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Liver Disease in Pregnancy

Fabiana S. Benjaminov M.D., and Jenny Heathcote M.D., F.R.C.P., F.R.C.P. (C)
Department of Gastroenterology, "Meir" Medical Center, University of Tel-Aviv, Kfar-Saba, Israel; and Department of Medicine, The University Health Network, University of Toronto, Toronto, Ontario, Canada

Liver dysfunction during pregnancy can be caused by conditions that are specific to pregnancy or by liver diseases that are not related to pregnancy itself. This review attempts to summarize the epidemiology, pathophysiology, and management of the different pregnancy-related liver diseases, and to review different liver diseases not related to pregnancy and how they may affect or be effected by pregnancy. Some of the liver diseases specific to pregnancy can cause significant morbidity and mortality both to the mother and to the fetus, while most of the liver diseases not specific to pregnancy do not have a deleterious effect on the pregnancy itself.

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NORMAL LIVER BIOCHEMISTRY DURING PREGNANCY

During pregnancy, the liver metabolic, synthetic, and excretory functions are affected by the increased serum estrogen and progesterone (1). Serum albumin concentration decreases during pregnancy and reaches a nadir towards the end of the pregnancy, secondary to increase in plasma volume (2). Alkaline phosphatase activity is increased during the third trimester both because of leakage of placental alkaline phosphatase into the maternal circulation and because of increased maternal bone turnover (3). Because of this lack of specificity, the alkaline phosphatase activity is a poor test for the diagnosis of cholestasis during the third trimester of pregnancy. Serum transaminases levels are within normal values during pregnancy (3). Increase in transaminases levels was found during labor and is, most probably, secondary to leakage from the contracting uterine muscle (4). Serum levels of Υ-glutamyl-transferase (ΥGT) and 5′ nucleotidase are normally unchanged (2). Total and free bilirubin serum levels are lower in pregnancy, both because of hemodilution and the low albumin concentration (albumin being the protein that transports bilirubin) (3).

LIVER DISEASE ASSOCIATED WITH PREGNANCY (TABLE 1)

Hyperemesis Gravidarum

Hyperemesis gravidarum (HG), is characterized by nausea and vomiting that can be extreme enough to require hospitalization. Up to 50% of women with HG are hospitalized (5). This condition occurs in 1–20 patients per 1,000, generally during the first trimester of pregnancy (6). Up to 25% of hospitalized patients will have liver enzymes abnormalities (7). Bilirubin level rise up to 4 mg/dl, all unconjugated. Aminotransferases values can rise up to 200 IU/L and the alkaline phosphatase can be elevated to twice the normal value (8). Amylase level can be elevated, but its origin is from the salivary glands and not the pancreas (9). The etiology of this condition is unknown. Although high or rapidly rising steroid level seem to play a part in the etiology, when investigated individually, ACTH, cortisol, estrogen, progestron, and FSH and LH levels were not found to be elevated (10). Transient hyperthyroidsm, which causes a rise in β-human chorionic gonadotropin level and its stimulatory effect, has been observed in the first trimester in women with HG (11). In addition, higher concentration of prostaglandin E2 has been found in women with HG. Several risk factors for the development of HG were identified, such as: female sex of the fetus, multiparity, and high daily intake of saturated fat before pregnancy (8). Both benign and malignant complications of HG are secondary to the repeated vomiting. Disturbances in electrolytes, water and acid-base balance are some of the benign complications. Severe complications include esophageal rupture, retinal hemorrhage, pneumomediastinum, and renal damage, secondary to severe intravascular volume depletion (12). Fetal outcomes are favorable and do not differ from the general population (13).

Preeclampsia/Eclampsia

Preeclampsia, which affects 5–7% of all women during pregnancy, is characterized by a triad of hypertension, proteinuria, and peripheral edema. Eclampsia is marked by seizures and coma in addition to the signs of preeclampsia. Preeclampsia usually occurs in the second or third trimester. The etiology of this condition is, as yet, unknown but it seems that uteroplacental ischemia plays a major role (14). The placental ischemia causes activation of the endothelium with initiation of the coagulation cascade, increased adhesiveness of platelets, and greater thrombogenicity (15). In addition, elevated levels of nitric oxide, thromboxanes, isoprostanes and lipid peroxidases, and reduced prostacyclin (PGI2) levels may contribute to the increased vascular sensitivity (16).

Table 1. Liver Diseases Associated with Pregnancy

Disease	Time of Appearance	Treatment
Hyperemesis gravidarum	First trimester	Supportive
Preeclampsia/eclampsia	Second/third trimester	Supportive/delivery
HELLP syndrome	70% mid-second to mid-third trimester 30% postpartum	Delivery/supportive
AFLP	Third trimester	Delivery/supportive
Liver hematoma/rupture	Third trimester to postpartum	Surgery
ICP	Third trimester	UDCA/delivery at fetal maturity

Genetic factors have also been implicated, because of increased occurrence in females from the same family, and lately, because of a high compatibility in the human leucocyte antigen (HLA-DR) between the preeclamptic woman and her spouse (17). Risk factors for preeclampsia include preexisting hypertension, extreme of childbearing age, first pregnancy, and multiple fetal pregnancies. Twenty to thirty percent of women with preeclampsia have abnormal liver enzymes, the alkaline phosphatase is elevated beyond the normal increase seen in pregnancy, and aminotranseferase levels are also increased (18). Liver histology shows deposition of fibrin in the hepatic sinusoids, periportal hemorrhage, and liver cell necrosis, and even infarction. This is believed to be secondary to vasoconstriction of the hepatic vascular bed (18). Fifty percent of patients will be found to be thrombocytopenic, usually moderate (>70,000). Complications of preeclampsia include hypertensive crisis, renal impairment and infarction, and neurological complications (including seizures and cerebrovascular accidents). Maternal mortality is less than 1%. Over 80% of the deaths are attributed to central nervous system complications, and the remainder to hepatic complications (subcapsular hematoma and rupture, hepatic infarction, and fulminant failure) (19). Increased perinatal morbidity and mortality is caused by abruptio placenta, prematurity, and intrauterine growth retardation.

HELLP Syndrome

The hemolysis (H), elevated liver enzymes (EL), and low platelets (LP) syndrome is a grave condition that threatens the patient and her fetus. This condition affects 0.1–0.6% of all pregnancies. Although it is considered a complication of preeclampsia, only 4–12% of women with severe preeclampsia experience the HELLP syndrome (20). HELLP syndrome and preeclampsia differ in several aspects. The HELLP syndrome develops before delivery only in 70% of the cases while the other 30% develop postpartum. It may present at an earlier gestational age and the incidence is increased in White multiparous women, in contrast with preeclampsia (20, 21). As in preeclampsia, the etiology is believed to be activation of the complement and the coagulation cascades, increased vascular tone, platelet aggregation, and an alternation of the thromboxane:prostacyclin ratio. These changes induce generalized endothelial and microvascular injury resulting in microangiopathic hemolytic anemia, EL (due to periportal hepatic necrosis), and thrombocytopenia (22). Most patients present typically with right upper quadrant pain, malaise, nausea, and vomiting. In 20% of patients hypertension is absent. The differential diagnoses in a pregnant woman with these complaints include hepatitis of any etiology, pancreatitis, cholecystitis, and appendicitis (Table 2). Obtaining liver enzyme values and platelet counts will support the diagnosis (23). The differential diagnosis of thrombocytopenia in pregnancy is wide (Table 3). Gestational thrombocytopenia (which accounts for 75% of pregnancy-related thrombocytopenia) (24) and immune thrombocytopenia (ITP) are usually asymptomatic and difficult to differentiate (unless there is a prior history of easy bruising or gingival bleeding). Pregnancy is a predisposing factor for the development of thrombotic thrombocytopenic purpura (TTP) and the hemolytic uremic syndrome (HUS). Up to 10% of female patients with TTP are pregnant. It is very difficult to distinguish between the HELLP syndrome and these two conditions, since all involve microangiopathic hemolytic anemia. TTP/HUS could be differentiated from the HELLP syndrome by the lack of hepatic dysfunction in the former, and the lack of significant central nervous system/renal impairment in the latter (25). The final arbiter is delivery as this leads to improvement in

Table 2. Differential Diagnosis of Right Upper Quadrant Pain in Pregnancy (32)

Obstetric
Ruptured uterus
Labor
Extrauterine pregnancy
Fetal movement/rib pain
Gynecologic
Adnexal torsion
Rupture of adnexal cyst
Gastrointestinal
Liver hematoma/rupture
Cholelithiasis/cholecystitis/cholangitis
Hepatitis
Pancreatitis
Peptic ulcer
Cardiac
Myocardial infarction
Pericarditis
Pulmonary
Pulmonary emboli
Pneumonia
Genitourinary
Pyelonephritis
Nephrolithiasis

Table 3. Effect of Liver Disease on Pregnancy

HBV	No deleterious effect on liver—precautions for vertical transmission
HCV	No deleterious effect on liver—precautions for vertical transmission
HEV	Can cause fulminant hepatitis—maternal mortality: up to 16%
AIH	Exacerbation mainly postpartum—enhance immunosuppressive therapy
PBC/PSC	No deterioration of liver status
Cirrhosis	No deleterious effect on mild portal hypertension—close monitoring and treatment of possible complications

HELLP but not in TTP/HUS. Some features of acute fatty liver of pregnancy (AFLP) may overlap with HELLP but in AFLP the degree of hepatic impairment is much more significant, overt failure in terms of hypoglycemia, and marked coagulopathy being evident. Other causes for thrombocytopenia such as systemic lupus erytematosus (SLE) and the antiphospholipid syndromes have, usually, prior history and do not involve the liver. Disseminated intravascular coagulation (DIC) occurs usually postpartum and is associated with obstetric disorders such as placenta abruptio, amniotic fluid embolism, *etc*. Maternal mortality from HELLP syndrome ranges between 1–3.5% (20). Complications include DIC (20% of patients), abruptio placenta (16%), acute renal failure (7%), and pulmonary edema (6%). Hepatic rupture occurs in approximately 1% of patients and can herald profound hemorrhage and shock, as well as present a difficult surgical emergency (20). Hepatic intraparenchymal hemorrhage, infarction, and subcapsular hematoma without rupture may occur. The perinatal mortality rate ranges from 56–367 per 1,000 births. Perinatal death is most commonly experienced in very early gestational age, in the setting of severe growth retardation or abruptio placenta (26). The definitive treatment for the HELLP syndrome is delivery. Close monitoring of the patient should be performed a few days postpartum, since laboratory abnormalities could worsen (18). The risk of recurrent HELLP syndrome in subsequent pregnancies is 3–27% (27).

AFLP

AFLP occurs in the third trimester. The incidence is estimated to be 1:10,000–15,000 pregnancies, with a maternal mortality of 18%. (28). Fourteen to nineteen percent of pregnancies in patients with AFLP are twin pregnancies. AFLP is also commoner in male pregnancies and in nulliparous (29). Recently, an association between AFLP and a deficiency of the enzyme long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHA) was suggested. This enzyme is one of the four enzymes, which break down long-chain fatty acids in the liver. Deficiency of this enzyme results in the increased accumulation of long-chain fatty acids. The most common mutations have been localized to a G1528C mutation in over 60% of cases (30), and a E474Q mutation in 19% of the cases (31), both on the mitochondrial trifunctional complex on chromosome 2 (32). Few studies have been reported of children born with LCHA deficiency. These children suffer from failure to thrive, hepatic failure, cardiomyopathy, microvesicular steatosis, hypoglycemia, and death. Most of those children were born to mothers who had AFLP (33, 34). Under normal circumstances an individual heterozygote for these mutations will have no abnormal fatty acid oxidation. When a heterozygous woman has a fetus which is homozygous for these mutations, it is unable to oxidize long-chain fatty acids. These fatty acids accumulate, having returned to the mother's circulation via the placenta. The heterozygous mother cannot cope with the load of long-chain fatty acids. Triglycerides accumulate within the liver (microvessicular fat), especially in the mitochondria, of hepatocytes leading to impaired function and liver failure. Symptoms of AFLP include nausea and vomiting, abdominal pain, anorexia, and jaundice. Half of the patients will have signs of preeclampsia. The size of the liver is usually normal or small (35). Transaminases levels are raised and the bilirubin level is almost always elevated. Typically, hypoglycemia, prolongation of prothrombin, partial thromboplastin times, and thrombocytopenia distinguish AFLP from HELLP (36). Delivery of the infant stops the overload on the mother's hepatic fatty-acid oxydation system, which then returns to normal. Appropriate supportive measures (*e.g.*, blood, glucose) are required while making preparations for urgent delivery. Genetic counseling should be offered since AFLP can recur in subsequent pregnancies (37). Obtaining chorionic villous sampling or amniocentesis can assist in the prenatal identification of fetuses with LCHAD deficiency (38). Since early diagnosis may improve outcome, screening for LCHAD deficiency should be done on all babies born to mothers given the diagnosis of AFLP. Babies who are positive for reducing substances in the urine should undergo genetic testing. These babies should be managed with the right diet (medium chain triglycerides formula) and followed-up for sequela (38).

Liver Hematoma and Rupture

Liver hematoma and rupture is a devastating complication of pregnancy. The majority of cases occur in the third trimester, at term or immediately postpartum (39). The majority of the cases are a result of a complicated course of HELLP syndrome. Sibai *et al.* (20) reported an incidence of 1% of liver rupture among women with HELLP syndrome. Other conditions associated with this complication are: cocaine abuse (40), liver neoplasms, liver abscesses (pyogenic or amebic), AFLP, and trauma. (39). Eighty percent of the affected women are multiparous with an average age of 32 yr (39). The pathophysiology of liver rupture is not clear. In all cases, intraparenchymal hemorrhage precedes the rupture itself (in contrary to liver rupture secondary to trauma). Autopsy specimens show periportal fibrin deposition, hepatocytes necrosis, and parenchymal hemorrhage (41). These findings can also be seen in patients with HELLP syndrome. Other theories include increased sensitivity of the hepatic vasculature to vasopressors (41), "desensitization" of the reticuloendothelial

system in the liver during prior pregnancies, which leads to an accumulation of fibrin deposits, blockage of sinusoids, cellular necrosis, and eventual hemorrhage and rupture (42). The majority (74%) of the hematomas occurs in the superior and anterior aspects of the right lobe of the liver, while the rupture itself occurs in the inferior edge of the right lobe (39). The clinical presentation consists of a prodromal period that can last up to a month with vague complaints of malaise, headache, and nonspecific gastrointestinal symptoms. This period is followed by an acute phase, when the actual rupture occurs, which quickly leads to maternal cardiovascular collapse and death.

Eighty to ninety percent of patients will have signs and symptoms of preeclampsia. Liver hematoma and rupture should be suspected in any pregnant woman who presents with right upper quadrant pain, preeclampsia, and profound hypotension and shock (Table 2). The diagnosis of liver hematoma or rupture is made by ultrasound or CT. CT is more accurate since it can detect a very small amount of intraparenchymal and subcapsular hematoma, when done with contrast. Occasionally, diagnosis is made during explorative laparoscopy. Henny *et al*. (39) reported a fetal mortality of 62–77%. The mortality was caused by a combination of maternal hypotension, abruptio placenta, and prematurity. The maternal mortality rate was reported to be 56–75%, the major cause being massive hemorrhage and coagulopathy.

Intrahepatic Cholestasis of Pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is a rare condition with prevalence estimated at 1/1,000 to 1/10,000 pregnancies. Scandinavia and Chile have the highest prevalence (43). ICP usually presents in the third trimester and rarely before the 26th week of gestation. ICP is more common in women with advanced maternal age, in multiparous women, and in the winter months. This condition clusters in families and is more common in women with a personal history of cholestasis on oral contraceptives (43). Pruritus is the main complaint, starting in the periphery and advancing centrally to the trunk and face. The pruritus can be of a devastating degree causing deprivation of sleep and irritability. Jaundice, which develops in 20–60% of ICP patients, appears 1–4 wk after the onset of pruritus. Except for excoriations from scratching, a skin rash is typically absent (44). Laboratory data show high bilirubin concentration that rarely exceeds 6 mg/dl. The alkaline phosphatase level can range from normal to four times normal, and the transaminases may be elevated two to ten times. The most sensitive laboratory abnormality in ICP is the level of serum bile acids, which can be elevated 10–25 fold (44). The etiology of ICP is, of yet, unknown. Although genetics seem to play an important role, it is clearly not the cause but merely plays a role in the susceptibility of this disease. Multi Drug Resistance 3 gene (MDR3) is a canalicular phospholipid transporter involved in the biliary excretion of phospholipids (45). Jacquemin *et al.* (46) provided evidence that the heterozygote state for the MDR3 gene defect predisposes women to the development of ICP. Female sex hormones and metabolites during pregnancy can modify heterogeneous MDR3 expression directly by decreasing normal allele expression, or indirectly by impairing the function of the transport systems involved in bile secretion, which could lead to ICP. The metabolism of bile acids and progesterone in ICP is different than in healthy pregnancies. Women with ICP make more sulfated progesterone than glucoranated progesterone metabolites (47). It seems that in ICP there is a defect in the biliary excretion of sulfated steroid metabolites, resulting in the saturation of the hepatic transport system (48). Another theory involves a defect in the human steroid and xenobiotic receptor (SXR). This receptor, when activated by bile acids, induces cytochrome P-450 protein CYP3A. CYP3A plays a role in detoxification of drugs and bile acids (49). Naloxone, an opioid receptor antagonist, alleviates the pruritus in ICP, suggesting an increased endogenous opioid neurotransmission in the setting of ICP (50). Finally, evidence suggests a role of bile acids on the activity of the myometrium. In sheep, cholic acid infusion increases meconium staining, premature labor, and preterm delivery (44). The maternal outcome is favorable with symptoms and laboratory abnormalities resolving 1–2 wk after delivery. Forty to sixty percent of women with ICP will experience a recurrence in subsequent pregnancies (44).

ICP is associated with preterm delivery, increased perinatal mortality, and meconium staining. When untreated, fetal mortality ranges from 11% to 20% (51). The treatment of choice is ursodeoxycholic acid (UDCA), which is a hydrophilic bile acid. UDCA alters hydrophilicity and thus the overall distribution of bile acids from the fetal circulation. In addition, in cholestatic conditions, UDCA displaces hydrophobic toxic bile acids from hepatic membranes (52). UDCA was proven in a randomized, double-blind, placebo-controlled study to improve pruritus and liver enzymes, and to allow delivery to occur significantly closer to term (53). It is also recommended to deliver patients when fetal maturity has been achieved to avoid late fetal death (54).

LIVER DISEASE DURING PREGNANCY

Viral Hepatitis

HEPATITIS A. The incidence of acute hepatitis A (HAV) during pregnancy is no different to the incidence of the acute infection in the specific geographic area (55). In endemic areas such as Africa, Asia, and Central America, most of the population has acquired natural immunity by the age of 10 yr. In the United States the reported incidence for HAV is 9/100,000 (56, 57).

The clinical presentation, disease course, treatment, and sequela are similar to those of nonpregnant patients except that pruritus is more common due to the high estrogen state. Perinatal transmission, as reported in case reports, is most probably secondary to horizontal transmission at the time of delivery. Both the inactivated vaccine against HAV and the postexposure immunoglobulin prophylaxis are safe in pregnancy (58).

HEPATITIS B. Hepatitis B (HBV) is a double-stranded, enveloped DNA virus, a member of the hepadena-virus group. It is highly infectious and transmitted parenterally by percutaneous or mucosal exposure, sexually, and from mother to infant. The clinical presentation and course of the disease is similar to nonpregnant infected individuals. Diagnosis of acute HBV infection is made by the detection of HBV surface antigen (HBsAg) in the serum, and confirmed by the presence of IgM antibodies to HBV core antigen (HBcAg). Hepatitis e (envelope) antigen is present in almost all acute infections and represents high infectivity. As long as HBsAg is present, the individual is infectious. As anti-HBe antibody develops, infectivity decreases. Chronic HBV infection is present in approximately 1% of pregnancies in North America (much higher than this in other parts of the world) and acute HBV complicates 1–2 per 1,000 pregnancies (58).

If the acute maternal infection occurs in the first trimester and resolves, the risk for neonatal infection is minimal. In contrast, an infection during the second and third trimesters poses a threat of 10% and 90%, respectively, for vertical transmission. Most perinatal transmission occurs intrapartum (95%). Intrauterine infection is rare. Recently, a study by Xu *et al.* (59) described the risk factors for intrauterine transmission, which were: maternal serum HBeAg positivity, history of threatened preterm labor, and HBV in the placenta. A child born to a HBeAg positive mother has 70–90% chance of being infected (60). In the Mediterranean basin, Middle East, and Asia, where a variant HBV with a precore/base core promotion mutation, which causes loss of HBeAg synthesis is common (61), infants, when infected, do not develop chronic HBV infection (62) but rather an acute hepatitis (63). A child infected with HbeAg at birth has a 90% chance to progress to chronic infection, while an infection between 7 and 12 months will progress to chronicity in 40% of cases and only 10–20% of cases if the infection occurred between 1 to 3 yr of age (64). The presence of HBsAg in pregnant women does not pose additional risk for the pregnancy and its outcome (65). Since 1991, there is a recommendation to vaccinate individuals in high risk groups such as children born to HBsAg negative mothers (with an addition of immunoprophylaxis with HBV immunoglobulin for children of HBsAg positive mothers) (66). The vaccine is safe to use in pregnancy. Passive and active immunization, given together, are very effective in preventing neonatal transmission, reducing the carrier state of infants born to HBeAg/HBsAg positive women, from 70–90% to almost zero.

With this proper immunoprophylaxis, breastfeeding of infants to chronic HBV carrier women poses no additional risk factor for the transmission of the HBV virus (67).

HEPATITIS D. Hepatitis D (HDV) is a single-stranded circular RNA virus, which depends for its replication on the presence of HBV virus. One of the main routes of transmission is mother to infant. Coinfection with HBV and HDV causes a more severe disease with much higher chronicity rate (70–80% of infected patients will develop cirrhosis), and a much more rapid course of disease. Measures to prevent HBV infection are effective in preventing HDV (58).

HEPATITIS C. Hepatitis C (HCV) is an enveloped single-stranded RNA virus, related to the flavivirus family. It is less common than HBV, but HCV infection becomes chronic in a larger proportion of cases (80%) (58). Percutaneous transmission accounts for at least 60% of cases; others may have no identifiable risk factor. To date, childhood acquisition of HCV infection through maternal-infant transmission has become the most important mode of spread (68). The prevalence of detectable HCV antibodies in pregnant women is 1% overall (range 0.1–2.4%,) not different than that in the general age-matched population. Approximately two-thirds may be expected to have active infection with detectable serum HCV RNA (69). Different studies have shown different conclusions regarding the effect of pregnancy on chronic infection with HCV. The data from these studies is inconsistent and currently no definitive conclusion can be drawn. To date, HCV is not considered a contraindication for pregnancy. Since HCV RNA levels fluctuate during pregnancy, HCV RNA levels should be measured in the third trimester, since the first trimester levels may not be representative or predictive of HCV-RNA concentrations at the time of delivery. Chronic infection with HCV does not have an adverse effect on the pregnancy and its outcome (70). Since passive transmission of IgG antibodies to HCV is present through the placenta, detectable anti-HCV antibodies in the newborn do not mean that a perinatal infection has occurred. Detectable anti-HCV antibodies in infants more than 18 months old or a detectable HCV RNA in infants 3–6 months old can define mother-to-infant transmission of the infection (69). If the mother is viremic with a detectable HCV RNA, the transmission rate reaches 4.3%. The higher the viral load, the higher likelihood of transmission. Geographic location also plays a role, with higher transmission rates reported in Italian and Japanese studies than in studies from other locations (5.6%, 6.9%, and 3.1%, respectively). Coinfection with HIV increases significantly the risk for HCV transmission, being 19.4% in coinfected mothers, compared to a much lower risk of transmission in mothers with HCV alone. Antiretroviral treatment for HIV during pregnancy decreases the rate of HCV transmission to levels of women not coinfected with HIV (71). The HCV genotype has no effect on transmission. Amniocentesis or fetal blood monitoring via scalp vein catheter is considered a relative contraindication during pregnancies of mothers with HCV infection. The type of delivery (cesarean *vs* vaginal) does not seems to influence the rate of mother to infant transmission (69). Although HCV virus can be detected in breast milk and colostrum, breastfeeding is not considered a risk factor for HCV transmission (72). Treatment of HCV infection with α-interferon and ribavirin is contraindicated during pregnancy. α-interferon is contraindicated in children under the age of 2 yr because of severe neurotoxicity and because ribavirin is teratogenic. Screening of all prospective mothers is still not indicated. However screening of high risk groups, such as

women positive for HIV, previous or current use of injection drugs, current or previous sex partners known to use injection drugs, women who received blood transfusions before 1992, and people from certain geographic areas, can have its advantages (69). The outcome of the children infected perinataly is still not clear. Several studies have demonstrated spontaneous clearance of HCV by 6–24 months of age (73, 74). It is still to be investigated if HCV acquired from mother-to-infant transmission is different than transfusion related HCV and from adult onset HCV.

HEPATITIS E. Hepatitis E (HEV) is a nonenveloped, single-stranded RNA virus. It is endemic in developing countries and shares the route of transmission, risk factors, and chronicity rate with HAV. During pregnancy, HEV can cause fulminant hepatitis indistinguishable from AFLP. There is a significant mortality rate of 16% in pregnant women with acute HEV infection. Transmission occurs intrapartum and peripartum through close contact of mother and neonate. Evidence suggests significant vertical transmission among HEV-RNA positive mothers of up to 50%. Among women with symptomatic infection the rate of transmission is up to 100%, with significant perinatal morbidity and mortality (75, 76).

Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is a chronic liver disease of unknown etiology. It is characterized by a progressive destruction of liver parenchyma leading frequently to cirrhosis. This disease often affects women in their childbearing years, but since cirrhosis is often present at the time of diagnosis, pregnancy is not expected in the untreated patient. Oligoamenorrhea, which at times is the presenting symptom, is frequent in AIH and is probably due to hypothalamic pituitary dysfunction (77). When disease activity regresses under adequate immunosupression, normal menstruation returns, and a pregnancy is achievable. Two recent studies (78, 79) have described the natural history of AIH during pregnancy. Both studies found a significant decrease in disease activity during pregnancy. Heneghan and colleagues (78) found 11.5% incidence of flare-up during pregnancy, with 11.3% occurring during the 3 months period following delivery. Buchel and colleagues (79) found no exacerbation during pregnancy but relapse was observed in 86% of pregnancies in the postpartum period. In both series the perinatal morbidity and mortality was significantly reduced compared to previous studies. No perinatal death was recorded. Prematurity was observed in 6% of newborns and the caesarian section rate was 3%, compared to 30% and 26%, respectively, in previous studies (80). This improvement is attributed to better immunosupression leading to better disease control. Pregnancy induces a state of immunotolerance, accommodating the fetus, and causes a shift of a T_H1 to T_H2 immune response (81). This shift causes an amelioration in disease activity which is T_H1 dependent, like rheumatoid arthritis, and an exacerbation in disease post partum when the immune status is back to the T_H1 predominance (79). Since the pathogenesis of AIH is still not clear, the relevance of a shift from T_H1 to T_H2 immune response remains speculative. The high hormone levels in pregnancy also play a part in the immunotolerance. Estrogen, in high levels, may inhibit immune response and progesterone and testosterone promote T_H2 cells and have antiinflammatory property (82). The use of prednisone is considered safe during pregnancy and lactation but is associated with a small but significant risk of cleft palate in babies to women using the drug in the first trimester of pregnancy (83). Azathioprine seems a safe drug to use during pregnancy, with expanding experience in women with rheumatoid arthritis, inflammatory bowel disease, and after renal transplantation.

Although only 1.2% of the absorbed amount of azathioprine is excreted in breast milk, it is only classified as "probably safe" for use during breastfeeding. Since exacerbation was observed in high frequency postpartum, it is advisable to closely monitor these patients and even enhance the immunosuppressive therapy to prevent serious flare-ups (79).

Primary Biliary Cirrhosis (PBC) and Primary Sclerosing Cholangitis (PSC)

Little data exist regarding pregnancy in patients with PBC and PSC as most patients are postmenopausal at diagnosis. Traditionally, pregnancy in PBC is considered rare. Recently, normal gravidy was found in 182 PBC patients (84). Although embriotoxicity of UDCA was not reported in humans, there is not sufficient data regarding this issue. Therefore UDCA is not approved for the use during early pregnancy. UDCA could be administered in cholestatic liver disease, when the pregnant woman is symptomatic during the second or third trimesters. UDCA is not approved during breastfeeding, although the substance cannot be found in milk during lactation (85). In a study of 10 women with PSC, no deterioration in liver function was found, although two women experienced severe pruritus. No fetal loss was described and the outcome of all babies was favorable (86).

Gallstones

Pregnancy induces several changes in the biliary tract and in the bile. These changes contribute to the formation of gallstones and biliary sludge during pregnancy. Impaired motility of the gallbladder was demonstrated in several studies. Both increased volume and incomplete emptying of the gall bladder in all stages of pregnancy were recorded, returning to baseline values a few days postpartum (87, 88). Tierney *et al*. (89) demonstrated a reduced gallbladder ejection fraction and emptying rate under increasing doses of progesterone, mimicking pregnancy. The bile in pregnant women is supersaturated with cholesterol (90), a fact that contributes to its lithogenicity. The rise in the cholesterol secretion is attributed to the increasing levels of estrogen during pregnancy. Progesterone also causes decreased small intestinal motility during pregnancy (87). Decreased small bowel transit time has been shown to contribute to the formation of gallstones (91). Another factor that contributes to the formation of

gallstones is biliary sludge that has been shown to be present in 30% of pregnant women and to resolve a few months postpartum (92). The prevalence of gallstones during pregnancy ranges between 6.9–8.4% in nulliparous women and 18.4–19.3% in multiparous women (93). The prevalence of symptomatic gallstones varies significantly in different studies, from "no relation between pain and stones" (94) to 29% (92).

Venous Thromboembolism

The incidence of deep vein thrombosis (DVT) in pregnant women is five times higher than in age-matched nonpregnant women (95). Pregnancy induces major changes in the blood coagulation and fibrinolytic systems, with increased concentration of coagulation factors (factors I, VII, VIII, and X), decreased levels of coagulation inhibitors (protein S), and reduced fibrinolytic capacity (96). In addition, an occult thrombophilia, such as the factor V Leiden mutation or the antiphospholipid syndrome, may become unmasked during pregnancy and confers an additive risk of thromboembolism. The experience with portal vein thrombosis and hepatic vein thrombosis (Budd-Chiari syndrome), both uncommon conditions complicating pregnancy is currently too brief to form a definitive conclusion.

In contrast to slow blood flow in the pelvis and lower extremities venous systems secondary to pressure by the gravid uterus (96), which contributes to the formation of lower extremities DVT, the flow in the portal vein is increased due to increased blood return (97). To date, 94% of Budd-Chiari syndrome cases are attributed to thrombophilia, even in the presence of conditions previously considered as risk factors for the Budd-Chiari syndrome (such as contraceptive pills and pregnancy) (98).

Cirrhosis and Portal Hypertension

A woman with decompensated cirrhosis has a low chance of becoming pregnant, mostly because of hypothalamic pituitary dysfunction. Becoming pregnant, her chances to rear her child to adulthood without liver transplantation are 10% (99). Cirrhosis is not a contraindication for pregnancy since the pregnancy does not have a deleterious effect on well-compensated cirrhosis with mild portal hypertension (100). Pregnancy should be planned to a period of time when the liver disease is well compensated. All medications should be reviewed for potential teratogenicity. Early termination of the pregnancy should be considered when hepatic decompensation is present. If an infectious disease is the cause, than proper prophylactic measures should be taken, as detailed previously. Maternal complications arise in nearly half of cirrhosis-affected pregnancies with significant portal hypertension (101). These complications include variceal hemorrhage, hepatic failure, encephalopathy, splenic artery aneurysm, and rupture and malnutrition.

Gastrointestinal hemorrhage are reported to occur in up to 24% of pregnancies in cirrhotic patients with significant portal hypertension and in patients with known varices, up to 78% of cases are reported to have bled prior to the introduction of prophylactic β-blockers or banding (102). The bleeding occurs mostly in the second or third trimester and is related to the time of maximal blood volume expansion and increased compression on the inferior vena cava by the gravid uterus. Maternal mortality when acute variceal bleeding occurs is high, ranging from 20% to 50% (99). Thus, all pregnant patients with cirrhosis should be screened for varices during the second trimester and treated with selective β-blockers, when required. It is recommended to keep a short second stage of the labor, to avoid too much valsalva maneuver, which may also promote variceal hemorrhage. The treatment of variceal bleeding in pregnancy is similar to the treatment in nonpregnant patients and consists of endoscopic and pharmacologic treatment. Of note, there is still little experience in pregnancy with the use of octreotide. Vasopressin causes placental ischemia, necrosis, and amputation of digits in the fetus. Twenty-four percent of pregnant cirrhotic patients will experience hepatic decompensation that can lead to rapid deterioration (99). Successful liver transplantation has been described in pregnant women with good results to both woman and fetus (103). Cirrhotic pregnant patients have a 2.6% chance of rupturing a splenic artery aneurysm. There is a female predominance in rupturing a splenic artery aneurysm in all cirrhotic patients. Twenty percent of the ruptures occur during pregnancy. When associated with pregnancy, 70% of ruptures occur in the third trimester. Maternal and fetal mortality is very high, 70% and 80%, respectively (104). Ascites rarely occurs during pregnancy but may suggest Budd-Chiari syndrome.

Aside from the potential complications of variceal hemorrhage, pregnancy does not have a deleterious effect on the cirrhotic liver with mild portal hypertension. The high estrogen state may induce pruritus particularly in those with background cholestatic liver disease, and repeated plasmaphoresis may be required to control this symptom. Similarly, any drug reaction occurring during pregnancy is more likely to be cholestatic.

Liver Adenoma

Hepatic adenomas are uncommon benign neoplasms that usually occur in young women taking oral contraceptives. Other risk factors are glycogen storage disease, steroid hormone use, diabetes, and pregnancy (105). The etiology of hepatic adenomas is, to date, unknown. It is hypothesized that a change in endogenous or exogenous sex steroid levels predisposes for its development. During pregnancy the high levels of sex steroids increase the liver vascularity, thus predisposing the liver for rupture. Rupture of hepatic adenoma during pregnancy causing intraperitoneal hemorrhage bares very high maternal and fetal mortality rates, 59% and 62%, respectively (106). Small adenomas ($<$5cm) should be closely followed. Once large ($\geq$5cm) or symptomatic, they should be resected (107). Surgical procedure during the second trimester is associated with minimal operative risks for the mother and fetus (108).

Liver Transplantation

Nearly 90% of patients resume normal menstruation within 7 months of transplantation (109). Conception should be postponed for at least 6 months posttransplant. This period coincides with the period of maximal immunosuppression. Infections with herpesviruses, especially cytomegalovirus (CMV), are very common at this period and can cause very high maternal and fetal morbidity and mortality. Many of the important considerations about pregnancy after liver transplantation are directly related to the use of immunosuppressant medications during pregnancy.

Corticosteroids are considered safe during pregnancy although they have been associated with fetal growth restriction, suppression of fetal adrenal axis, and premature rupture of membranes (110). As mentioned above, there is a small risk of cleft palate in babies to mothers using steroids in the first trimester (83). Although azathioprine (AZA) crosses the placenta, teratogenicity has not been reported (79). Neonatal bone marrow suppression correlates with maternal leukopenia, which should be avoided. AZA does not cross into breast milk, but breastfeeding experts should be consulted in these situations (111). Cyclosporine readily crosses the placenta and is secreted in high concentrations in breast milk, thus its use is not recommended during pregnancy and lactation. Cyclosporine is highly bound to erythrocytes. In pregnancy, the plasma volume expansion exceeds red cell volume expansion so whole plasma drug levels will be lower than in plasma. In addition, metabolism and clearance are unpredictable during pregnancy, thus prudent monitoring of drug level should be performed (112).

Tacrolimus (FK506) crosses the placenta and is found in significant concentration in the fetal blood and in breast milk. Teratogenicity has not been reported in a study of 27 pregnancies (113). Regarding mycophenolate mofetil (MMF), data remain limited and are insufficient to determine a specific malformation incidence (114). Pregnant women after liver transplantation are at higher risk for hypertension, preeclampsia, premature rupture of membranes, infection, and first trimester abortions. Pregnancy does not seem to alter the function of the grafted liver. A mild-to-moderate elevation in liver enzymes is noted periconception, but does not require aggressive evaluation. Neonatal and perinatal outcomes are favorable (115).

Reprint requests and correspondence: Fabiana S. Benjaminov, M.D., Department of Gastroenterology, "Meir" Medical Center Kfar-Saba, 44425, Israel; e-mail: fabianabe@clalit.org.il

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