEMALES	
	Number	Percent	Number	Percent
Yes	14	15.1%	19	24.7%
No	79	84.9%	58	75.3%

GRAPH 6



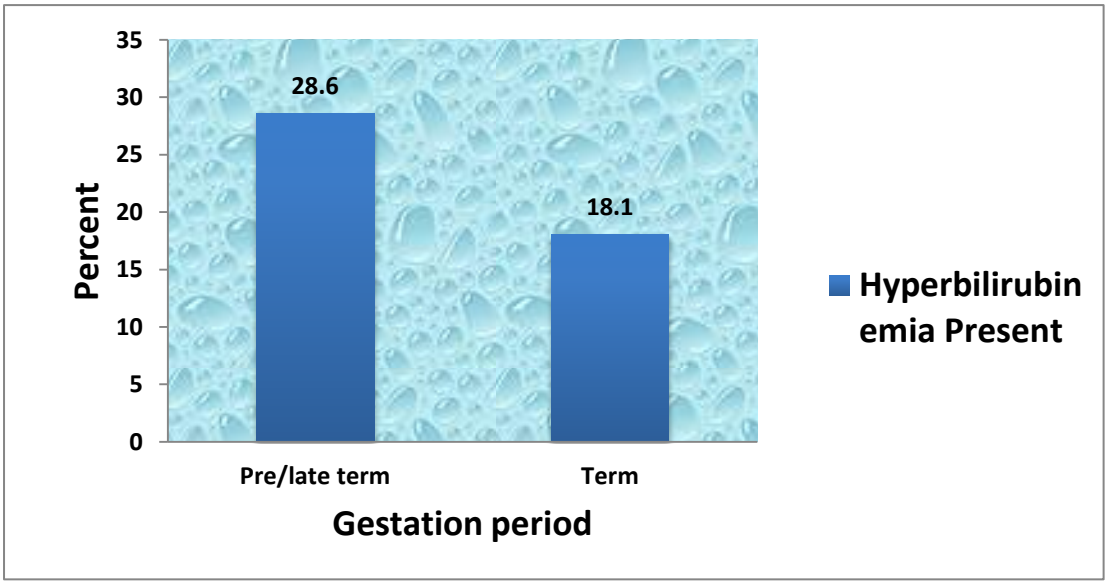
In this study, the number of female neonates who developed significant hyperbilirubinemia (15%) were more than the male neonates.

GESTATION PERIOD AND HYPERBILIRUBINEMIA

TABLE 7

Hyperbilirubinemia	Late preterm		Term	
	Number	Percent	Number	Percent
Present	6	28.6%	27	18.1%
Absent	15	71.4%	122	81.9%

GRAPH 7



Late preterm neonates developed more significant hyperbilirubinemia (28.6%) compared to the term neonates.

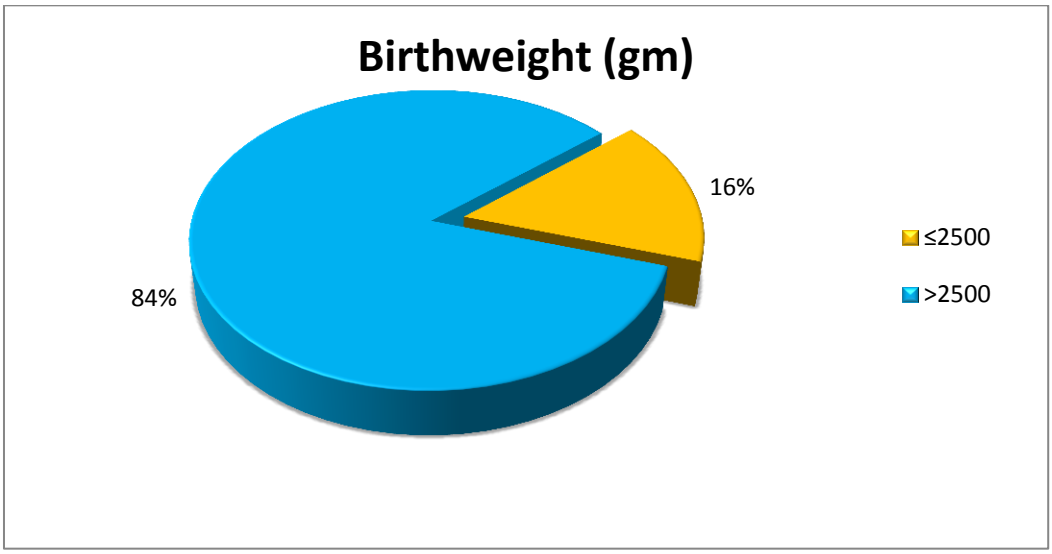
Among term neonates, only 18% developed significant hyperbilirubinemia.

BIRTH WEIGHT DISTRIBUTION

TABLE 8

Birth weight (grams)	Number of neonates	Percent
<2500	27	16%
>2500	143	84%
total	170	100%

GRAPH 8



In this study, 84% of the neonates were of normal birth weight and remaining 16% were low birth weight.

MEAN BIRTH WEIGHT AND MEAN TOTAL SERUM BILIRUBIN ON DAYS 1 AND 3 OF LIFE

TABLE 9

	MEAN	STANDARD ERROR	MINIMUM	MAXIMUM
BIRTH WEIGHT	2836.9	22.8	2250	3900
TSB DAY 1	5.8	0.1	1.8	12
TSB DAY 3	10.7	0.3	3.5	27

A mean birth weight of 2836.9 grams was recorded in this study. The minimum birth weight was found to be 2250grams and maximum birth weight was 3900grams.

A mean total serum bilirubin level on day 1 of life was obtained as 5.8.

The minimum TSB on day 1 of life was found to be 1.8 and maximum as 12.

A mean total serum bilirubin level on day 3 of life was found to be 10.7.

The minimum TSB on day 3 of life was recorded as 3.5 and maximum as 27.

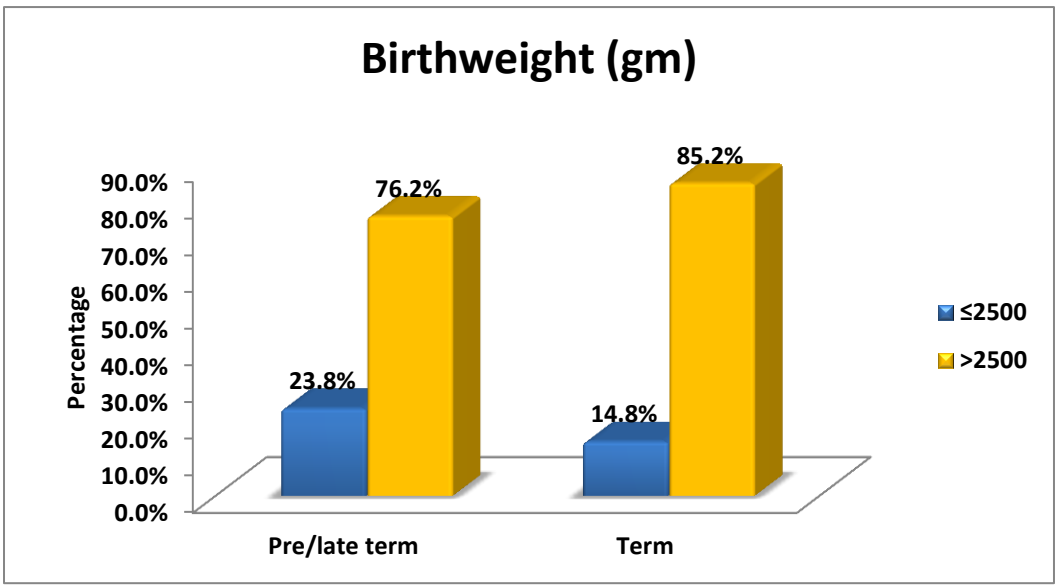
(These serum bilirubin values, minimum and maximum are not taking into consideration the gestational age).

BIRTH WEIGHT AND GESTATIONAL AGE DISTRIBUTION

TABLE 10

Birthweight (gm)	Pre/late term		Term		Total		p value
	N	%	N	%	N	%	
≤2500	5	23.8%	22	14.8%	27	15.9%	0.288
≥2500	16	76.2%	127	85.2%	143	84.1%	
Total	21	100.0%	149	100.0%	170	100.0%	

GRAPH 10



Among late preterm neonates in the study, 23.8% were low birth weight and 76.2% were normal birth weight.

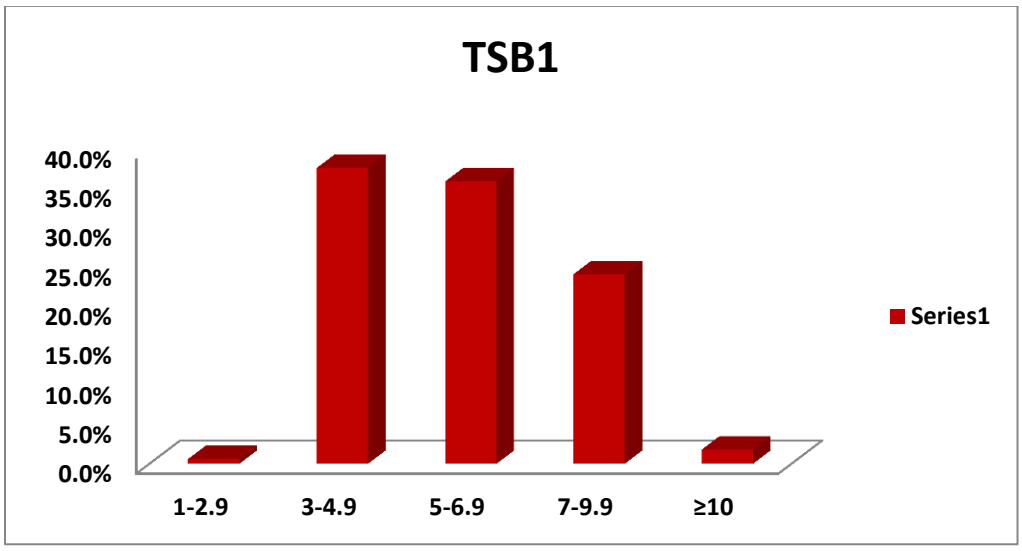
Among term neonates, 14.8% were low birth weight and 85.2% were normal birth weight.

DISTRIBUTION OF TSB1 LEVELS AMONG NEONATES

TABLE 11

TSB 1	Number of neonates	%
1-2.9	1	0.6%
3-4.9	64	37.6%
5-6.9	61	35.9%
7-9.9	41	24.1%
>10	3	1.8%
total	170	100%

GRAPH 11



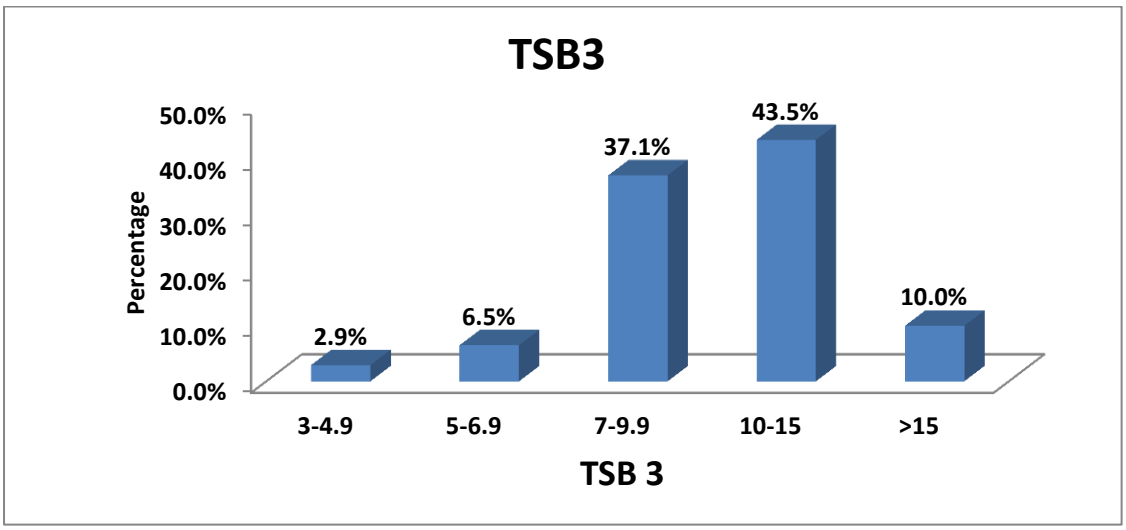
Maximum number of neonates (37.6%), on day 1 of life, irrespective of gestational age, had total serum bilirubin level of 3-4.9mg/dl

DISTRIBUTION OF TSB3 LEVELS AMONG NEONATES

TABLE 12

TSB3	Total	
	N	%
3-4.9	5	2.9%
5-6.9	11	6.5%
7-9.9	63	37.1%
10-15	74	43.5%
>15	17	10.0%
Total	170	100.0%

GRAPH 12



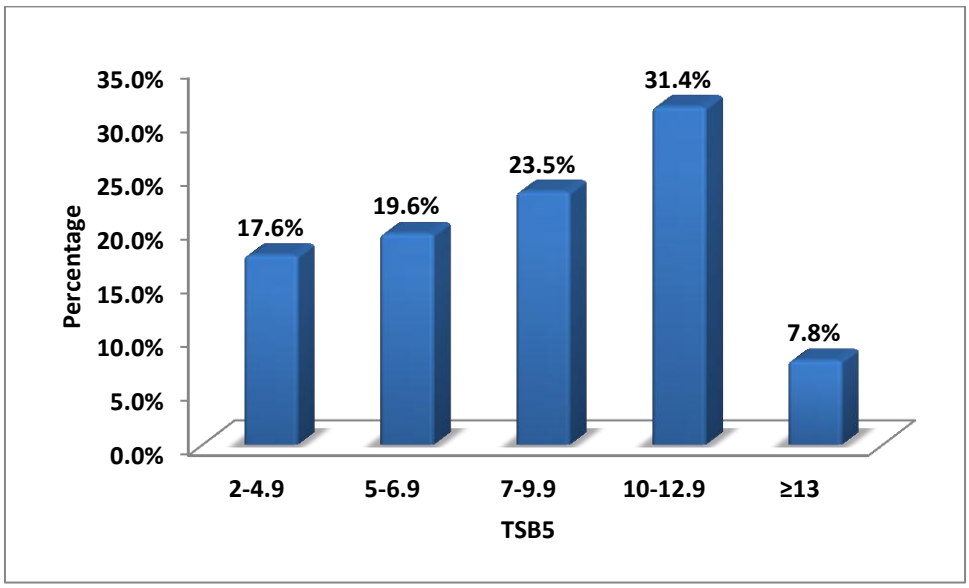
On day 3 of life, maximum number of neonates (43.5%) had total serum bilirubin level in the range 10-15mg/dl irrespective of gestational age.

DISTRIBUTION OF TSB5 LEVELS AMONG NEONATES

TABLE 13

TSB5	Total	
	N	%
2-4.9	9	17.6%
5-6.9	10	19.6%
7-9.9	12	23.5%
10-12.9	16	31.4%
≥13	4	7.8%
Total	51	100.0%

GRAPH 13



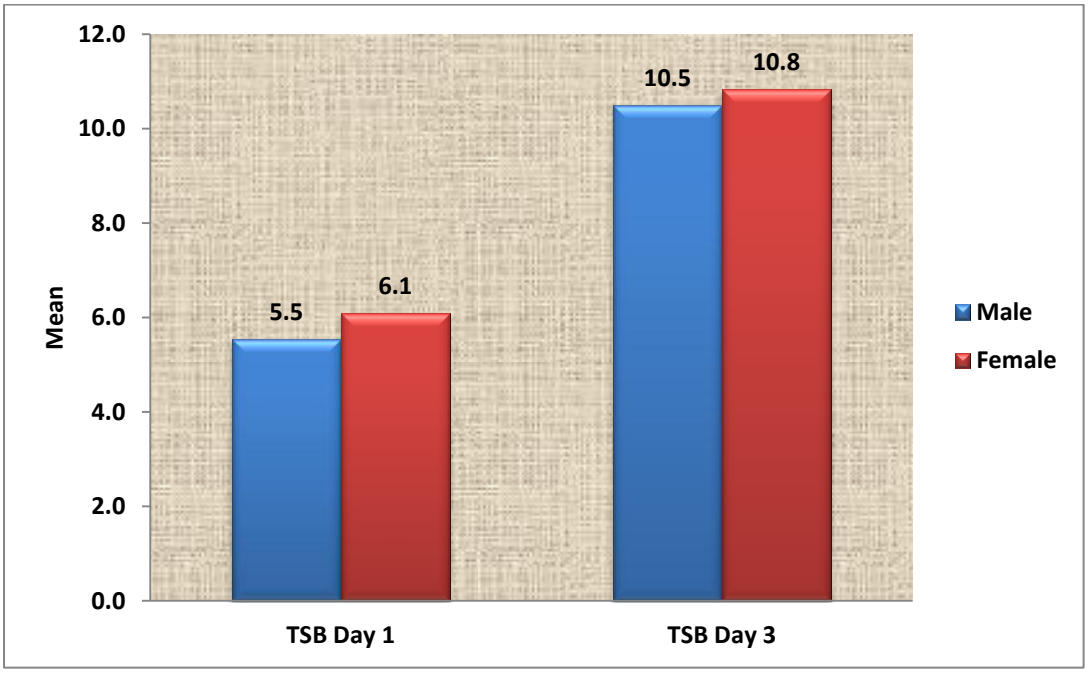
On day 5 of life, maximum number of neonates (39.2%) had total serum bilirubin in the range more than10mg/dl.

GENDER CORRELATION WITH HYPERBILIRUBINEMIA

TABLE 14

Day of life	MALES		FEMALES		P value
	Mean TSB	SE	Mean TSB	SE	
Day 1	5.5	0.2	6.1	0.2	0.052
Day 3	10.5	0.3	10.8	0.5	0.556

GRAPH 14



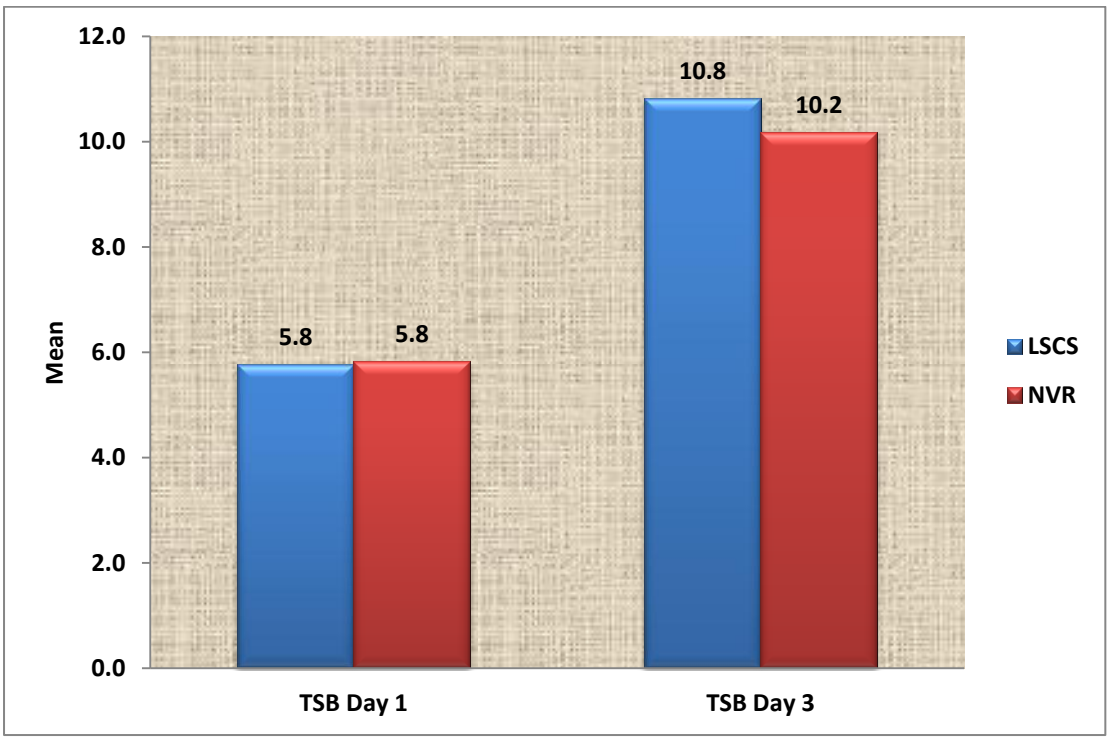
This study revealed that there was no significant difference in gender with regard to mean TSB values on days 1 and 3 of life.

HYPERBILIRUBINEMIA AND MODE OF DELIVERY

TABLE 15

Day of life	Mean TSB	SE	Mean TSB	SE	P value
Day 1	5.8	0.2	5.8	0.3	0.892
Day 3	10.8	0.3	10.2	0.4	0.302

GRAPH 15



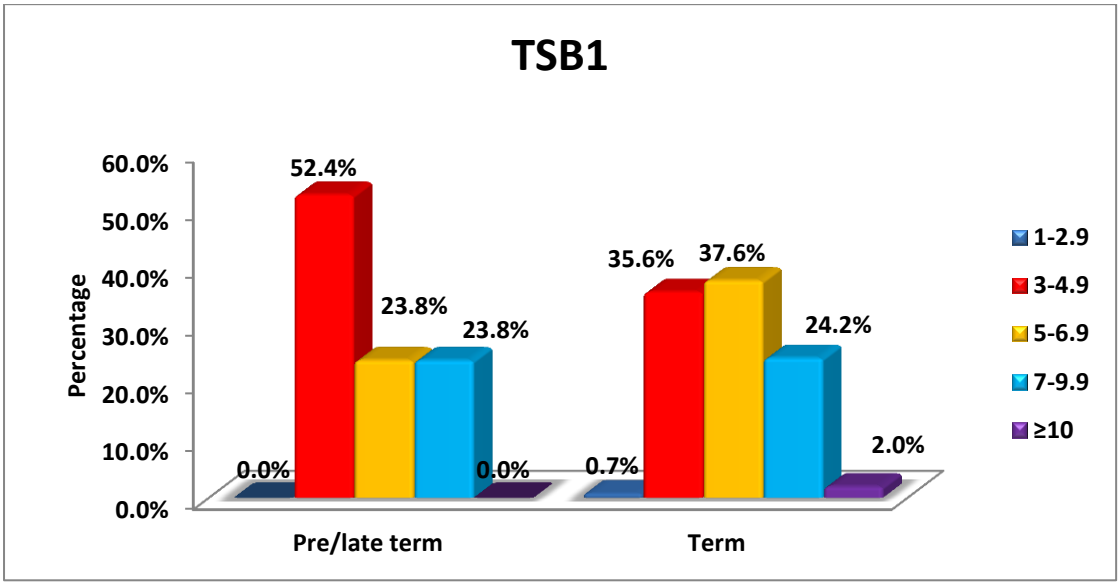
There is no significant difference in mean TSB on days 1 and 3 of life in neonates borne by LSCS or NVR

TSB 1 LEVEL DISTRIBUTION FOR TERM AND LATE PRETERM NEONATES

TABLE 16

TSB1	Pre/late term		Term		Total	
	N	%	N	%	N	%
1-2.9	0	0.0%	1	0.7%	1	0.6%
3-4.9	11	52.4%	53	35.6%	64	37.6%
5-6.9	5	23.8%	56	37.6%	61	35.9%
7-9.9	5	23.8%	36	24.2%	41	24.1%
≥10	0	0.0%	3	2.0%	3	1.8%
Total	21	100.0%	149	100.0%	170	100.0%

GRAPH 16



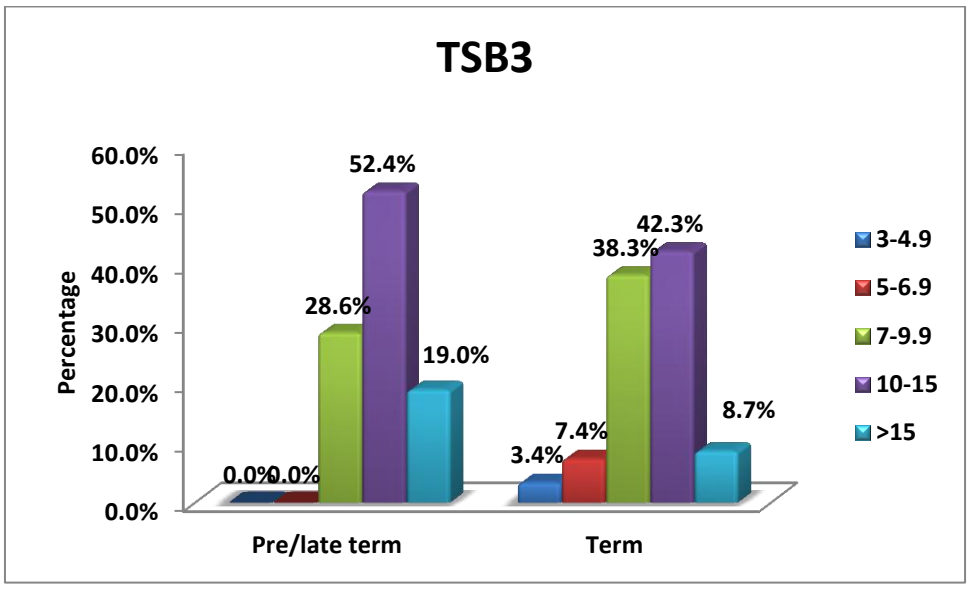
On day 1 of life, 52% late preterms had a TSB range of 3-4.9mg/dl and term neonates of 38% had TSB range 5-6.9mg/dl.

TSB 3 LEVEL DISTRIBUTION FOR TERM AND LATE PRETERM NEONATES

TABLE 17

TSB3	Pre/late term		Term		Total	
	N	%	N	%	N	%
3-4.9	0	0.0%	5	3.4%	5	2.9%
5-6.9	0	0.0%	11	7.4%	11	6.5%
7-9.9	6	28.6%	57	38.3%	63	37.1%
10-15	11	52.4%	63	42.3%	74	43.5%
>15	4	19.0%	13	8.7%	17	10.0%
Total	21	100.0%	149	100.0%	170	100.0%

GRAPH 17



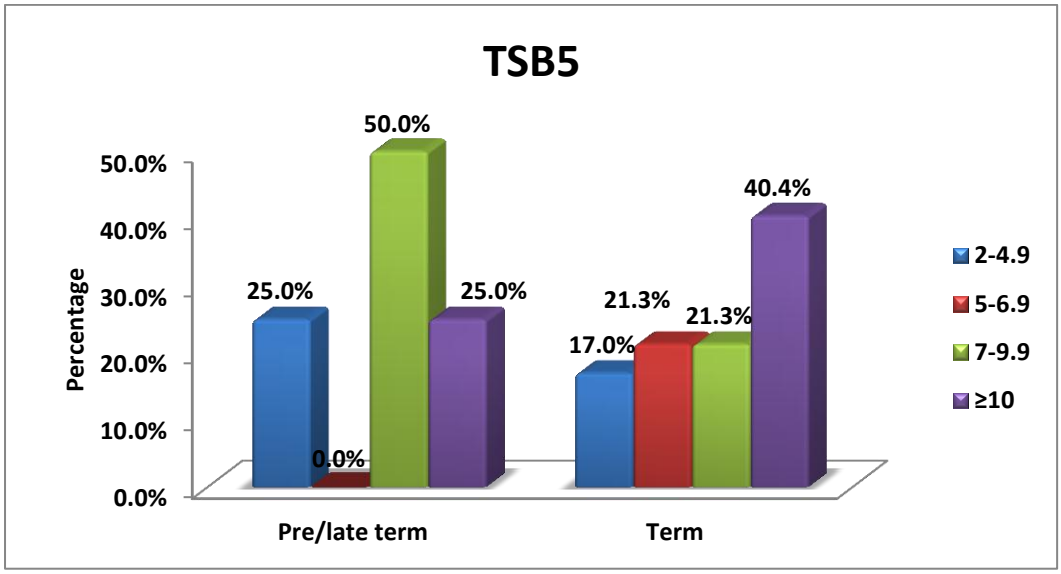
On day 3 of life, 52% late preterms had a TSB range of 10-15mg/dl and term neonates of 42% had the same range of TSB.

TSB 5 LEVEL DISTRIBUTION FOR TERM AND LATE PRETERM NEONATES

TABLE 18

TSB5	Pre/late term		Term		Total	
	N	%	N	%	N	%
2-4.9	1	25.0%	8	17.0%	9	17.6%
5-6.9	0	0.0%	10	21.3%	10	19.6%
7-9.9	2	50.0%	10	21.3%	12	23.5%
≥10	1	25.0%	19	40.4%	20	39.2%

GRAPH 18



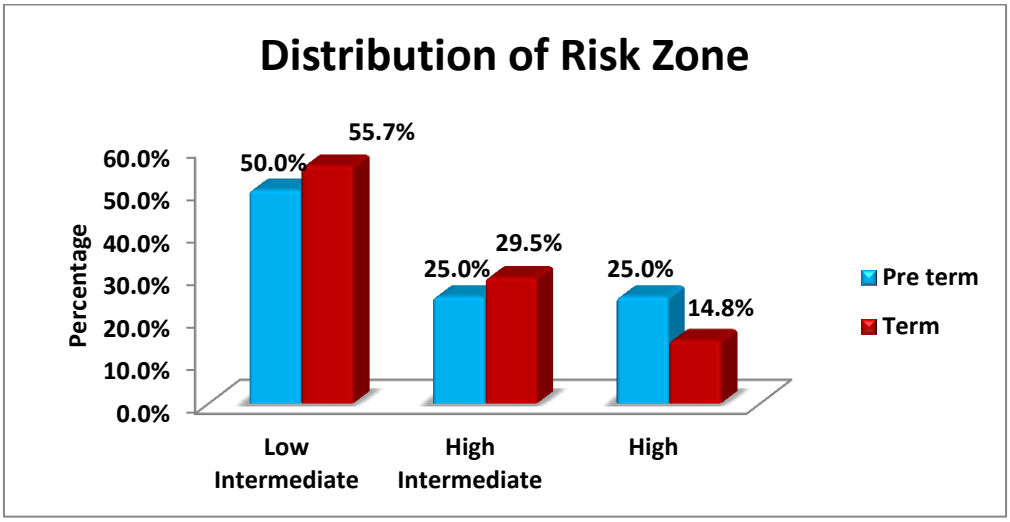
On day 5 of life, most late preterms (50%) had 7-7.9mg/dl of TSB and term neonates (40%) had a range of more than 10mg/dl

RISK ZONE STRATIFICATION FOR TERM AND LATE PRETERMS (WITH REFERENCE TO TSB 3)

TABLE 19

Risk Zone	Pre term		Term		Total		p value
	N	%	N	%	N	%	
Low Intermediate	6	50.0%	34	55.7%	40	54.8%	0.715
High Intermediate	3	25.0%	18	29.5%	21	28.8%	0.752
High	3	25.0%	9	14.8%	12	16.4%	0.381
Total	12	100.0%	61	100.0%	73	100.0%	--

GRAPH 19



Among the late preterm neonates who developed significant hyperbilirubinemia, 25% were in the high risk and high intermediate risk zones each. In term neonates who developed significant hyperbilirubinemia, 30% were in high intermediate risk and 15% in high risk zones respectively. Neonates in low intermediate risk zone were not considered to have significant hyperbilirubinemia.

DISTRIBUTION OF THE 33 NEONATES WITH SIGNIFICANT HYPERBILIRUBINEMIA BASED ON TSB 1 CUT OFF VALUE

TABLE 20

TSB1	Total Neonates		Total Neonates with Significant Hyperbilirubinemia				
	N	%	N	%	Range	Mean±SD	P value
>3.3 (Pre term)	20	45.3%	6	18.2%	3.4-8.4	6.4±2.3	
>4.2 (Term)	141	54.7%	27	81.8%	4.3-12.0	7.5±2.0	0.031
>3.3 (Total)	161	100.0%	33	100.0%	3.4-12.0	7.3±2.1	

In this study, 18% late preterm neonates who developed significant hyperbilirubinemia had a TSB1 of more than 3.3mg/dl.

In term neonates who developed significant hyperbilirubinemia (82%), had a TSB1 of more than 4.2mg/dl.

In preterms, TSB1 which predicts significant hyperbilirubinemia ranges from 3.4-8.4mg/dl and in terms, it is 4.3-12 mg/dl.

Both the TSB values predictive of significant hyperbilirubinemia on day 3 of life (for term and late preterm) were statistically significant.

DISCUSSION

Hyperbilirubinemia is the most common condition requiring evaluation and treatment in newborns. The clinical manifestation of hyperbilirubinemia - jaundice - occurs in 60% of normal newborns and nearly all preterm infants. This can get overshadowed and it may lose the attention it deserves resulting in potentially devastating effects. The best clinical strategy to avoid the development of marked hyperbilirubinemia and risk of acute bilirubin encephalopathy in late preterm neonate is preventive and includes screening for jaundice in the newborn nursery provision of lactation support, parental education, timely post-discharge follow up and appropriate treatment when clinically indicated.[34] The provision of lactation support during this period and during early postdischarge period, coupled with regular neonatal weight checks, is helpful to address lactation difficulties and also in early identification of those mother-infant pairs prone to suboptimal lactation or lactation failure. A shortened hospital stay (less than 48hours after delivery), although permitted for selected healthy term neonates, is not recommended for late preterm neonates. The AAP recommends close post discharge follow up for all newborns, a recommendation strongly reinforced in the current 2004 practice parameter, and one that is particularly relevant to the late preterm neonates [21]. When significant hyperbilirubinemia occurs, attention to phototherapy and exchange transfusion treatment thresholds as a function of gestational age and risk is a critical component in efforts to prevent brain injury. The gold standard for deciding therapy to prevent encephalopathy continues to be serum bilirubin levels.[35] After 48 hours of life, serum bilirubin should be evaluated 8-12 hourly if levels are above 14mg/dl; 6th hourly if above 16mg/dl; 4th hourly if above 18mg/dl and more frequently at higher values [27].

Our study aimed to determine the predictive ability of 1st day total serum bilirubin level for subsequent significant hyperbilirubinemia in term and late preterm newborns which require treatment.

170 Neonates were included in the study carried out in tertiary care hospital in Bijapur, Karnataka for predicting significant hyperbilirubinemia in term and late preterm neonates using first day serum bilirubin. Among them 149 neonates were term and 21 neonates were late preterm. We have considered peak serum bilirubin level >15mg/dl as "hyperbilirubinemia" since specific treatment is usually considered at or above this level [21].

EXCLUSION CRITERIA :

- Rh incompatibility
- ABO incompatibility
- Newborns with obvious life threatening congenital malformation
- Newborns with moderate to severe birth asphyxia
- Sepsis
- Hypothyroidism

BIRTH WEIGHT AND GESTATIONAL AGE(tables 2, 8,9,10) :

The birth weight of the newborns was recorded. All babies above 2 kg were included in the study. 16% of the neonates had low birth weight. Remaining 84% had normal birth weight.

The maximum birth weight recorded was 2836 grams and minimum was 2250 grams.

Majority of the late preterms (76%) and term neonates (84%) had their birth weight above 2500grams.

In a study by Agarwal et al[32], all newborns with gestational age of 35weeks or more were included. The range of birth weight for these children was from 1.75 - 4.0kg.

In a study by Bhutani et al [30], babies with birth weight more than 2kg for gestational age of more than 36weeks and birth weight of >2.5kg for gestational age of 35weeks were included.

SEX DISTRIBUTION (tables 1, 6,14) :

Among 170 neonates enrolled, 45% (77) were females and 54% (93) were males.

Male gender is a known risk factor for hyperbilirubinemia.[36]

In a study by Narang et al, incidence of hyperbilirubinemia in males was 64.2%. [37]

In another study, by Singhal et al, incidence of hyperbilirubinemia in males was 56.8%.[38]

But, in this study, 19 female neonates and only 14 male neonates developed significant hyperbilirubinemia. Also, there existed no correlation between gender and mean total serum bilirubin, was revealed from our study.

METHOD OF DELIVERY (tables 3,5,15) :

Only 26/126 neonates borne by LSCS developed significant hyperbilirubinemia

By vaginal route, 7/44 neonates developed significant hyperbilirubinemia.

It was found that peak serum bilirubin levels are higher in neonates borne by cesarean section than vaginal delivery and similar findings have been reported by others.[39]
Our study showed that there was no significant difference in the mean TSB value of newborns borne by LSCS or vaginal delivery

ESTIMATION OF BILIRUBIN (tables 11,12,13)

First day total serum bilirubin (TSB) is estimated within the first 24 hours, then subsequent TSB estimation is done on 3rd and 5th days respectively. Daily clinical examination of the newborns are done with particular reference to development of hyperbilirubinemia. Thereby, subsequent estimation of TSB is done on babies who develop significant hyperbilirubinemia and requiring phototherapy.

Bhutani and co-workers obtained serum bilirubin levels between 20-28 hours of age in 1097 neonates. Those neonates with serum bilirubin level less than 5mg/dl at 24hours developed a serum bilirubin level of more than or equal to 17mg/dl; whereas 33% neonates whose 24hours serum bilirubin level was atleast 8mg/dl developed a serum bilirubin level of atleast 17mg/dl.

Seidman et al [40] used a similar approach in Israeli newborns and found that the risk of bilirubin level of atleast 17mg/dl was 1.6% in those whose bilirubin levels were less than 5mg/dl at 24 hours of life versus 6.6% in those neonates whose bilirubin levels were atleast 5mg/dl at 24 hours.

The average bilirubin value on day 1 of life in our study was found to be 5.8 and that on day 3 of life was 10.7.

This was different for males and females, with higher average bilirubin value for females on both days 1 and 3 of life (6.1,10.8) versus average bilirubin value for males on days 1 and 3 of life (5.5,10.5).

Moreover, day 1 TSB for most of the neonates was in range of 3-4.9mg/dl. Then, on day 3 of life, TSB was maximum in range 10-15 mg/dl. By day 5 of life, the TSB range was >10mg/dl for the neonates in our study.

All newborns in our study were exclusively breast fed and feeding was initiated within first 4 hours of birth. This is in contrast with the study done by Bhutani et al where significant proportion of newborns (40%) were formula fed for various reasons.

In our study, initiation of breast feeding within 4 hours was not found to be associated with peak serum bilirubin of the first 3 days. This lack of association may be compounded by the feeding given in the next few days, but as this was not our study question, we do not have data on the daily intake.

EVALUATION OF BILIRUBIN VALUE TO PREDICT SIGNIFICANT HYPERBILIRUBINEMIA(tables4,7,20)

Out of 170 newborns, 33 newborns developed significant hyperbilirubinemia.

In these, 27 newborns were term gestation and 6 newborns were late preterm gestation.

Our study showed that all late preterms with TSB1 of > 3.3mg/dl and term neonates with TSB1 of >4.2mg/dl can predict statistically significant hyperbilirubinemia.

In one study Alpay et al[31] reported that TSB level >6mg/dl in the first 24hours of life will predict nearly all of the term newborns who will have significant

hyperbilirubinemia and will determine all those who will require phototherapy treatment later during the first days of life.

Agarwal et al [32] did one study to evaluate predictive value of TSB level 6mg% at 24 ± 6 hours postnatal age in identifying near term and term newborns that do not develop hyperbilirubinemia subsequently. In this study, first bilirubin estimation was done whenever clinical suspicion of jaundice exceeded 10mg%. Out of 220 newborns studied, 22 developed significant hyperbilirubinemia requiring phototherapy. TSB level of 6mg% or less was present in 136 newborns and only one developed hyperbilirubinemia. In the remaining 77 (36.2%) neonates with TSB> 6mg/dl, subsequent hyperbilirubinemia developed in 21 (sensitivity 95%, specificity 70.6%). They concluded that ideal cut off value was 5mg/dl and babies with TSB levels higher than 6mg% had a significant risk of developing hyperbilirubinemia.

In the study done by Awasthi S et al[30], a value of 3.99mg/dl (average value of first day TSB) was used to predict occurence of subsequent hyperbilirubinemia. The sensitivity and specificity of this test was 67%. However, this study had major flaws. Complete follow up was present in newborns who stayed in hospital for neonatal illness or some maternal reason, such as cesarean section. More than 50% newborns, who were healthy thus discharged early, were not followed up.

RISK STRATIFICATION

Bhutani et al did a study to assess the predictive ability of universal predischarge serum bilirubin measurement to screen for the risk of subsequent significant hyperbilirubinemia in direct coomb's negative healthy term / near term newborns during the first postnatal week. TSB was obtained at the time of routine metabolic screen in all term/near term newborns. A percentile based nomogram for the first

week was constructed from hour specific predischarge and postdischarge TSB values of newborn.

The normogram has 3 risk zones:

- Low risk zone < 40th centile
- Intermediate risk zone
  - Low intermediate (40th - 75th centile)
  - High intermediate (75th - 95th cenile)
- High risk zone >95th centile

Newborns were divided into three risk zones as mentioned above (table 19)

Of the 27 term neonates who developed significant hyperbilirubinemia, 9 neonates were in high risk zone, 15 neonates in high intermediate risk zone and 3 neonates in low intermediate risk zone.

Of the 6 late preterm neonates who developed significant hyperbilirubinemia, 4 of them were in high risk zone and 1 each in high intermediate and low intermediate risk zones.

SUMMARY

Our study was conducted in a tertiary care hospital over a period of one and half years wherein all neonates (term and late preterm) fulfilling the inclusion criteria were included in the study. This was done after obtaining the informed parental consent.

These neonates in postnatal ward were clinically examined for jaundice till day 5 of life. Along with that, exclusive breast feeding was ensured.

Then, serum bilirubin level (total and unconjugated fraction) was assessed on days 1, 3 and 5 of life. If on day 3 of life, baby developed significant hyperbilirubinemia, that is, the bilirubin value was in high / intermediate risk zone, then phototherapy was started.

The risk stratification into high risk / intermediate risk / low risk zones were based on the study by Bhutani et al.[26]

Results are summarised below :

- ✓ Among 170 neonates in the study, 33 neonates developed significant hyperbilirubinemia (19%)
- ✓ 27 term neonates (18%) and 6 late preterm neonates (28.6%) developed significant hyperbilirubinemia
- ✓ In late preterm neonates, the TSB value on day 1 predictive of significant hyperbilirubinemia was 3.3mg/dl
- ✓ In term neonates, the TSB value on day 1 predictive of significant hyperbilirubinemia was 4.2mg/dl
- ✓ Mean TSB on day 1 for a late preterm neonate was 6.4mg/dl
- ✓ Mean TSB on day 1 for a term neonate was 7.5mg/dl.

- ✓ By risk stratification, among preterm neonates 25% were in both high risk and high intermediate risk zones.
- ✓ In term neonates, 15% were in high risk zone and 30% in high intermediate risk zones.

  (Low intermediate risk zone neonates were not included)

Hence, the concept of prediction of jaundice helps to pick up neonates at risk for hyperbilirubinemia.

Kernicterus, one of the most easily preventable causes of brain injury from severe neonatal jaundice has re-emerged in our country as a public and societal health concern. This can be prevented, provided excessive hyperbilirubinemia for age is promptly identified and treated.

So, risk based guidelines available to target, evaluate, intervene and follow up neonates according to AAP's practice parameter should be used.

CONCLUSION

Our study helps to predict the risk of a late preterm / term neonate developing significant hyperbilirubinemia using first day serum bilirubin.

Cut off values need to be defined in individual popultions, so that it could guide the clinician in safe discharge, targeted follow up and withhold of discharge.

Our study has shown a TSB on day 1 for late preterm >3.3mg/dl and for term neonates >4.2mg/dl is predictive of significant hyperbilirubinemia.

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ANNEXURES

ETHICAL CLEARANCE CERTIFICATE

B.L.D.E. UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR-586 103
INSTITUTIONAL ETHICAL COMMITTEE

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 22-11-2014 at 3-30 pm to scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected & revised version synopsis of the Thesis has been accorded Ethical Clearance.

Title "prediction of significant hyperbilirubinemia in late preterm and term babies using first day serum bilirubin level - A prospective study"

Name of P.G. student Betsy Mathew.
Dept of paediatrics.

Name of Guide/Co-investigator Dr S.S. Kalyanshettar.
Professor of paediatrics.

DR.TEJASWINI. VALLABHA
CHAIRMAN
INSTITUTIONAL ETHICAL COMMITTEE
BLDEU'S, SHRI.B.M.PATIL
MEDICAL COLLEGE, BIJAPUR.

Following documents were placed before E.C. for Scrutinization
1) Copy of Synopsis/Research project.
2) Copy of informed consent form
3) Any other relevant documents.

CONSENT FORM

TITLE OF THE PROJECT : **"PREDICTION OF SIGNIFICANT HYPERBILIRUBINEMIA IN LATE PRETERM AND TERM BABIES USING FIRST DAY SERUM BILIRUBIN LEVEL – A PROSPECTIVE STUDY "**

P.G GUIDE **:** **DR. S.S. KALYANSHETTAR**
PROFESSOR
DEPARTMENT OF PEDIATRICS
SHRI B.M PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE, VIJAYAPUR

PG STUDENT **:** **DR. BETSY MATHEW**
DEPARTMENT OF PEDIATRICS

1: PURPOSE OF RESEARCH:

I have been informed that this is a study to predict significant hyperbilirubinemia in late preterm and term babies using first day total serum bilirubin level

2: PROCEDURE:

I am aware that the investigator will ask a series of questions about the antenatal period and subject the baby for thorough clinical examination. Thereafter, the baby shall be investigated for significant hyperbilirubinemia

3: RISK AND DISCOMFORTS:

I understand that this study may cause some pain and discomfort to the baby but does not pose any risk to the baby's health

4: BENEFITS: I understand that my baby's participation in this study will help to predict significant hyperbilirubinemia in the later part of 1st week of life so as to initiate treatment as soon as possible.

5: CONFIDENTIALITY:

I understand that medical information produced by this study will become part of institutional records and will be subject to the confidentiality and privacy regulation of the said institute. Information of a sensitive personal nature will not be a part of medical record, but will be stored in investigator's research file and identified only by a code number. The code key connecting name two numbers will be kept in a separate secured location.

If the data to be used for publication in the medical literature and for teaching purpose, no names will be used and other identities such as photographs will be used only with my special written permission. I understand that I may see the photographs before giving this permission.

6: REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time. Dr. Betsy Mathew is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of this study which might influence my baby's continued participation. If during the study or later, I wish to discuss my participation in all concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me. A copy of this consent form will be given to me to keep for careful reading.

7: REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my baby's participation is voluntary and may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand that Dr. Betsy Mathew may terminate my baby's participation in this study at any time after she/he has explained the reasons for doing the same

8: INJURY STATEMENT

I understand that in unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, then medical treatment will be available to me, but no further compensation would be provided. I understand that by my agreement to participate in this study I am not waiving any of my legal rights.

9: PARENT'S/GUARDIAN'S CONSENT STATEMENT

I confirm that Dr. Betsy Mathew has explained to me the purpose of research, the study procedure that my baby will undergo, and the possible risk and discomforts as well as benefits that the baby may experience in my own language. I am willing to allow my baby to undergo the study. Therefore, I agree to give consent for my baby to participate as a subject in this research project.

_____ _____

Parent/Guardian Date:

_____ _____

Signature of witness Date:

I have explained to _____ the purpose of research, the procedures required and possible risks and benefits to the best of my ability in patient's own language

_____ _____ _____

Dr.Betsy Mathew Dr. S.S. Kalyanshettar Date

(Investigator) (Guide)

PROFORMA

"PREDICTION OF SIGNIFICANT HYPERBILIRUBINEMIA IN LATE PRETERM AND TERM BABIES USING FIRST DAY SERUM BILIRUBIN LEVEL – A PROSPECTIVE STUDY "

Sl. No IP No: DOA : DOD :

- Name :
- Address :
- Date and time of delivery :
- Sex of the infant : Gestational Age :
- Wt. of the infant :

- Antenatal Factors
- Age :
- Parity :
- Past H/o Jaundice in other children :
- H/o intake of Drugs :
- Hbs Ag :
- HIV :
- Blood Group :

- Intranatal Factors

- Type of Delivery
- FTND
- LSCS Elective
  Emergency
- Instrumentation Vaccum
  Forceps
- CIAB (Cried Immediately After Birth)
- Postnatal Factors
- F/S/O illness in the Neonate :
- Frequency of feeding :
- Meconium passed at :
- Frequency of stools :
- Investigations
- Hb % :
- Total serum bilirubin(TSB) within 24hrs of birth :
- TSB on 3rd day :
- TSB on 5th day
- T_3 , T_4 , TSH (wherever applicable)

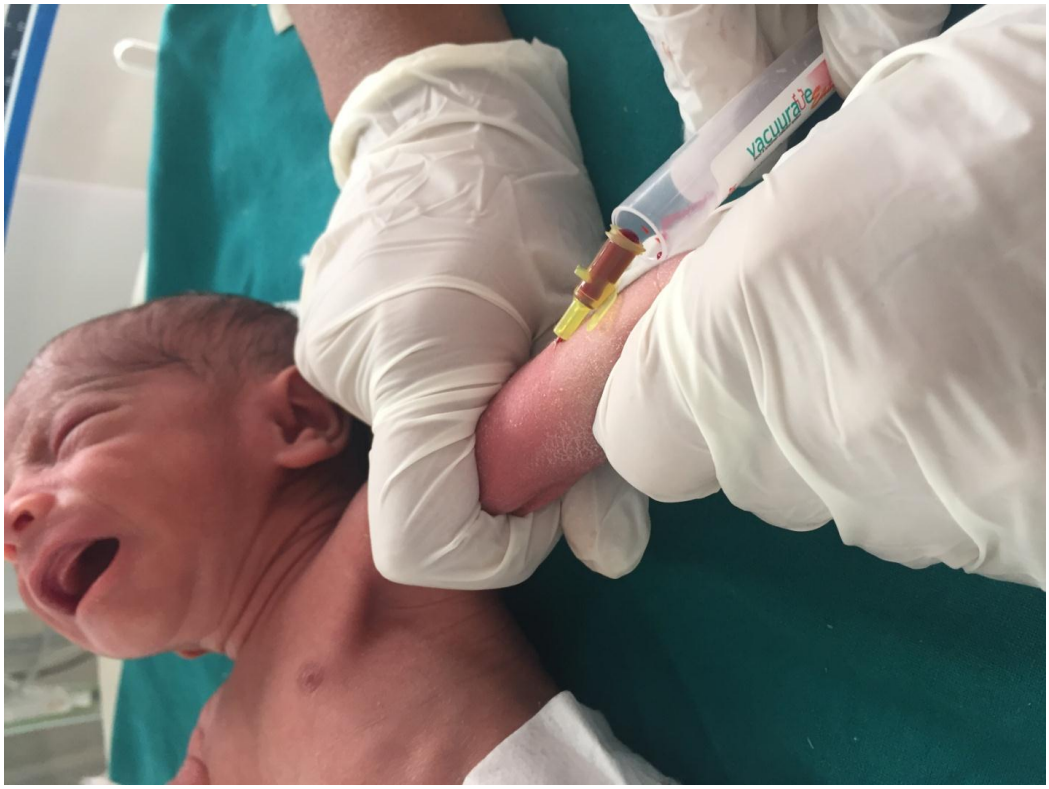

Photo 1 - Serum bilirubin collection

Photo 2 : Fujifilm Dri-chem 7000i

KEY TO MASTER CHART

LSCS - Lower Segment Cesarean Section

NVR - Normal Vaginal Route

NICU - Neonatal Intensive Care Unit

PRIMI - Primi gravida

TSB - Total Serum Bilirubin

TSB1 - Total Serum Bilirubin on 1st day of life

TSB3 - Total serum bilirubin on 3rd day of life

TSB5 - Total serum bilirubin on 5th day of life

BO - Baby Of

BLOOD GROUP < M > - blood group of mother

BLOOD GROUP < B > - blood group of baby

PT - preterm