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Jaundice in Pregnancy

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Abnormal liver function tests occur in 3%-5% of pregnancies. Pregnancy encompasses a wide variety of physiological changes with increased, decreased or unchanged parameters. Liver function abnormality can represent a physiological change, but elevations of transaminase, bilirubin, and prothrombin time almost always indicate a pathologic state. The major physiologic changes in pregnancy, that peak in second trimester and plateau at delivery, relating to liver functions are summarised in Table 1. Histology of the liver remains essentially normal during pregnancy. Lack of understanding of these changes can be misinterpreted as pathologic and can alter the criteria for diagnosis and therapy. The presenting clinical features of liver disease in pregnancy are often nonspecific and consist of jaundice, nausea, vomiting and abdominal pain. All liver diseases occurring during pregnancy can lead to increased maternal and foetal morbidity and mortality.

Causes of Liver Disease and Jaundice in Pregnancy

The jaundice can be classified in pregnancy on the basis of jaundice in existing liver disease, co-incidental liver disease and specific to pregnancy (Table 2).

Table 1: Physiological changes in pregnancy pertaining to liver

Increases
• Alkaline phosphatase levels rise three- to fourfold because of placental production
• Clotting factors I, II, V, VII, VIII, X, and XII
• Ceruloplasmin level
• Transferrin level
Decreases
• Gallbladder contractility
• Albumin and total protein levels
• Antithrombin III and protein S level
No Changes
• Liver transaminase levels (aspartate aminotransferase, alanine aminotransferase)
• γ-Glutamyl transferase (GGT) level
• Bilirubin level
• Prothrombin time

JAUNDICE IN PRE-EXISTING LIVER DISEASE AND PREGNANCY

Although it is difficult to conceive with the an existing chronic illness like liver disease, a prompt diagnosis and treatment of a liver disorder before conception, will help in preventing foetal loss and exacerbations leading to liver failure.

Cirrhosis and Portal Hypertension

The prevalence of cirrhosis in women of reproductive-age group is approximates 0.45 cases per 1000. As the disease is pre-existing the aetiology is same as in non pregnant state. The most common cause being viral hepatitis B and C, autoimmune, alcohol induced or idiopathic. Cirrhosis can affect ovulation, due to hypothalamic-pituitary dysfunction and cause infertility. However, if their liver function is well compensated, and treatment is

Table 2: Causes of Jaundice in Pregnancy

Preexisting Liver Disease
• Cirrhosis and portal hypertension
• Autoimmune hepatitis
• Primary biliary cirrhosis, primary sclerosing cholangitis
• Wilson's disease
• Chronic viral hepatitis B and C
• Chronic liver Disease
Liver Disease Coincidental with Pregnancy
• Budd-Chiari syndrome
• Hepatitis
Viral hepatitis E
Herpes simplex virus hepatitis
Acute hepatitis A, B, and C
Cytomegalovirus hepatitis
• Alcohol and pregnancy
• Gallstone disease
Liver Disease Unique to Pregnancy
• Acute fatty liver of pregnancy
• Preeclampsia, Eclampsia
• HELLP syndrome (hemolysis, elevated liver enzyme levels, low platelet count)
• Intrahepatic cholestasis of pregnancy
• Hyperemesis gravidarum

maintained during pregnancy, women might still become pregnant and outcome can be good. However there is an increased risk of premature delivery. Oesophageal varices should be screened in second trimester and can be treated with banding or octreotide, beta-blockers can also be given. Diuretics and spironolactone, are not advisable during pregnancy or lactation. It is recommended to have caesarean section to avoid increased straining.

Autoimmune Hepatitis

Autoimmune hepatitis is common in women of all ages. The disease activity is usually attenuated during pregnancy due to immune tolerance induced by the pregnancy. There is an increased risk of prematurity, low-birth-weight infants, and fetal loss. Immunosuppressive therapy in the form of prednisone and azathioprine can be given with reduced doses.

Primary Biliary Cirrhosis and Primary Sclerosing Cholangitis

Primary biliary cirrhosis and primary sclerosing cholangitis are autoimmune diseases that can overlap with autoimmune hepatitis. Pregnancy carries a high risk of prematurity, stillbirths, and liver failure. Serum bilirubin increase depends on the type of disease and presence of antinuclear, smooth muscle, liver-kidney microsomal antibodies or antibodies to soluble liver antigen/liver pancreas antibodies. Diagnosis is not different from that in the non pregnant woman. Ursodeoxycholic acid (UDCA) can be continued safely.

Wilson's disease

Wilson's disease is an inherited autosomal recessive disorder of copper transport. The disease is associated with amenorrhea and infertility; however fertility can improve with therapy. Treatment initiated before conception, should not be interrupted during pregnancy because of the risk of haemolysis, fulminant liver failure and death due to sudden copper release. The treatment of choice is zinc sulfate because of its efficacy and safety for the foetus. D-penicillamine or trientine treatment requires a dose reduction by 25% to 50% of that in the pre-pregnancy state especially during the last trimester.

Chronic viral hepatitis B and C

The prevalence chronic hepatitis B and C is quite high in India. Usual presentation is elevation of liver transaminases and bilirubin levels and diagnosis is similar to a non-pregnant woman. Mothers who are hepatitis B e antigen (HBeAg) positive have higher rates of perinatal transmission than do mothers with negative HBeAg. Without treatment 90% of infants born to HBeAg positive mothers and 10% of infant born to HBeAg negative mothers develop hepatitis B virus infection. The infants should receive hepatits B immunoglobulin at birth and also hepatitis B vaccine during the first day of life and at ages 1 and 6 months. Women with chronic hepatitis B are not treated with interferon during pregnancy however therapy with the nucleoside analogue, lamivudine is probably safe and has been reported to reduce the incidence of neonatal vaccination failure.

The risk for vertical or perinatal transmission of HCV is about 5%-10% and is associated with the presence of HCV RNA in maternal blood at the time of birth. HIV coinfection in pregnant women increases the risk of perinatal HCV transmission by 2-fold. Combination antiviral therapy is not recommended in pregnancy.

Chronic Liver Disease

Aetiology of chronic liver disease in pregnant state is same as in non-pregnant state as the disease is pre existent. The treatment depends on the aetiology of the disease and drugs that can be used in pregnancy. The pregnancy in chronic liver disease is associated with increased foetal loss.

JAUNDICE IN LIVER DISEASES COINCIDENTAL WITH PREGNANCY

Budd-Chiari Syndrome

It is an occlusive syndrome of the hepatic veins that leads to sinusoidal congestion and necrosis of hepatocytes around the central vein. Most cases occur during the postpartum period. Underlying predisposing condition, such as factor V Leiden, antithrombin III, protein C or S deficiency, or the presence of antiphospholipid antibodies are present in 25% cases if seen during pregnancy. Complete anticoagulation throughout pregnancy and the puerperium is required.

Viral Hepatitis

Acute viral hepatitis is the most common cause of jaundice in pregnancy, with an incidence of approximately 1 to 2 per 1000. The outcome is usually benign, except in viral hepatitis E and herpes simplex virus (HSV) hepatitis.

Viral Hepatitis E

Acute viral hepatitis E is transmitted via the fecal-oral route and is associated with high morbidity and a maternal mortality rate of 30%. Vertical transmission occurs in 50% of cases if the mother is viremic at the time of delivery. Treatment is supportive.

Herpes Simplex Hepatitis

HSV hepatitis is a rare condition but is associated with a 40% risk for fulminant liver failure and death. Treatment of choice is intravenous acyclovir. Transmission to the foetus is high (≤50%) when maternal acquisition occurs near the time of delivery. Caesarean section is strongly advisable if lesions are present at delivery.

Acute Viral Hepatitis A (HAV)

HAV infection is usually self-limited but transmission to the newborn can occur when delivery takes place during the incubation period because of viral shedding and contamination during vaginal delivery. Treatment is supportive.

Viral Hepatitis B and C (HBV, HCV)

Acute HBV and HCV infections during pregnancy do not seem to affect the course of pregnancy but are associated with an increased risk of transmission to the newborn as discussed in previous section.

Cytomegalovirus Hepatitis

The overall prevalence in women of childbearing age is 50% to 80%. The risk of transmission to the foetus is high, occurring at a rate of 30% to 40% when the infection is

Table 3: Pregnancy specific causes of Jaundice

Disease	Symptoms	Lab values	Jaundice	Trimester	Treatment	Outcome	Prevalence
ICP	Pruritus	**ALT/AST** <1000 **Bilirubin** <6mg/dl, **PT** normal	1-4 week after pruritus 20-60%	2nd	UDCA and Delivery	Gall stones Recurrence Foetal distress	<1% Multi-foetal gestation
AFLP	Nausea, Vomiting, Fulminant hepatic failure	**ALT/AST** >300, **Bilirubin** increased **PT** elevated **DIC**	Common	3rd	Delivery	Maternal mortality <20% Foetal mortality up to 45%	Primiparous Multi-foetal <0.01%
Eclampsia Preeclampsia	High blood pressure Oedema Seizures Renal failure Pulmonary edema	**Uric acid** elevated **ALT** <500 **Proteinuria** **DIC** - 7%	Late 25%	2nd and 3rd Beyond 20 wks Recurrence	Beta blocker Methyldopa Magnesium sulphate Delivery	Maternal mortality 1-15 % Prematurity and fetal death 5%-30%	5% Multiparous Multifetal gestations
HELLP syndrome	Abdominal pain Seizures Renal failure Pulmonary edema Liver hematoma and rupture	**Platelets** <100,000/mm^3 **Hemolysis** **High LDH** **AST/ ALT** 70-6000 IU/L **DIC**	Late 5-14%	Beyond 22 wk and after delivery 20% progress from severe eclampsia	Prompt delivery	Hepatic rupture, with 60% maternal mortality; fetal death, 1%-30%	0.5% Multiparous
HG	Nausea Vomiting Pruritus	**AST/ALT** <1000 IU/L **ALT >AST**	Mild	First trimester resolves after 20 wk	IV fluids Thiamine Pyridoxine Promethazine	Benign for mother and child	<2% Primiparous

acquired before 22 weeks of gestation. There is no effective and safe therapy during pregnancy.

Alcohol and Pregnancy

Mothers who consume alcohol during pregnancy can have premature babies, stillbirths, babies with neonatal alcohol withdrawal (characterized by jitteriness, irritability, and poor feeding in the first 12 hours of life), and infants with foetal alcohol syndrome.

Gallstone Disease

Pregnancy promotes lithogenesis due to biliary cholesterol saturation and inhibition of the hepatic synthesis of chenodeoxycholic acid. In addition, pre-pregnancy obesity, low activity level, low serum leptin levels, and a history of gallbladder disease are risk factors for gallbladder disease. Approximately 10% of pregnant women may have gallstones by the third trimester, compared with 5% at the beginning. Gallstones regress in the postpartum period.

Laparoscopic cholecystectomy for symptomatic cholelithiasis is particularly safe when performed during the second trimester.

JAUNDICE IN LIVER DISEASES UNIQUE TO PREGNANCY (TABLE 3)

Acute Fatty Liver of Pregnancy (AFLP)

AFLP is a rare disorder of the third trimester, affecting less than 0.01% of pregnant women. It is most common in primiparous women older than 30 years, with multiple gestations and male foetus. Free fatty acids (FFAs) increase in pregnancy because of the effects of hormone-sensitive lipase and gestational insulin. Defects in the genes encoding for the transport and oxidation pathways are inherited as autosomal recessive traits and are known as *fatty acid oxidation disorders*. The most common disorder in AFLP is a deficiency of long-chain 3-hydroxylacyl-CoA dehydrogenase (LCHAD). During the last trimester when the metabolic demands of the foetus increase, mothers heterozygous for a fatty acid oxidation disorder and having homozygous foetus can develop AFLP because of their inability to metabolize fatty acids for energy production and foetal growth. Fatty acids then deposit in the liver. The foetal complications include failure to

thrive, hepatic failure, cardiomyopathy, microvesicular steatosis, hypoglycemia, and death

Liver biopsy may be necessary for diagnosis. AFLP is characterized by microvesicular fat deposition in centrilobular hepatocytes. Delivery of the foetus leads to rapid recovery without sequel of chronic liver disease.

Preeclampsia and Eclampsia

Preeclampsia and eclampsia affect 5% of pregnancies and are more common in primiparous women with multifetal gestations. Other risk factors include preeclampsia in a previous pregnancy, chronic hypertension, pregestational diabetes, nephropathy, obesity, and antiphospholipid syndrome. Symptoms include hypertension of 140/90 mm Hg or higher and proteinuria higher than 0.3 g in 24 hours. Eclampsia is defined by the additional occurrence of new-onset seizures. Liver test abnormalities are present in 25% of cases. Overlap with the HELLP syndrome occurs in 20% of cases. In a woman with a prior history of eclampsia, the recurrence rate is 20% to 30% for preeclampsia and 2% to 6% for eclampsia.

Liver histology is distinct from that of AFLP. It indicates fibrin deposition in sinusoids, periportal hemorrhage, and liver cell necrosis. Hypertensive crisis, abruptio placentae, and liver failure can occur. Maternal mortality is noted in 1% to 15% of cases. Fetal mortality rates range from 5% to 30%. Labetolol and methyldopa are the drugs of choice for hypertension. Magnesium sulfate is the drug of choice for preventing and treating seizures.

HELLP (haemolytic anaemia, elevated liver enzyme and low platelet) Syndrome

The HELLP syndrome complicates 0.5% of pregnancies and the recurrence rate is as high as 20%. It is characterized by microangiopathic hemolysis with burr cells and schistocytes; elevated liver enzyme levels; and a platelet count lower than 100,000/mm.

It is more common in multiparous women and can manifest in 30% after delivery. Abdominal pain, disseminated intravascular coagulation, renal failure, subcapsular liver hematoma, and hepatic rupture are described. Maternal mortality is about 1% but reaches 60% in cases of hepatic rupture. Pathophysiology involves alterations in platelet activation, increases in proinflammatory cytokines, and segmental vasospasm with vascular endothelial damage. An association with a defect in LCHAD has also been described, suggesting a possible overlap of HELLP syndrome and acute fatty liver of pregnancy. Immediate delivery is the definitive treatment for HELLP syndrome.

Intrahepatic Cholestasis of Pregnancy (ICP)

ICP affects less than 1% of all pregnancies in the second half of pregnancy. It is more common in multiparous women with twin gestations, advanced maternal age, and history of cholestasis with oral contraceptive use. It resolves after delivery and usually recurs in subsequent pregnancies. Mutations in the phospholipid translocator known as the ATP cassette transporter B4 (ABCB4) or multidrug resistant protein-3 (MDR3) are associated with the development of ICP. High levels of bile acids have been implicated in premature labour, chronic placental insufficiency, meconium staining and sudden death.

UDCA is the treatment of choice for reducing pruritus. Other medications, such as cholestyramine and S-adenosyl-L-methionine, can be used but studies have found UCDA to be superior.

Hyperemesis Gravidarum (HG)

HG occurs in less than 2% of pregnancies, starting in the first trimester and resolving by week 20 of gestation. It is characterized by severe nausea and vomiting, and electrolyte disturbances. Weight loss exceeds 5% of pre-pregnancy body weight. HG is more common in primiparous women and may be associated with mild elevation of transaminase levels. The predisposing factors include female gender of the foetus. Vomiting may cause esophageal rupture, vascular depletion, and renal damage. Prematurity and low birth weight is rare. Treatment is primarily supportive. Patients should avoid triggers and eat small, frequent, low fat meals. Intravenous fluids, thiamine and folate supplementation, and antiemetic therapy may be administered. Promethazine is a first-line agent, but other medications such as metoclopramide, ondansetron, and steroids have also been used.

CONCLUSION

Jaundice in pregnancy can manifest as a benign disease with abnormal elevation of liver enzyme levels and a good outcome, or it can manifest as a serious entity affecting hepatobiliary function and resulting in liver failure and death of the mother and foetus. The overall mortality attributed to liver disorders in pregnancy has dramatically decreased in the past few years because of clinicians' understanding of the physiologic changes that occur during pregnancy, their ability to identify and treat preconception liver disorders, and their vigilance in recognizing clinical and laboratory abnormalities in a timely manner.

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