Liver Function Tests

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Some of the more well-known functions include the following:

- Production of bile, which helps carry away waste and break down fats in the small intestine during digestion
- Production of certain proteins for blood plasma
- Production of cholesterol and special proteins to help carry fats through the body
- Conversion of excess glucose into glycogen for storage (glycogen can later be converted back to glucose for energy) and to balance and make glucose as needed
- Regulation of blood levels of amino acids, which form the building blocks of proteins
- Processing of hemoglobin for use of its iron content (the liver stores iron)
- Conversion of poisonous ammonia to urea (urea is an end product of protein metabolism and is excreted in the urine)
- Clearing the blood of drugs and other poisonous substances
- Regulating blood clotting
- Resisting infections by making immune factors and removing bacteria from the bloodstream
- Clearance of bilirubin, also from red blood cells.

Liver function tests are blood tests used to help find the cause of the symptoms and monitor liver disease or damage.

The tests measure the levels of certain enzymes and proteins in the blood.

Some of these tests measure how well the liver is performing its regular functions of producing protein and clearing bilirubin, a blood waste product.

Other liver function tests measure enzymes that liver cells release in response to damage or disease.

Liver function tests can be used to:

- 1- Screen for liver infections, such as hepatitis
- 2- Monitor the progression of a disease, such as viral or alcoholic hepatitis, and determine how well a treatment is working
- 3- Measure the severity of a disease, particularly scarring of the liver (cirrhosis)
- 4- Monitor possible side effects of medications.

Levels that are higher or lower than usual can mean liver problems.

The pattern and degree of elevation of these tests along with the overall clinical picture can provide hints to the underlying cause of these problems.

One way is to monitor the following symptoms of liver disorders.

1-The skin and white areas of the eyes appear yellowish (jaundice).
2-Swollen abdomen and abdominal pain. 3-There is swelling in the ankles and feet.
4-Itchy skin. 5-Dark urine. 6-Pale stools. 7-Weakness and fatigue. 8-Nausea or vomiting. 9-Decreased appetite. 10-The body bruises easily.

The Reasons why you should take a Liver Function Test

1.To screen for liver infections, such as hepatitis C.
2. To monitor the side effect of certain medications known to affect the liver
3. To monitor a liver disease and how well a particular treatment is working
4. To measure the degree of scarring(cirrhosis) on the liver

The liver is a multifunctional organ involved in various functions, such as excretory, synthesis, detoxification, storage, and metabolism.

It can store (storage function):

1. Amino Acids. 2.Carbohydrates. 3.Lipids. 4.Vitamins. 5.Minerals.

It can synthesize (metabolic function):

1. Protein, like albumin, alpha, and beta globulins.
2. Coagulation factors.
3. Transport proteins.

The liver is the site for detoxification of: 1.Drugs. 2.Toxins.

Its major function is Conjugation:

1. bilirubin combines with glucuronic acid as:
    1. Bilirubin Monoglucuronide.
    2. Bilirubin diglucuronide.

The liver has an excretory function:

1. Excrete bilirubin into bile.
2. Bile acid is excreted into the bile.

The liver is also the site of catabolism of:

1. Thyroid hormone. 2.Steroids hormones. 3.Few other hormones as well.

The importance of liver function tests are:
1. To assess the severity of liver damage.
2. To differentiate different types of jaundice.
3. To find out the presence of latent liver diseases.

The first group of tests includes regarding secretory, excretory and enzymatic functions are: Serum bilirubin test, bilirubin and urobilinogen in urine, BSP excretion test, Serum alkaline phosphatase estimation and SGPT.
Second group of tests meant for assessing the protein synthetic functions are: Total protein estimation, A/G ratio and prothrombin time.
The final group include that are meant for lipid metabolic functions are: Estimation of serum cholesterol and determination of free and esterified cholesterol ratio.

Tests Are Included In Routine LFT:

1. Serum Bilirubin.

A.Total Bilirubin
B.Direct and Indirect Bilirubin.

1. SGPT.
2. SGOT.
3. Alkaline phosphatase
4. Total protein.
5. Albumin.

The Additional Liver Function Tests:

1. γ – GT (gamma – GT)
2. Viral hepatitis profiles like HBV, HCV, HAV, HDV, HEV, etc.,

SERUM BILIRUBIN

Bilirubin (BR)is a yellow-orange pigment which gives the serum its characteristics yellow colour.
It's the breakdown product of normal heme catabolism, caused by the body's clearance of aged red blood cells which contain haemoglobin.

At the end of their life span red blood cells are broken down by the reticuloendothelial system, mainly in the spleen .

The released haemoglobin is split into globin, which enters the general protein pool and haem, which is converted to bilirubin after removal of iron,the iron is reutilized.

Bilirubin consists of an open chain tetrapyrrole. It is formed by oxidative cleavage of a porphyrin in heme,which affords biliverdin then Biliverdin is reduced to bilirubin.

Porphyrins are a group of heterocyclic macrocycle organic compounds, composed of four modified pyrrole subunits interconnected at their α carbon atoms via methine bridges (=CH−).

Reticuloendothelial cells are macrophages which are responsible for the maintenance of the blood, through the destruction of old or abnormal cells. They take up red blood cells and metabolise the haemoglobin present into its individual components; haem and globin.

Globin is further broken down into amino acids which are subsequently recycled.

Meanwhile, haem is broken down into iron and biliverdin, a process which is catalysed by haem oxygenase.

The iron gets recycled, while biliverdin is reduced to create unconjugated bilirubin.

The breakdown of heme to bilirubin occurs by a two-step process.

First, heme is converted to biliverdin by heme oxygenase , which functions predominantly as an integral membrane protein of the smooth endoplasmic reticulum.

Second, biliverdin is converted rapidly to bilirubin by the cytosolic protein biliverdin reductase .

Catabolism of erythrocyte-derived hemoglobin to bilirubin takes place primarily in reticuloendothelial cells in the spleen, liver, and bone marrow.

Bilirubin in plasma is mostly produced by the destruction of erythrocytes . Heme is metabolized into biliverdin (via heme oxygenase) and then into bilirubin (via biliverdin reductase) inside the macrophages.

Bilirubin is then released into the plasma and transported to the liver bound by albumin , since it is insoluble in water in this state. In this state, bilirubin is called unconjugated (despite being bound by albumin).

In the liver, unconjugated bilirubin is up-taken by the hepatocytes and subsequently conjugated with glucuronic acid (via the enzyme uridine diphosphate- glucoronyl transferase). In this state, bilirubin is soluble in water and it is called conjugated bilirubin.

Conjugated bilirubin is excreted into the bile ducts and enters the duodenum. During its transport to the colon, it is converted into urobilinogen by the bacterial enzyme bilirubin reductase.

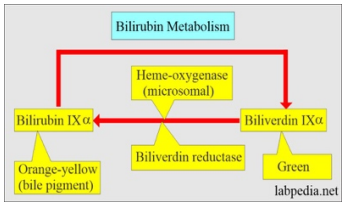
Most of the urobilinogen is further reduced into stercobilinogen into and is excreted through feces (air oxidizes stercobilinogen to stercobilin , which gives feces their characteristic brown color).

A lesser amount of urobilinogen is re-absorbed into portal circulation and transferred to the liver. For the most part, this urobilinogen is recycled to conjugated bilirubin and this process closes the enterohepatic circle.

There is also an amount of urobilinogen which is not recycled, but rather enters the systemic circulation and subsequently the kidneys, where it is excreted.

Air oxidizes urobilinogen into urobilin , which gives urine its characteristic color.

In parallel, a small amount of conjugated bilirubin can also enter the systemic circulation and get excreted through urine.

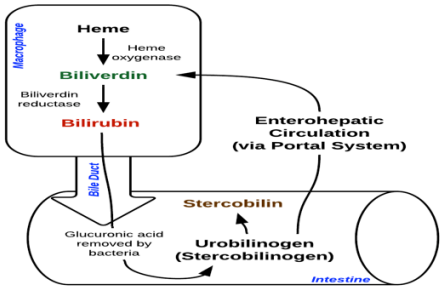


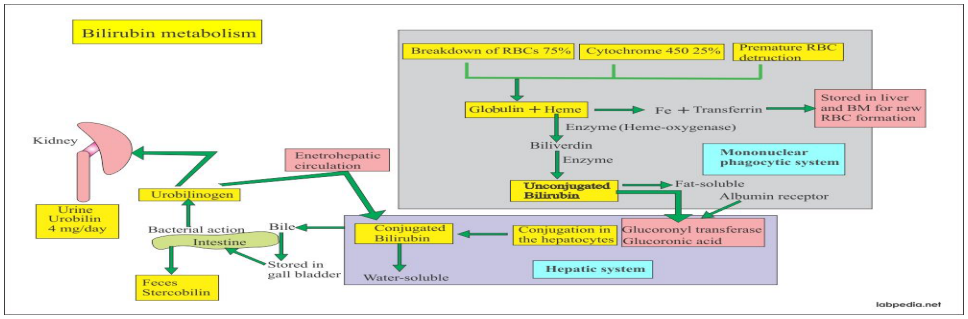
Bilirubin exists in two forms; unconjugated and conjugated. Unconjugated bilirubin is insoluble in water. This means it can only travel in the blood stream if bound to albumin and it cannot be directly excreted from the body.

In contrast, conjugated bilirubin is water soluble. This allows it to travel through the blood stream without requiring transport proteins like albumin, which means that it can also be excreted out of the body.

Total bilirubin = direct bilirubin + indirect bilirubin

- In the liver, bilirubin is conjugated with glucuronic acid by the enzyme glucuronyltransferase, making it soluble in water: the conjugated version is also often called "direct" bilirubin.
- Conjugated bilirubin is not absorbed and instead passes into the colon.
- There, colonic bacteria deconjugate and metabolize the bilirubin into colourless urobilinogen, which can be oxidized to form urobilin and stercobilin: these give stool its characteristic brown colour.





Bilirubin metabolism (How bilirubin forms):

1- Changes in the mononuclear phagocytic system(MNS):

The breakdown of the RBCs is a major source for the formation of Globin and heme.

Heme changes into Biliverdin and releases iron which is recycled for the formation of RBCs in the bone marrow.

Biliverdin forms the unconjugated bilirubin which is fat-soluble.

2- Changes in the liver cells:

1- Unconjugated bilirubin is in the presence of glucoronyl transferase enzyme is conjugated with glucuronic acid.

2- There is the formation of monoglucuronide and diglucuronide (conjugated bilirubin).

3- Conjugated bilirubin enters the enterohepatic circulation.

4- Bilirubin 95% is excreted into bile in the form of:

a- Glucuronide.

~90% is diglucuronide.

~10% is monoglucuronide.

b- Glucosides.

c- Xylosides.

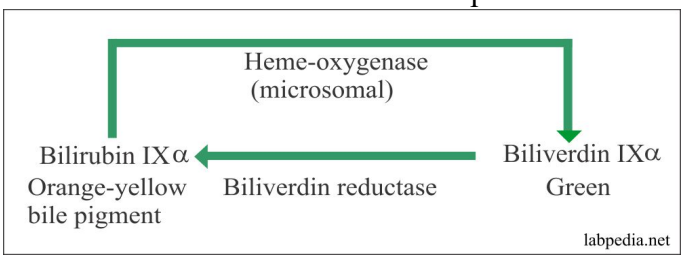
3- Changes in the intestine:

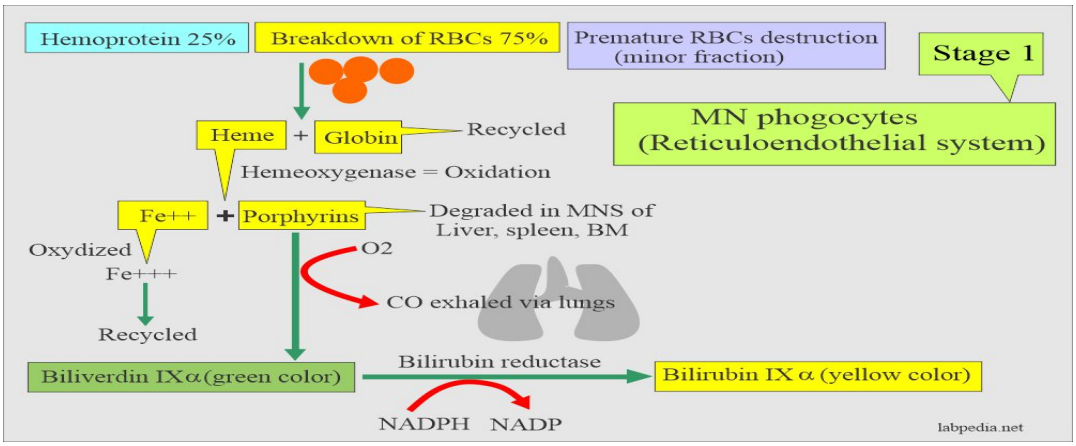
1-Bilirubin is hydrolyzed by the catalytic action of β-glucuronidase from the liver, intestinal epithelial cells, and bacteria.

2-The unconjugated bilirubin is reduced by the anaerobic intestinal bacterial flora to form a group of three colorless tetrapyrroles called urobilinogen:

Stercobilinogen. , Mesobilinogen. And Urobilinogen.

(20% reabsorbed from the intestine and enters the enterohepatic circulation.)





4- The extrahepatic fate of bilirubin:

1-Water-soluble bilirubin is stored in the gallbladder and it is released into the intestine.

2-Through enterohepatic circulation excreted in the feces and in the urine.

a-In the urine is excreted as urobilinogen.

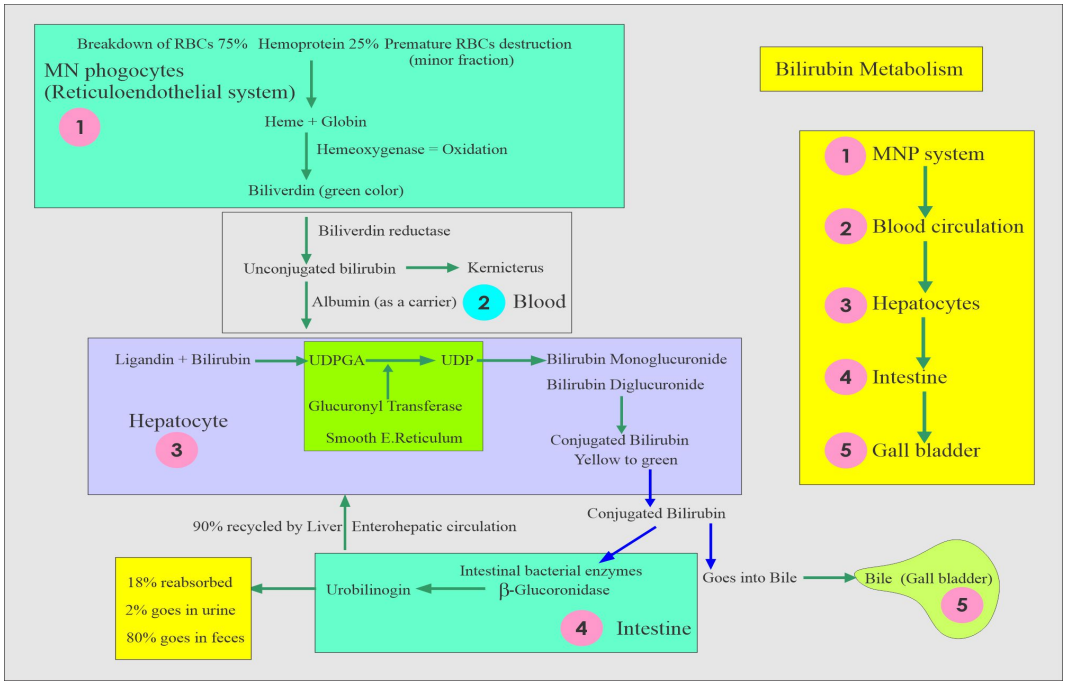
b-In the stool as stercobilinogen.

c-The three urobilinogen in the lower intestinal tracts produce bile pigments: Stercobilin , Mesobilin , and Urobilin.

These are orange-brown and are major pigments of the stool.

Major differences between unconjugated and conjugated bilirubin

FEATURE	Unconjugated bilirubin	CONJUGATED BILIRUBIN
Normal serum level	More	Less (less than 0.25mg/dl)
Water solubility	Absent	Present
Affinity to lipids (alcohol solubilty)	Present	Absent
Serum albumin binding	High	Low
Van den Bergh reaction	Indirect (Total minus direct)	Direct
Reanal excretion	Absent	Present
Affinity to brain tissue	Present (kernicterus)	Absent



Hyperbilirubinemia

- Imbalance of bilirubin production and elimination
- Hyperbilirubinemia: the concentration of blood bilirubin are more than 1mg/dl
- Jaundice : (also called icterus) refers to the yellow color of the skin and sclera caused by deposition of bilirubin, secondary to increased bilirubin levels in the blood.
- Although not a disease itself, jaundice is usually a symptom of an underlying disorder.

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Causes:

1. Increased bilirubin production
2. Reduced bilirubin uptake by hepatic cells
3. Disrupted intracellular conjugation
4. Disrupted secretion of bilirubin into bile canaliculi

} Lead to increases in free (unconj.) bilirubin

5. Intra/extra-hepatic bile duct obstruction

} Result in rise in conj. bilirubin levels

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Congenital hyperbilirubinemia

Bilirubin is elevated in blood due to inherited defects in the bilirubin metabolic pathway

1- Crigler-Najjar syndrome

- **Low activity** of glucoronyltransferase (conjugating enzyme)
- Severe hyperbilirubinemia in neonates (unconjugated bilirubin), Complicated by kernicterus & early death

2- Gilbert`s syndrome

- **Decreased production** of glucoronyltransferase
- More common in men, Occurs in 2-3 % of men.
- Usually asymptomatic hyperbilirubinemia with Normal Liver function tests.

3- Dubin-Johnson syndrome

- Defect in transfer of conjugated bilirubin into the biliary canalculi Conjugated hyperbilirubinemia.

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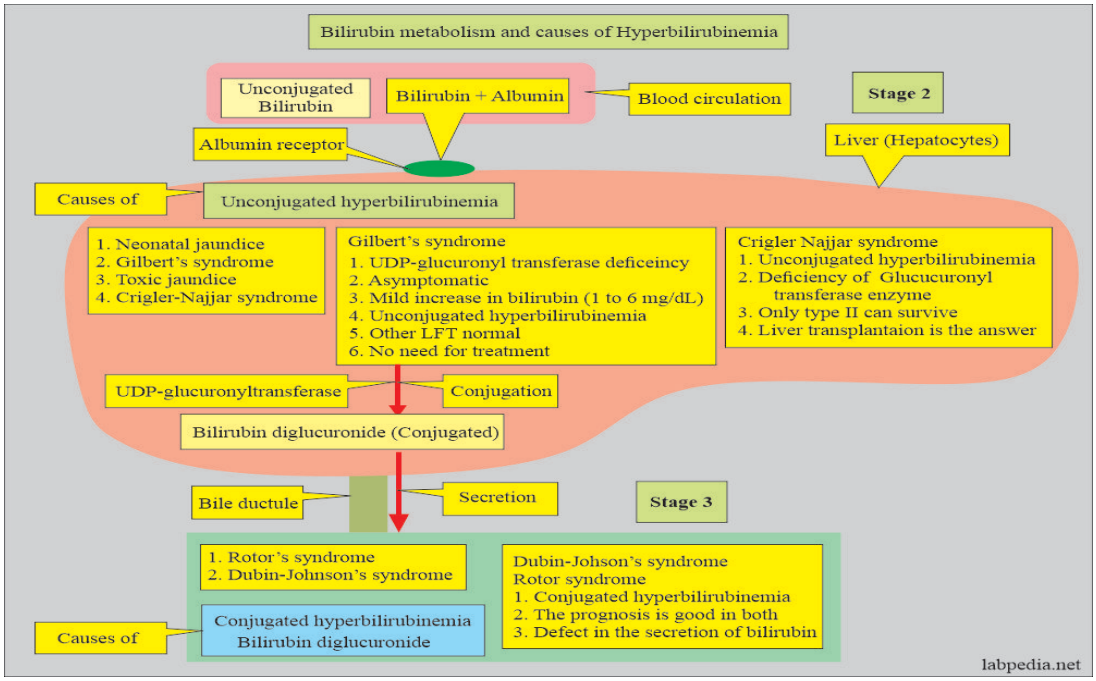

- **Clinical Significance**
- Increased serum bilirubin may result from:
- 1-Increased destruction of hemoglobin (hemolysis).
- 2-Decreased excretion (or retention) due to either hepatocellular or excretory duct disease of the liver.
- **Jaundice**, is a yellowish pigmentation of the skin, the conjunctival membranes over the sclerae (whites of the eyes), and other mucous membranes caused by high blood bilirubin levels.
- Jaundice is manifested clinically when **total serum bilirubin exceeds 2 mg/dl**.
- This hyperbilirubinemia subsequently causes increased levels of bilirubin in the extracellular fluid.

Jaundice: This is defined as the yellow discoloration of the skin and sclera because of the deposition of bile pigments.

It appears when the serum bilirubin level is above 2 mg/dl.

Jaundice may be classified as:

On the basis of etiology:

Pre-hepatic.

Hepatic.

Post-hepatic

Physiological classification:

Unconjugated hyperbilirubinemia (indirect bilirubin).

Conjugated hyperbilirubinemia (indirect bilirubin).

Causes of Jaundice:

Pre hepatic: Hemolysis.
Hemolytic disease of the newborn.

Hepatocellular: Viral hepatitis.
Alcohol.
Advanced chronic liver disease.
Gilbert's syndrome.

Post-hepatic(Obstructive):Common bile duct gallstone
Pancreatic tumor.
Ca of the extrahepatic duct.

Unconjugated hyperbilirubinemia:

This may be due to:

a- Increased production:

1-Hemolysis (hemolytic disease of the newborn). 2- Hereditary. 3- acquired. 4- Ineffective erythropoiesis.

5- Increased turnover like in neonates. 6- Physiologic jaundice of the newborn.

b- Decreased delivery:

1- Congestive heart failure. 2-Portacaval shunt.

c- Decreased uptake by the hepatocytes:

1-Drugs. 2- Gilbert's syndrome. 3- Sepsis. 4- Fasting.

d- Decreased storage of unconjugated bilirubin:

1- Fever. 2- Competitive inhibition.

e- Decreased conjugation:

1-Physiologic jaundice e.g. Neonatal jaundice. 2-Drugs.

3- Hereditary like Crigler-Najjar syndrome.

1-Complete enzyme deficiency, Type 1

2-Partial enzyme deficiency, Type 2

4-Hepatocellular dysfunction. 5-Gilbert's syndrome.

Conjugated Hyperbilirubinemia:

1- Decreased secretion into bile canaliculi:

Hepatitis.

Cholestasis (Intrahepatic).

Dubin – Johnson syndrome.

Rotor syndrome.

2- Decreased drainage or excretion.

1-Extrahepatic obstruction: Stones. , Carcinoma.

2-Sclerosing cholangitis.

3-Intrahepatic obstruction: Drugs. , primary biliary cirrhosis. , Tumors. , Idiopathic neonatal hepatitis (cholestatic jaundice).

	Normal	Prehepatic jaundice	Hepatic jaundice	Post hepatic jaundice
Serum total bilirubin	<1mg/dL	Increased	Increased	Increased
Serum conjugated bilirubin	0.1 to 0.4mg/dL	Normal	Increased ↑↑	Increased ↑↑↑↑
Serum unconjugated bilirubin	0.2-0.7mg/dL	Increased ↑↑↑↑	Increased ↑↑	Normal
Urine bilirubin	Absent	Absent	Present +	Present +++
Urine urobilin	0.4mg/day	Increased	Decreased	Absent
Fecal stercobilin	40-280mg/day	Increased	Decreased	Absent
Urine bile salts	Absent	Absent	Present +	Present +++

- Newborn Jaundice occurs because the baby's body has more bilirubin than it can get rid of.
- Bilirubin leaves the body through urine and stool. In pregnant woman, the body removes bilirubin from the baby through the placenta . After birth, the baby's body must get rid of the bilirubin on its own.
- Jaundice is common in newborn babies because babies have a high number of red blood cells in their blood, which are broken down and replaced frequently.Also, a newborn baby's liver is not fully developed, so it's less effective at removing the bilirubin from the blood.

By the time a baby is about 2 weeks old, their liver is more effective at processing bilirubin, so jaundice often corrects itself by this age without causing any harm.

- The baby will need treatment if the bilirubin level is above the normal range for newborns. He or she will be put under a type of fluorescent light to treat the jaundice.

This is called phototherapy . The skin absorbs the light, which changes the bilirubin so that the body can more easily get rid of it. The treatment is usually done in a hospital.

ABO incompatibility is one of the diseases which can cause jaundice.

ABO incompatibility happens when a mother's blood type is O, and her baby's blood type is A or B. The mother's immune system may react and make antibodies against her baby's red blood cells.

In ABO hemolytic disease of the newborn (also known as ABO HDN) maternal IgG antibodies with specificity for the ABO blood group system pass through the placenta to the fetal circulation where they can cause hemolysis of fetal red blood cells which can lead to fetal anemia and HDN.

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