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JAUNDICE IN PREGNANCY AN APPROACH

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ABSTRACT: Jaundice is a visible yellow discolouration of the skin, sclera, and mucosa when plasma bilirubin rises above 2 mg/100ml [normal range 0; 2-1.0mg/100 ml]¹. Jaundice when associated with pregnancy has an increased mortality and morbidity in comparison to jaundice in non-pregnant woman. There is a paucity of original published work from nations of third world on jaundice during pregnancy. Icterus of varying degree and varied etiology have been reported in one out of 1000 pregnancies. Majority of these cases occur in the third trimester of pregnancy.² Most liver function tests are unchanged during pregnancy. Exceptions are albumin, total protein and bilirubin [decreased] and alkaline phosphatase and cholesterol [Increased]. Several conditions, which are unique to pregnancy may lead to hepatic impairment.³ Hyperemesis gravidarum, often in the first trimester invariably before the 20th week of pregnancy. Intrahepatic cholestasis of pregnancy [IHCP], often in the third trimester (Pruritus and mild liver tests abnormalities). Acute fatty liver disease of pregnancy (AFLP) in the third trimester (nausea and vomiting, jaundice, and oliguria; typically mild increase in transaminases, hyperbilirubinemia, coagulopathy, thrombocytopenia, and hypoglycaemia). Preeclampsia (Classic triad of hypertension, proteinuria, and oedema) and eclampsia (Preeclamptic triad plus seizures and coma) in the second or third trimester. HELLP syndrome (Hemolysis, elevated liver enzymes, and low platelets), between the start of the third trimester and the immediate postpartum period, often manifesting with right upper quadrant pain, oedema, and hypertension.

KEYWORDS: HG, IHCP, AFLP, HELLP SYNDROME, AFLP, DIC, SGPT, SGOT, GGPT, IHCP.

INTRODUCTION: Jaundice, from the French Jaune (yellow), is the yellow-orange discoloration of the skin, conjunctivae, and mucous membranes that results from elevated concentrations of bilirubin in plasma. Mild hyperbilirubinemia may be clinically undetectable, but jaundice becomes evident at plasma bilirubin concentrations of 3 to 4 mg/dL, depending on the patient's normal pigmentation, the conditions of observation, and the bilirubin fraction that is elevated. Optimal interpretation of an elevated plasma bilirubin concentration is based on an appreciation of its sources and disposition.

In a pregnant patient with liver enzyme abnormalities, it is important to distinguish between liver diseases that are unique to pregnancy and those that occur commonly in pregnancy. In normal pregnancy, levels of alkaline phosphate, bile acids, globulins, fibrinogen, and triglycerides may be increased, whereas levels of albumin, antithrombin³, protein⁵, and γ -glutamyltransferase may be reduced.

Causes of jaundice during pregnancy³ have been classified as follows:

(A) Jaundice Peculiar to Pregnant State:

1. Cholestasis of pregnancy.
2. Acute fatty liver of pregnancy.

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3. Severe pre-eclampsia – eclampsia syndrome.
4. Severe neglected hyperemesis gravidarum.
5. Endotoxic shock (DIC).
6. HELLP syndrome.

(B) Hepatic disorders during Pregnancy:

1. Acute viral hepatitis
 - a) Infective hepatitis.
 - b) Homologous serum jaundice.
2. Haemolytic jaundice due to mismatched blood transfusion
3. Herpes simplex hepatitis
4. Drug induced hepatitis
5. Obstruction jaundice

(C) Systematic disorder Presenting with Jaundice with Pregnancy:

1. Septicemia.
2. Disseminated tuberculosis.
3. Advanced Intra-Abdominal Malignancies.

In order to understand the spectrum of icteric disorders in pregnancy it is important to know the physiological alteration in hepatobiliary system in normal pregnancy. During pregnancy the following physiological changes related to hepatobiliary system have been observed.⁴

There is increase in the normal blood flow. Azygous vein flow and GB volume. There is a decrease in cheno-chelate synthesis. Increase in lithogenicity of the bile. On examination a decrease in blood pressure, increase in pulse volume, palmar erythema spider angioma will be seen while the liver is mostly not palpable. Laboratory investigations show an increase in fibrogen, ceruloplasmin, Globulin, BSP retention, serum Alkaline Phosphatase and a decrease in Blood urea nitrogen. Uric acid and Haemoglobin. There is no alteration in SGOT. SGPT, Serum Bile acid, GGPT and Serum nucleotidases.

A meticulous history and thorough checkup provides clues to the cause of Jaundice in a pregnant female. A very high SGPT with moderate elevated SGOT indicates viral hepatitis while an elevated SGOT and alkaline phosphatase with mild SGPT indicates obstructive Jaundice. Hepatobiliary imaging as Ultrasonography helps to differentiate hepatocellular jaundice from obstructive jaundice. Study of viral markers from A to G will help to establish the etiology and in planning of preventive measures.

(A) Jaundice peculiar to Pregnancy:

1. **Intrahepatic cholestasis of Pregnancy:** Patients with IHCP present with cholestasis in the third trimester of pregnancy will have Pruritus³ occurs in 80% of patient, which usually begins peripherally and then progresses centrally. In approximately 20% of patient with pruritus, jaundice may occur. The major risk factor for IHCP includes multiparity, advanced maternal age, family history of IHCP and pruritus while on oral contraceptive medicines. Most cases are associated with a mutation in a multiple drug resistance³ gene. The diagnosis is often made by

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clinical history, and laboratory abnormalities generally include hyperbilirubinemia less than 6mg/dl. The alkaline phosphatase is always raised, and amino transferase levels may be 2 to 10 times the upper limit of normal. Serum bile acids are also markedly increased at 30 to 100 times the upper limit of normal. If liver biopsy is performed, a bland cholestasis is identified. Ultrasonography is normal.

Treatment includes ursodeoxycholic acid (UDCA) or cholestyramine to bind bile salts. S-adenosyl-L-methionine (SAME) was tested in two trials but outcomes were not encouraging. Phenobarbital has also been used. Finally, there are reports that dexamethasone can be used for controlling pruritus and also in enhancing fetal lung maturity. The syndrome resolves after delivery but is likely to recur with subsequent pregnancy. There are usually no postpregnancy sequelae for the mother, and pruritus usually resolves postpartum. Fetal complications include prematurity (38%), meconium staining, fetal distress, and intrauterine fetal demise.^{5,6,7,8,9}

2. **Acute fatty liver of pregnancy (AFLP):** AFLP is a potentially fatal disease that occurs most often in the third trimester and is reported in 1 in 13000 pregnancies. Abnormalities in mitochondrial function and adenosine triphosphate (ATP) synthesis have been described, and about 20% of cases have a deficiency in long chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD), with an abnormality in the beta oxidation of fatty acid. There is at least one case report of a deficiency in palmitoyl transferase that led to AFLP. The clinical presentation may be nonspecific, with nausea and vomiting present in 70% of patients. However, jaundice, encephalopathy, and oliguria often follow. Laboratory evaluation may show mild serum transaminase elevation, hyperbilirubinemia, coagulopathy, thrombocytopenia, and hypoglycaemia. Ultrasound and computed tomography (CT) scans often show fatty infiltration of the liver. Liver biopsy examination shows microvesicular steatosis, easily discernible on oil red O staining. Treatment requires urgent delivery. There are no long term sequelae for the mother as most recover. However, at least one case report exists of liver transplantation in AFLP. For the child, mortality is estimated at 13-18%, and developmental delay, hypoglycaemia, and striated muscle dysfunction are all potential complications. Therapy with medium chain fatty acid (MCFA) is often necessary for infants with homozygous LCHAD deficiency.¹⁰

3. **Preeclampsia-eclampsia:** This complication of pregnancy, which occurs during the second or third trimester, is characterized by hypertension (defined as an elevation of at least 30mm Hg systolic, 15 mm Hg diastolic, or a blood pressure 140/90) and proteinuria and edema. Preeclampsia or eclampsia occurs in 5 – 10 % of all pregnancies.

Eclampsia includes the above triad plus seizures and coma. The risk factor includes pre-existing hypertension, family history of preeclampsia, primigravida, multiple gestations, and early and late ages at the time of childbearing. Clinical presentation may include headache or visual changes, right upper quadrant pain with or without signs of liver failure, pulmonary edema, oliguria, hemolysis with or without thrombocytopenia and grand mal seizures. The ALT level is abnormal in 20% of patients (approx). The diagnosis is often made on clinical grounds with elimination of other potential causes of late pregnancy liver abnormalities. Endothelial dysfunction due to placental function is felt to be major culprit in preeclampsia.

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Abnormality in placentation ultimately leads to a systemic vascular dysfunction characterized by leaky capillaries and vasospasm.

Management of preeclampsia relies on the delivery of the (abnormal) placenta. Complication includes seizure, coma, hepatic rupture, and fulminant hepatic failure.^{11,12}

4. **HELLP SYNDROME (Hemolysis, Elevated Liver Enzymes, & low Platelets):** This syndrome is a potential complication of preeclampsia, occurring in 0.1 – 0.6 % of all pregnancies and in 4–12 % of all preeclamptic patients. Seventy percent of patients with HELLP syndrome develop this problem between the 27th week of pregnancy and the time of delivery. However, approximately 30% develop the problem postpartum.

Signs and symptoms are right upper quadrant pain, occurring in 65 – 90 % of patients; jaundice in around 5%; edema in 60%; and hypertension, in 80%. Laboratory abnormalities include a mean ALT of around 150 IU/L; serum bilirubin is often normal or minimally elevated. Platelet count is low and urea, creatinine and prothrombin time is high. Treatment is by delivery. Complication of HELLP syndrome include a mortality rate of 1 – 3 %, disseminated intravascular coagulation (DIC) in 20% of patients, placenta abruption in 16%, acute renal failure in 7%, and pulmonary edema in 6%. Perinatal mortality is approximately 35%.¹⁵

5. **Hyperemesis Gravidarum:** Hyperemesis gravidarum is a syndrome of unknown cause in which patients have fairly intractable nausea and vomiting. It generally occurs in the first trimester, usually before 10 weeks of pregnancy. Risk factors include young age, obesity and nulliparity. Aminotransferases levels may be increased up to 200 u/L, and bilirubin may be elevated up to 4 mg/dl. Liver biopsy shows fatty changes or mild cholestasis. Treatment is symptomatic with antiemetics.

(B) Hepatic Disorders during Pregnancy:

1. **Acute Viral Hepatitis:** Acute viral hepatitis from hepatitis A, B, C, D, and E virus can occur in pregnant women as in nonpregnant patients. Nonhepatotropic viruses such as cytomegalovirus, Epstein-Barr virus, and herpes simplex virus [HSV] can also cause hepatic injury in pregnant women. Other viruses causing hepatitis are rare and are not included in the term viral hepatitis. A study of 1338 viral hepatitis in pregnancy was conducted in a tertiary referral centre. Diagnosis of hepatitis was made and studied according to standard criteria. The study revealed that out of 1338 females, most of them belonged to rural area and were from low income group, mean age was 24 yrs. The clinical profile revealed varying degree of jaundice in all cases, Anaemia in 10 cases, oedema 7, Encephalopathy 5, persistent anorexia, fever, bleeding tendency, vomiting and a decrease in liver span in 9 cases each. Normal liver in 5 cases and just palpable liver in 16 cases are recorded. Splenomegaly was seen in 4 and Ascites in 5 cases. Biochemical profile has been depicted in Table 1. A comparative study of hepatitis in pregnant and non-pregnant women is shown in Table 2. The effect of hepatitis on mother and foetus is shown in Table 3 which showed high intrauterine death, premature delivery and fetal wastage in hepatitis during pregnancy.

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Test	Mean value
S.Bilirubin (mg %)	10.03±5.31
Total Protein (g %)	5.48±0.55
S.ALBUMIN ((g %)	2.64±0.47
AlkPO4(KA)	21.80±6.15
SGOT(IU)	82.40±17.72

Table 1: Biochemical profile in viral hepatitis in Pregnancy (30 cases)

	Pregnant Series (30)	Non Pregnant Series (246)
Fulminant	5 (16.6%)	40 (16.2%)
Fatal	5 (16.6%)	21 (11.2%)
Severity rate(Total Fulminant cases)	5 (16.6%)	40 (16.2%)
Fatality rate(Total Depth)	5 (16.6%)	29 (11.7%)
Recovery rate in fulminant cases	NIL	11 (4.0%)

Table 2: Severity and mortality of viral hepatitis in pregnancy and in non- pregnant cases

	Fulminant Group	Non Fulminant Group
No. of cases	5	25
IUD	3 (60%)	4 (16%)
Premature delivery	2 (40%)	4 (18%)
Pregnancy	NIL	19 (76%)
Term delivery	NIL	17 (68%)
Foetus wastages	5 (100%)	9 (36%)

Table 3: Effect of hepatitis in pregnancy on foetus

A statistically significant difference was recorded between pregnant and non- pregnant cases in intra uterine death and foetal wastage. On this basis of the finding of the hepatitis during pregnancy is the serious condition in the developing countries and it warrants high clinical suspicion indexes, frequent checkup of pregnancy in ant-natal clinic and hospitalization before term and clinical monitoring for foetal well-being.

Viral Hepatitis from viruses A to G is acute and marking them helps in prevention to other population through their various routes of transmission.

Other viruses are herpes simplex virus etc. Are extremely rare and are not included in most of studies conducted on this subject.

Management of hepatitis in Pregnancy: No specific Treatment is available for cases of jaundice in pregnancy but the following guidelines have been advised:

1. Absolute bed rest to improve hepatic circulation.
2. Hepatoprotective drugs as Phyllanthus Niruri are helpful.

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3. Nutrition- should be ample in carbohydrates and vitamins (B complex, and Vitamin C -100 mg daily), IV Fluids, if needed glucose at least 200gm/day should be administered, fruit juices and barley may be given.
4. For Hyperemesis Gravidarum, treatment is symptomatic with antiemetic and intra venous hydration.
5. Intrahepatic Cholestasis Of Pregnancy, treatment includes Ursodiol or Ursodeoxycholic acid Cholestyramine to bind the bile salt Phenobarbital has also been used the syndrome resolve the softer delivery.
6. Preeclampsia And HELLP Syndrome-Delivery remains the mainstay of management, and it is recommended that if the pregnancy has progressed beyond 34 weeks, the infant should be delivered. Observation for 24-48 hours is recommended, but only if hypertension and central nervous system abnormalities are not present.
7. Acute Fatty Liver Disease in Pregnancy, treatment requires urgent delivery.
8. Hepatitis A, management of hepatitis A is conservative. Hepatitis A vaccine and immunoglobulin are safe during pregnancy.
9. Hepatitis B, the primary treatment of acute hepatitis of any type is mainly supportive. Patient generally do not require hospitalization unless the disease is complicated by significant hepatic failure, as evidence by encephalopathy, coagulopathy with bleeding, renal failure, or inability to maintain adequate nutrition and fluid intake. In women who are positive for hepatitis B e antigen (HBeAg), there is a 70-90% chance of vertical transmission. Hepatitis B vaccine is safe during pregnancy, and once infants are administered protective immunoglobulin (hepatitis B immunoglobulin [HBIG]) at the time of birth, there is no additional risk from breast-feeding. All children born to hepatitis B surface antigen-positive mother should be receive HBIG at the time of birth and the first of their hepatitis B vaccine before discharge from the hospital. It is known that combination of HBIG and vaccination decreases the vertical transmission rate from around 90% to between 3 and 7%.
10. HCV-infected women should be told that hepatitis C transmission via breast-feeding has not been documented according to NIH(National Institute Of Health) breast-feeding is not contraindicated for HCV-positive mother and the maternal to baby transmission of HCV infection through breast milk has not been documented. Immunoglobulin therapies ineffective, there are currently no data to determine whether anti-viral therapy reduces peri-natal transmission.
11. Other hepatic condition that can occur in pregnancy including Gall Stone Budd-Chiari syndrome acute herpes hepatitis caused by herpes virus 2 occurs in second and third trimesters, treatment is conservative or with antiviral therapy.
12. During labour:
 - a) Hepatotoxic drugs should be avoided for seduction (paraldehyde-is preferred).
 - b) To administer vitaminK1 to rise Prothrombin level.
 - c) Prophylactic ergometrine.

Prophylaxis:

1. Improvement in sanitation and supply of drinking water.
2. Adequate personal hygiene.

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3. Use of sterile and disposable syringes.
4. Screening of blood donors for HBS Ag.
5. Vaccines, Immunoglobins against HAV in doses of 0.02 ml/kg body weight given to contacts in endemic areas. IG against HBV (0.06 ml/kg) in proved cases.
6. Universal screening HBsAg is recommended for all pregnant women administration of 3 doses of vaccine and 1 dose hepatitis B immunoglobulin is recommended for infant of acutely or chronically infected mother. Vaccine must be injected intra muscularly preferably in the deltoid. Booster doses are not currently recommended.
7. All infants born of HBS Ag positive mother should get 0.3 ml IG repeated at 3 and 6 months of age.

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