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Review Article

Liver disease in pregnancy

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ABSTRACT

Deranged liver function tests are encountered in 3% of pregnancies. The potential causes are classified as those unique to and those just incidental to pregnancy. Pregnancy-related diseases are the most frequent causes of liver dysfunction during pregnancy and exhibit a trimester-specific occurrence during pregnancy. Differentiation of liver dysfunction as that related to and just incidental to pregnancy is the key to management, especially when liver dysfunction is encountered after 28 weeks of pregnancy. It can be judged from the fact that delivery remains the cornerstone of management of pregnancy-related diseases except hyperemesis gravidarum. This is an overview of the causes of liver dysfunction during pregnancy; an update on the underlying mechanisms of their occurrence, especially liver diseases unique to pregnancy; and a methodological approach to their diagnosis and management.

Introduction

Nearly 3% of pregnancies are complicated by liver disorders. Liver disorders during pregnancy are classified as those related to pregnancy and those just coincidental (occurring during pregnancy or pre-existing). Pregnancy-related disorders are the most common causes of liver dysfunction during pregnancy and are further divided into those associated with or without preeclampsia. Hyperemesis gravidarum (HG), intrahepatic cholestasis of pregnancy (ICP), preeclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, and acute fatty liver of pregnancy (AFLP) are conditions affecting the liver that are unique to pregnancy. Pregnancy-related liver disorders display characteristic trimester-specific clustering in their occurrence, whereas coincidental liver disorders can occur at any time.

Physiological changes during pregnancy

Blood supply to the liver during pregnancy remains unchanged despite an increase in cardiac output, and so does the liver size. Telangiectasia and palmar erythema, which are otherwise clinical markers of liver disease, are seen commonly during pregnancy (due to a hyperestrogenic state). Decreased *gall bladder* motility with increased secretion of cholesterol in the second and third trimesters increases the lithogeneicity of bile.

Liver function tests

Serum alanine transaminase (ALT), aspartate transaminase (AST), gamma-glutamyl transpeptidase, and bilirubin values remain unchanged during pregnancy; however, their ranges are changed, with a reduction in the upper end. This is a consequence of hemodilution occurring during pregnancy. Alkaline phosphatase is elevated (up to 300%) but is placental in origin. There is an increase in the hepatic synthesis of coagulation factors VII, VIII, and X and fibrinogen; however, the ranges for prothrombin time and activated partial thromboplastin time remain unchanged. It is believed that prolonged prothrombin time is a good early marker of hepatic synthetic dysfunction. Serum albumin concentrations fall due to hemodilution.

Hyperemesis gravidarum

HG complicates 0.3–2.0% of pregnancies [1,2]. It is characterized by intractable vomiting in the first trimester (typically 4–10 weeks), leading to dehydration, ketosis, and weight loss of ≥5%, necessitating hospitalization. HG is not a liver disease in the strict sense, but it leads to liver dysfunction in 50% of cases. The mechanism of liver involvement in HG is multifactorial and not well

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understood. Transient hyperthyroidism is seen in 60% of cases [3]. This form of gestational transient thyrotoxicosis is not associated with any unfavorable pregnancy outcome and does not require any treatment. HG-associated liver dysfunction should be a diagnosis of exclusion. A woman presenting with liver dysfunction with or without HG in the first trimester must be carefully investigated to rule out other causes of liver dysfunction (viral hepatitis and drug-induced liver injury).

Liver function abnormalities

There are mild to up to 20-fold elevations in AST and ALT (ALT > AST) and rarely mild jaundice. Liver function abnormalities and other biochemical abnormalities resolve upon resolution of vomiting. Other biochemical abnormalities seen are hypokalemia, hyponatremia, and ketonuria.

Management

Management of HG is supportive and includes intravenous rehydration with a short period of fasting, followed by reintroduction of a diet rich in carbohydrates and low in fat. Antiemetics such as dopamine antagonists (metoclopramide and domperidone), phenothiazines (chlorpromazine and prochlorperazine), or antihistamine H1 receptor antagonists (cyclizine and promethazine) are used safely during pregnancy [3]. Thiamine supplementation is given with dextrose infusion, particularly in women with a history of prolonged (over weeks) vomiting, to prevent Wernicke's encephalopathy.

Intrahepatic cholestasis of pregnancy

ICP is the most frequent cause of cholestasis during pregnancy. However, occurrence of cholestasis during pregnancy does not always imply the clinical diagnosis of ICP, because pregnancy itself is a cholestatic condition and chronic liver diseases may be unmasked for the first time during pregnancy with clinical presentation of cholestasis. Differentiation of ICP from other chronic liver diseases is important, because both maternal and fetal prognosis vary. ICP prevalence varies according to countries and populations as there is considerable genetic influence. In European countries, 0.5–1.5% prevalence is seen. South Asia has a higher incidence of ICP.

Clinical presentation

Pruritus is the main and most characteristic symptom. Although it is generalized, it might be severe in the palms and soles, and worsens during the night. Pruritus usually develops after 25 weeks, with 80% of cases occurring after 30 weeks. There are no constitutional symptoms. It usually disappears within the first few days after delivery. Jaundice develops in 10% of cases, 2–4 weeks after the development of pruritus, and the bilirubin level is usually <5 mg/dL. Intense cholestasis is associated with steatorrhea, which is usually subclinical but can cause fat-soluble vitamin deficiencies, most notably deficiency of vitamin K. Recent updates point to lysophosphatidic acid, a potent neuronal activator, and autotaxin, the enzyme that forms lysophosphatidic acid, as key elements of the pruritogenic signaling cascade in cholestatic patients suffering from itching [4].

Liver function tests

Fasting serum bile acid levels of >10 μmol/L is the key diagnostic test; however, it is not available everywhere. ALT and AST are usually raised 2–10 times but may be elevated up to 20 times. Transaminases are elevated secondary to increased membrane permeability of hepatocytes. Gamma-glutamyl transpeptidase levels are not raised. In fact, raised gamma-glutamyl transpeptidase activity is considered as a marker of chronic liver disease.

How to make a diagnosis of ICP?

One should be mindful of the following clinical characteristics when making a diagnosis of ICP:

(1) Typical clinical presentation of pruritus occurring in the second half of pregnancy; a history of itching during a previous pregnancy or use of contraceptive pills lends weightage.
(2) Abnormal liver function tests as described above.
(3) Exclusion of other liver diseases (viral hepatitis and autoimmune liver disease).
(4) A complete recovery of pruritus and liver function tests soon after delivery.

Hence, ICP is a presumptive diagnosis until resolution of symptoms postpartum.

Pathogenesis

ICP is associated with abnormal biliary transport across the canalicular membrane, the etiology of which is complex and heterogeneous. Literature suggests that genetic, hormonal, and exogenous factors all play a role in the occurrence of ICP [5].

Genetic

Clustering of ICP cases in families and a high incidence in certain ethnic groups suggest a genetic predisposition. Identification of mutations and polymorphism of genes involved in hepatobiliary transport has provided evidence supporting this theory [6,7]. Mutations of the *ABCB4* gene, which encodes multidrug resistance protein 3 (MDR3), as well as those of *ABCB11*, which encodes the bile salt export pump, are likely responsible for about 15% of cases of cholestasis of pregnancy [8–11]. The *MDR3* gene product is a phospholipid flippase that translocates phosphatidylcholine from the inner to the outer leaflet of the canalicular hepatocyte membrane, where it is solubilized by bile acids to form mixed micelles. Other potential gene products of interest include the Farnesoid X receptor and transporting ATPase encoded by ATP8B1 [10,12]. There is, however, no relationship between cholestasis of pregnancy and human leukocyte antigen type.

Hormonal

The role of estrogens is supported by the facts that ICP is more common in twin pregnancies (where estrogen levels are higher) and ICP symptoms are sometimes seen in women given exogenous estrogens in the form of contraceptive pills. Abnormalities of progesterone metabolism with an accumulation of sulfate metabolites saturating the hepatobiliary transport system are also implicated in ICP. There are case reports of ICP triggered by a prescription of natural progesterone for preventing preterm delivery in the third trimester [13,14].

Exogenous

Had the etiology of ICP been only genetic, all the pregnancies of predisposed women should have been complicated by ICP. However, such is not the case, as ICP recurs only in 60–70% of subsequent pregnancies. This suggests a role of extraneous factors in influencing the occurrence of ICP in genetically predisposed women. Other facts that support the role of exogenous factors are

geographical variation in occurrence, seasonal variability in several countries, and a decreasing prevalence of ICP in Chile, possibly due to a fall in the mean plasma selenium levels [15]. Irrespective of the inciting agent(s), there is incomplete clearance of bile acids with subsequent accumulation in plasma.

Prognosis for mother and fetus

ICP has a benign prognosis for mothers. Recovery is complete, and no serious short- or long-term maternal morbidity is seen with ICP. However, a recent longitudinal retrospective population-based cohort study has shown an association of ICP with several liver diseases [16]. In addition, 60–70% of affected individuals develop cholestasis during subsequent pregnancies. As far as the fetal outcome is concerned, older literature suggested an adverse perinatal outcome in women with ICP due to prematurity, chronic placental insufficiency, anoxia, meconium passage, and sudden intrauterine fetal death (IUFD). However, data collected in the past 2 decades is ambiguous concerning excessive perinatal mortality and whether fetal surveillance strategies prevent this increased risk. To illustrate the point, a review of few studies is presented here. In a study by Glantz and colleagues [17], perinatal mortality was increased but was seen only in those women who had severe disease, characterized by very high total serum bile acid levels. By contrast, Sheiner and coworkers [18] did not find any difference in the perinatal outcomes when they compared 376 pregnancies with ICP with their general obstetric population. Lee and associates [19] described two cases of sudden fetal death despite close fetal surveillance. Two more studies did not report any excess risk of term fetal demise [20,21]. However, almost all these studies reported a very high rate of labor induction to avoid stillbirths. One of the studies reported novel associations of ICP with preeclampsia and gestational diabetes. It has been suggested that bile acids may cause fetal death by cardiac arrest after entering cardiomyocytes in enormous amounts [22]. The risk of sudden IUFD is currently 1% in developed countries and is rarely seen before the last month of pregnancy.

Medical and obstetrical management

Management of ICP is twofold: symptomatic therapy for the mother, and close surveillance and early delivery of the fetus.

Symptomatic management of mother

Ursodeoxycholic acid in doses of 10–15 mg/kg/d is the treatment of choice for ICP at present. It provides relief against pruritus, improves liver function tests, and appears to be safe during pregnancy. At the molecular level, it offers cytoprotection against hepatotoxic effects of hydrophobic bile acids, improves hepatobiliary bile acid transport, and decreases plasma bile acid. Hydroxyzine (25 mg/d) or an aqueous cream with 1% menthol may be used to alleviate pruritus. Treatment with bile-acid binders such as cholestyramine and guar gum may also relieve symptoms, however, it is important to keep in mind that therapy with these agents worsens steatorrhea and resultant fat-soluble vitamin deficiencies. Administration of *S*-adenosyl methionine to patients with cholestasis of pregnancy has had mixed therapeutic results; use in combination with ursodeoxycholic acid may increase its benefit. As in other cholestatic syndromes, no treatment is always and completely effective in persons with cholestasis of pregnancy, with the usual exception of delivery.

Management for fetus

Close fetal monitoring and early delivery (preferably 37 weeks, but no later than 38 weeks) remains the cornerstone of obstetric management, although the evidence is lacking. An even earlier delivery is advocated when cholestasis is severe [23]. However, sudden IUFD cannot be avoided totally even with this approach.

Preeclampsia/hypertension-related liver diseases and pregnancy

Preeclampsia/eclampsia

Preeclampsia is defined as hypertension and proteinuria after 20 weeks of pregnancy and within 48 hours of delivery. It complicates 10% of pregnancies. It is a multisystem disorder, and the liver is involved in 20–30% of preeclampsia cases. It is the most common cause of liver dysfunction and hepatic tenderness in pregnancy [24]. Liver involvement is secondary to vasospasm of the hepatic vascular bed. Aminotransferase levels are usually elevated mildly to up to 10 times normal values; however, they might occasionally be elevated up to 20 times normal values. Jaundice occurs only occasionally (5%) and the bilirubin level is usually <5 mg/dL. Liver involvement in preeclampsia is an indicator of the severity of preeclampsia, and no specific therapy for liver involvement is required.

HELLP syndrome

HELLP is a severe variant of preeclampsia and complicates around 2–12% of preeclampsia cases [25]. It is defined by the presence of: (1) hemolysis; (2) elevated liver enzymes; and (3) low platelet counts.

Etiology

There are endothelial injury and fibrin deposition in blood vessels, leading to microangiopathic hemolytic anemia (schistocytes and burr cells on smear) with platelet activation and consumption. Consequently, small to diffuse areas of hemorrhage and necrosis develop from Zone 1 to involve the whole lobule. This may occasionally lead to large hematomas, capsular tears, and intraperitoneal hemorrhage.

Clinical features

The majority of patients present in the third trimester (28–36 weeks of gestation), however, 30% of cases occur in the postpartum period. There is no typical presenting sign or symptom that distinguishes HELLP from preeclampsia. Midepigastric or right upper quadrant abdominal pain is the commonest feature. Other symptoms are nausea, vomiting, malaise, and headache. Jaundice is present in approximately 5% of cases [26].

Differential diagnosis

Occasionally, HELLP syndrome must be distinguished from other conditions, especially AFLP (with which it has a significant overlap) [27], or from the rare conditions of thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, or antiphospholipid syndrome (especially in the presence of hepatic infarction). Acute fatty liver is usually associated with signs of more significant liver disease and possibly liver failure, albeit with lower serum aminotransferase levels, and is not necessarily associated with thrombocytopenia.

Management

The cornerstone of management in HELLP syndrome is prompt delivery [28]. Women must be hospitalized and managed in high-

dependency obstetric units. Along with all relevant hematological and biochemical investigations, liver imaging with computed tomography scan (limited views) or magnetic resonance imaging should be done to identify hepatic complications of infarction, liver parenchymal hemorrhage, or subcapsular hematoma, because ultrasound is not a reliable tool for identifying these complications. Hypertension must be controlled aggressively, and blood or blood products should be used, if required, to improve anemia or coagulation disorders. After initial optimization, delivery must immediately be effected in pregnancies: (1) at or beyond 34 weeks of gestation or with evidence of; (2) multiorgan dysfunction; (3) disseminated intravascular coagulation (DIC); (4) renal failure; (5) abruption placentae; or (6) fetal distress.

Management of HELLP syndrome remote from term with fetal lung immaturity and stable maternal condition is controversial [27,28]. We believe that delivery must immediately be effected after temporizing management and corticosteroid therapy for 24–48 hours in such cases. A longer conservative therapy in such cases will lead to deterioration of maternal disease within 1–10 days with a high risk of fetal loss.

Hepatic complications of HELLP syndrome/preeclampsia

Major hepatic complications of HELLP syndrome are rare (5% of cases) [29] and are as follows:

(1) Intraparenchymal hemorrhage
(2) Liver infarction
(3) Subcapsular hematoma
(4) Hepatic rupture
(5) Hepatic failure

Hepatic infarction

Right upper quadrant pain and fever with marked elevation in serum aminotransferases are characteristics of liver infarction. It can be confirmed on computed tomography scan. Patients may have an underlying procoagulant state such as antiphospholipid antibody syndrome. It is less frequent than subcapsular hematoma formation.

Hepatic parenchymal hemorrhage and subcapsular hematoma

These complications correlate with the severity of thrombocytopenia. Presenting features are severe upper abdominal pain with pyrexia and anemia. Serum aminotransferase values are in the range of thousands. Hepatic intraparenchymal hemorrhage and contained hematomas in hemodynamically stable patients are managed conservatively with aggressive correction of coagulopathy and anemia. However, there is a possibility of rapid expansion of hematoma and liver rupture; hence, intensive hemodynamic monitoring should be done. Moreover, there should be immediate availability of large volumes of blood/blood products for transfusion and surgical intervention, should the need arise. Exogenous trauma such as abdominal palpation, convulsions, emesis, and unnecessary transportation must be avoided. Management of hemodynamically unstable patients is aggressive resuscitation with immediate laparotomy.

Liver rupture

It is a life-threatening complication and is usually preceded by intraparenchymal hemorrhage progressing to contained subcapsular hemorrhage in the right lobe in patients with severe thrombocytopenia. Maternal mortality is 50%, and survival depends on rapid aggressive supportive care and immediate laparotomy. The most effective surgical management is evacuation of hematoma with pressure packing and drainage, along with hepatic artery ligation.

Acute fatty liver of pregnancy

AFLP is a rare (1 in 20,000 deliveries) and catastrophic disease with high maternal and fetal mortality. It is the most common cause of acute liver failure during pregnancy and is also known as *acute yellow atrophy* or *acute fatty metamorphosis*. As a rule, AFLP is a disease of the third trimester. Abnormalities in fatty acid oxidation lead to microvesicular fatty infiltration of hepatocytes, resulting in widespread damage.

Etiology

Despite increasing understanding of the disease, much remains to be learned. The data are conflicting, and our interpretation is incomplete yet intriguing. The principal abnormality found in some, if not all, cases of AFLP is a defect in the mitochondrial fatty acid oxidation in the mother and her fetus. Two enzymes involved in mitochondrial fatty acid oxidation, whose mutations are closely linked with AFLP, are mitochondrial trifunctional protein and its alpha subunit long-chain 3-hydroxyacyl-CoA-dehydrogenase (LCHAD). The most common mutations are the G1528C and E474Q of the gene on chromosome 2 that code for LCHAD. There are other mutations for medium chain dehydrogenase as well as carnitine palmitoyltransferase 1 deficiency [30,31]. Our current understanding from a number of studies is that when a mother is heterozygous for LCHAD deficiency and carries a fetus that is homozygous or compound heterozygous for LCHAD mutation, then there is reduced maternal capacity to oxidize long-chain fatty acids coupled with placental and fetal deficiency to do so. This leads to abnormal accumulation of long-chain fatty acid metabolites in maternal circulation. These metabolites then get deposited in hepatocytes (fatty infiltration) and cause hepatotoxicity. Apart from AFLP, fatty acid oxidation defects in mother and fetus have also been reported with HELLP syndrome. Despite this controversial association, leading authorities have concluded that given the sufficiently disparate clinical, biochemical, and histopathological findings, HELLP syndrome and AFLP are different clinical syndromes [32].

Clinical features

Unlike HELLP, the majority of women with AFLP are nulliparous. Clinical presentation is variable; however, the most frequent symptoms are anorexia for a couple of weeks, nausea, vomiting, right upper abdominal pain, and headache. The women are ill looking and jaundiced, and may be hypertensive and edematous. Patients may have ascites (partly due to portal hypertension), and the liver is small or normal in size. In severe forms, patients may demonstrate hepatic encephalopathy with or without coma. Up to half of patients with AFLP will have hypertension and/or proteinuria (preeclampsia), and hence classified as those with preeclampsia/hypertension-associated liver disease in pregnancy [33]. Polyuria and polydypsia are pathognomic symptoms in the setting of liver disease in pregnancy; however, these are present in only 5% of cases. Affected individuals have a greater-than-expected number of male fetuses (2.7:1) [34].

Laboratory abnormalities

AST and ALT are elevated up to 300–500 times usually, but not as high as in viral hepatitis. Hyperbilirubinemia is common but

usually is not >5 mg/dL. In severe cases, prothrombin time is raised and fibrinogen levels are decreased (due to hepatic synthetic defect and DIC). Variable degrees of hypoalbuminemia and hypocholesterolemia are seen. A clinical vignette is that low platelets in late pregnancy should prompt one to perform liver function tests to rule out AFLP.

Hematological abnormalities

There is hemolysis evidenced by leukocytosis, nucleated red cells, thrombocytopenia, and raised lactate dehydrogenase (LDH). Peripheral blood smear demonstrates echinocytosis with normocytic normochromic anemia, however, hematocrit is usually within normal limits due to hemoconcentration. Hypoglycemia is characteristic and is a poor prognostic feature. Other biochemical abnormalities are metabolic acidosis, renal dysfunction, high ammonia, and biochemical pancreatitis.

Diagnosis

Microvesicular steatosis on liver biopsy is diagnostic, but it is rarely necessary. Moreover, coagulopathy precludes liver biopsy in most of the situations. Therefore, in the majority of cases, a presumptive diagnosis of AFLP is made based on clinical and laboratory findings. Swansea diagnostic criteria have been proposed as an alternative to liver biopsy (Table 1) [35]. The histologic hallmark of AFLP is microvesicular fatty infiltration of the liver that is most prominent in hepatocytes surrounding the central veins (Zone 3) and spares those surrounding portal areas.

Differential diagnosis

Hypertension, proteinuria, and other clinical and laboratory features have been observed to overlap between AFLP and HELLP syndrome. However, compared with HELLP syndrome, patients with AFLP are more likely to have hepatic failure with coagulopathy, hypoglycemia, encephalopathy, and renal failure (Table 2). Viral hepatitis must be ruled out by serological testing in every case.

Management

Prompt delivery with intensive supportive care is the primary therapy. There are no reports of recovery before delivery in literature. Management begins with hospitalization and initial stabilization (correction of coagulation and other abnormalities). Delivery should be effected promptly, which is usually by cesarean section after correction of coagulation disorders. Although a vaginal delivery would reduce the chances of major peritoneal bleeding, it should be tried only if it seems possible in <24 hours with an international normalized ratio of <1.5 and a platelet count of >50,000. Transfusions with whole blood or packed red cells along with fresh frozen plasma, cryoprecipitate, and platelets are usually required. A hepatologist should be involved early on. Prophylactic antibiotics are recommended to prevent uterine infections. Blood sugar levels must be monitored closely.

Most patients recover within 1–4 weeks (although a phase of cholestasis may persist longer). During postpartum recovery, a quarter of patients may develop transient diabetes insipidus and nearly 20% may develop acute pancreatitis. Recovery is complete with no signs of chronic liver disease. With early delivery and advances in supportive care, maternal mortality is now 7–18%. Infections and bleeding remain the most life-threatening complications. Liver transplantation has a limited role in patients with fulminant hepatic encephalopathy and those who fail to recover after delivery.

Recurrence and screening

Most women would not become pregnant again either by choice or due to necessity of hysterectomy to control post partum hemorrhage (PPH). There is 20–70% chance of recurrence in the case of repeat pregnancy. All women with AFLP and their offspring must be screened for abnormalities of fatty acid oxidation.

Table 1
Swansea diagnostic criteria for diagnosis of acute fatty liver of pregnancy.

Six or more of the following features in the absence of another explanation:
• Vomiting
• Abdominal pain
• Polydypsia/polyuria
• Encephalopathy
• High bilirubin (>14 μmol/L)
• Hypoglycemia (<4 μmol/L)
• High uric acid (>340 μmol/L)
• Leucocytosis (>11 × 10^6/L)
• Ascites or bright liver on ultrasound
• High AST/ALT (>42 IU/L)
• High ammonia (>47 μmol/L)
• Renal impairment (creatinine >150 μmol/L)
• Coagulopathy (PT >14 s or aPTT >34 s)
• Microvesicular steatosis on liver biopsy

ALT = alanine transaminase; aPTT = activated partial thromboplastin time; AST = aspartate transaminase; PT = prothrombin time.

Pre-existing liver diseases

Cirrhosis and pregnancy

Most women with advanced cirrhosis will not conceive, as they are amenorrheic and infertile due to hypothalamic dysfunction [36,37]. Nonetheless, pregnancy is achieved by many, and even successfully completed in those with well-compensated disease and mild portal hypertension. Fetal loss, and maternal morbidity and mortality remain high in pregnant women with cirrhosis, and hence such cases should be managed by obstetricians focusing on high-risk pregnancy and hepatologists. The most common complication is variceal bleeding seen in a third to half of affected women [38]. Variceal bleeding usually occurs from varices near the gastroesophageal junction, especially during the second trimester and the second stage of labor, due to worsening of portal hypertension [24]. All women with cirrhosis and portal hypertension planning to conceive should undergo variceal screening and banding of varices before pregnancy. Additionally, those with no varices before pregnancy should undergo endoscopy during the second trimester, and if found to have varices, they should be managed with beta-blocker therapy. Acute variceal bleeding is managed with endoscopic band ligation. Sclerotherapy is avoided, because there is a potential risk of injecting sclerotherapeutic chemicals. If endoscopy is not available, then balloon temponade can be lifesaving. Vasopressin is contraindicated during pregnancy. Other complications are hepatic decompensation with worsening synthetic liver functions, jaundice, thrombocytopenia, ascites, and, rarely, rupture of splenic aneurysms. The best route of delivery is unknown. However, those with known large varices are best delivered by cesarean section. In the absence of large varices, assisted vaginal delivery with shortening of second stage can be accomplished.

Acute viral hepatitis

Viral hepatitis due to hepatitis A, B, C, D, and E, and herpes simplex, cytomegalovirus, and Epstein–Barr virus accounts for40%

of cases of jaundice seen in pregnant women in the western world [39]. Most cases of acute viral hepatitis are subclinical and anicteric. Clinical presentation is similar in all with nausea, vomiting, headache, malaise, and subsequent development of jaundice. Viruses may not be hepatotoxic, however, the immunological response causes the hepatocellular necrosis. All cases of hepatitis A will recover completely, and so will most of the cases of hepatitis B. However, complete clinical and biochemical recovery will be seen only in a small proportion of cases of hepatitis C.

Hepatitis A

The course of hepatitis A in pregnancy is similar to that seen in the nonpregnant state. Symptoms are usually mild and last for <2 months. Early on immunoglobulin M antihepatitis A virus antibodies are detected, and immunoglobulin G antihepatitis A virus antibodies are seen in convalescence. Hepatitis A in the third trimester is associated with an increased risk of prematurity [40]. Treatment remains supportive, with a balanced diet and diminished physical activity. Fetal transmission is negligible, and the virus is not teratogenic. Centers for Disease Control (CDC) recommends a postexposure (close contact or sexual contact) immunoprophylaxis in pregnant women with a 0.02-mL/kg dose of immune globulin [41]. Literature reports high maternal and perinatal mortality rates in resource-poor countries. All cases have a complete recovery, and there is no chronic stage of hepatitis A.

Hepatitis B

This virus is found worldwide with endemic presence in Africa, Southeast Asia, China, and the Middle East. Fifty percent of cases are asymptomatic, and when symptoms are present, they are usually mild. Serological course during pregnancy is the same as that seen outside pregnancy, with hepatitis B surface antigen being the first serological marker detected. Core antigen (HBc) is not detected in serum; however, anti-HBc antibodies are detectable next. Hepatitis Be (HBe) antigen is a marker of viral replication. Complete resolution is seen in 90% of cases within 3–4 months, and this is evidenced by the disappearance of hepatitis B surface (HBs) antigen and the appearance of anti-HBs antibodies. Ten percent will remain chronically infected. One of the risk factors for chronic disease is the age at the time of infection—>90% in newborn, 50% in young children, and <10% in immunocompetent adults. Literature suggests a moderately increased risk of preterm in hepatitis B virus (HBV)-positive pregnant women [42]. Vertical transmission and measures to reduce vertical transmission are discussed separately.

Hepatitis C

Acute infection is usually asymptomatic or mild. Most of the cases are anicteric. Hepatitis C RNA testing is considered a "gold standard" for the diagnosis of hepatitis C virus. Recent literature suggests an excess risk for fetuses with increased incidences of low birth weight, preterm delivery, and admissions to neonatal intensive care units. Treatment for acute infection during pregnancy is supportive. Of the patients, 90% will remain chronically infected with hepatitis C virus.

Hepatitis E

This is probably the most common cause of acute hepatitis [43]. Hepatitis E is endemic in India, and pregnant women are more vulnerable to hepatitis E than hepatitis A, B, or C. Hepatitis E tends to run a severe course in pregnancy, especially in India, with increased propensity to develop fulminant hepatic failure in the third trimester [44,45]. Maternal and fetal mortality secondary to fulminant hepatic failure is very high (41–54% and 69%, respectively) [46]. High viral loads and very high cytokine secretion might be responsible for fulminant hepatic failure during pregnancy. Importantly, delivery does not change the outcome, and management remains supportive with the patient being ideally managed in an intensive care unit.

Herpes simplex virus hepatitis

Herpes simplex viral hepatitis is a rare entity; however, pregnant women are more susceptible than the general population. The course during pregnancy is usually severe and fulminant, with high maternal mortality. Herpes simplex viral hepatitis leads to "anicteric hepatitis" with normal levels of bilirubin in the presence of severe derangements in liver function tests. Mucocutaneous manifestation of herpes simplex infection occurs in only 50% of cases [45]. A high degree of suspicion would be lifesaving, as treatment with intravenous acyclovir is effective.

Viral hepatitis and vertical transmission

The primary concern with chronic hepatitis B infection in pregnancy is the possibility of vertical transmission. In fact, 35–50% of cases of chronic HBV infections in endemic areas are due to vertical transmission. Foremost in the strategy to reduce vertical transmission of HBV infection is routine screening of pregnant women for HBV at the initial booking visit. Women who are without immune antibodies and display a high-risk behavior (intravenous drug abuse and multiple sex partners) are at increased risk of acquiring hepatitis B during pregnancy and can be given hepatitis vaccine with little risk to the fetus. The key factors in vertical transmission are presence of HBe antigen (suggesting active viral replication), anti-HBe antibodies, and the viral load. Vertical transmission is maximum in the presence of HBe antigen and a high viral load (50–80%), lower with anti-HBe (25%), and lowest in carriers (5%) [23]. Vertical transmission can be reduced significantly (up to 95%) by passive–active immunoprophylaxis of babies with hyperimmune B immunoglobulin within 12 hours of birth and hepatitis B vaccination within first 6 months. Cesarean section does not reduce the transmission rates.

Use of antiviral therapy during pregnancy to reduce the vertical transmission of hepatitis B is a controversial issue, and no guidelines exist at present. Some people advocate the use of lamivudine (pregnancy category C drug) monotherapy after 32 weeks of pregnancy, when viral load is in excess of 10^6 viral copies/mL [46]. This can be considered in women who have infected their child in a previous pregnancy. However, there are concerns of viral resistance with lamivudine monotherapy. Reports of two other antiviral medications, telbivudine and tenofovir, in pregnancy are also encouraging [47–49]. The use of hyperimmune B immunoglobulin antenatally in women at the highest risk of vertical transmission also seems to be effective in decreasing transmission rates [50]. HBV infection is not considered a contraindication for breast feeding by the American Academy of Pediatrics.

Vertical transmission with maternal hepatitis C infection is very low. However, maternal coinfection with human immunodeficiency virus, and fetal exposure to a large volume of maternal blood or secretion during delivery in the presence of a high viral load increases the rates of vertical transmission [51–53]. Vertical transmission of hepatitis C is not prevented by treatment of the infant with immunoglobulin. Women are not treated with interferon and ribavirin during pregnancy because of teratogenic potential of ribavirin in animals.

Vertical transmission of hepatitis A and D is very rare, and occurs only with high viral loads (acute phase) during delivery. Hence, newborns of mothers contracting hepatitis A in the third trimester should be administered immune globulin within 48 hours of birth.

Gall bladder disease and pregnancy

Pregnancy favors gall stone formation for the following reasons. Cholesterol secretion increases in the second and third trimesters compared with other constituents of the bile, and hence the bile gets supersaturated with cholesterol. Second, gall bladder volumes are higher during pregnancy due to a decreased rate and volume of emptying. Thus, large residual volumes of supersaturated bile eventually lead to stone formation in up to 10% of pregnant women. Interestingly, despite a high prevalence of gall stone formation during pregnancy, women usually become symptomatic following the delivery. In fact, symptomatic gall stone disease remains the number one nonobstetric reason for hospital admission in the year following delivery.

The principal clinical presentations of gall stone disease, in order of frequency during pregnancy, are acute biliary colic, acute cholecystitis, and gall stone pancreatitis (rare). Initial management of uncomplicated acute biliary colic and cholecystitis during pregnancy is supportive, with bed rest, intravenous hydration, antimicrobials, and analgesics. However, cholecystectomy is indicated for intractable biliary colic, severe acute cholecystitis not responding to conservative management, and acute gallstone pancreatitis. In the past, most favored medical therapy. However, due to 50% recurrence of biliary colic before delivery, operative and endoscopic interventions are increasingly being favored. If cholecystitis recurs during late pregnancy, then preterm labor is likely and surgery is technically more difficult due to enlarged uterus. It has been reported that those managed conservatively had more pain, more emergency visits, and higher rates of hospitalization and cesarean section [54]. It is recommended that those presenting with symptomatic gall stone disease in the first and second trimesters should undergo cholecystectomy during the second trimester. Surgery is avoided in the first trimester due to risk of abortion with anesthesia and in the third trimester due to the risk of preterm labor. Extrahepatic ductal stones are best managed by endoscopic retrograde cholangiopancreatography, sphincterotomy, and stone extraction under antibiotic coverage.

Table 2
Key learning points.

- Three percent of the pregnancies are affected by liver diseases.
- Severe liver disease in pregnancy is rare.
- Liver diseases during pregnancy can be divided into those related to pregnancy and those just incidental to pregnancy, and this distinction is important as the cornerstone of management in most pregnancy-related diseases (except hyperemesis gravidarum) is termination of pregnancy.
- Pregnancy-related liver diseases are most frequent causes of liver dysfunction during pregnancy.
- Pregnancy-related liver diseases have characteristic timings in relation to the trimesters of pregnancy. Hyperemesis gravidarum occurs in the first trimester, intrahepatic cholestasis in late second and third trimesters, and HELLP, eclampsia, and AFLP mainly occur in the third trimester.

AFLP = acute fatty liver of pregnancy; HELLP = hemolysis, elevated liver enzymes, and low platelets.

Conflicts of interest

Authors state that they have no conflicts of interest.

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