Indian National Association for the Study of the Liver—Federation of Obstetric and Gynaecological Societies of India Position Statement on Management of Liver Diseases in Pregnancy

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Liver diseases occurring during pregnancy can be serious and can progress rapidly, affecting outcomes for both the mother and fetus. They are a common cause of concern to an obstetrician and an important reason for referral to a hepatologist, gastroenterologist, or physician. Liver diseases during pregnancy can be divided into disorders unique to pregnancy, those coincidental with pregnancy, and preexisting liver diseases exacerbated by pregnancy. A rapid differential diagnosis between liver diseases related or unrelated to pregnancy is required so that specialist and urgent management of these conditions can be carried out. Specific Indian guidelines for

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Abbreviations: ABCB4: ATP-binding cassette subfamily B member 4; AFLP: Acute fatty liver of pregnancy; ALF: Acute liver failure; ALP: Alkaline phosphatase; ALT: Alanine transferase; AST: Aspartate aminotransferase; ART: Antiretroviral therapy; BCS: Budd-Chiari syndrome; CT: Computerized tomography; DIC: Disseminated intravascular coagulation; DNA: Deoxyribonucleic acid; DPTA: Diethylenetriamine pentaacetic acid; ERCP: Endoscopic retrograde cholangiopancreatography; FDA: Food and Drug Administration; FOGSI: Federation of Obstetric and Gynaecological Societies of India; GGT: Gamma-glutamyl transpeptidase; GI: Gastrointestinal; GRADE: Grading of Recommendations Assessment Development and Evaluation; HBeAg: Hepatitis B envelope antigen; HBIG: Hepatitis B immune globulin; HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HELLP: Hemolysis, elevated liver enzymes, low platelet count; HG: Hyperemesis gravidarum; HIV: Human immunodeficiency virus; HV: Hepatic vein; ICP: Intrahepatic cholestasis of pregnancy; INASL: Indian National Association for the Study of Liver; IVF: In vitro fertilization; LFT: Liver function test; MDR: Multidrug resistance; MRI: Magnetic resonance imaging; NA: Nucleos(t)ide analog; MTCT: Mother-to-child transmission; PegIFN: Pegylated interferon; PIH: Pregnancy-induced hypertension; PT: Prothrombin time; PUQE: Pregnancy-Unique Quantification of Emesis; RNA: Ribonucleic acid; TAF: Tenofovir alafenamide; TDF: Tenofovir disoproxil fumarate; TIPS: Transjugular intrahepatic portosystemic shunt; UDCA: Ursodeoxycholic acid; UGI: Upper gastrointestinal; ULN: Upper limit of normal

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the management of these patients are lacking. The Indian National Association for the Study of the Liver (INASL) in association with the Federation of Obstetric and Gynaecological Societies of India (FOGSI) had set up a taskforce for development of consensus guidelines for management of patients with liver diseases during pregnancy, relevant to India. For development of these guidelines, a two-day roundtable meeting was held on 26–27 May 2018 in New Delhi, to discuss, debate, and finalize the consensus statements. Only those statements that were unanimously approved by most members of the taskforce were accepted. The primary objective of this review is to present the consensus statements approved jointly by the INASL and FOGSI for diagnosing and managing pregnant women with liver diseases. This article provides an overview of liver diseases occurring in pregnancy, an update on the key mechanisms involved in its pathogenesis, and the recommended treatment options. (J Clin Exp Hepatol 2019;9:383–406)

Symptomatic or asymptomatic liver diseases during pregnancy are a common reason of concern to an obstetrician and form an important cause for referral to a hepatologist, gastroenterologist, or physician. Thus, it is of prime importance to be aware of liver diseases occurring in pregnancy because they can be serious and progress rapidly, affecting outcomes for both the mother and fetus. It is also important to be aware of pregnancy-associated normal physiological changes in liver function tests (LFTs) that cause unnecessary alarm among obstetricians managing these women. Liver diseases during pregnancy can be divided into disorders unique to pregnancy, those coincidental with pregnancy, and preexisting liver diseases exacerbated by pregnancy. A rapid differential diagnosis between liver diseases related or and unrelated to pregnancy is required in women who present with liver dysfunction during pregnancy. Specialist and urgent management of these conditions are required because two lives, maternal and fetal, are at stake.

Specific Indian guidelines for the management of these patients are lacking. The Indian National Association for the Study of the Liver (INASL) in association with the Federation of Obstetric and Gynecological Societies of India (FOGSI) had set up a taskforce with a mandate to develop consensus guidelines for management of various aspects of liver diseases in pregnancy, relevant to India. For development of these guidelines, the taskforce first identified contentious issues on the topic of liver diseases in pregnancy, and these were allotted to individual members of the taskforce who reviewed them in detail. A two-day roundtable discussion was held on 26–27 May 2018 at New Delhi, to discuss, debate, and finalize the consensus statements. Each topic was discussed considering the most relevant data available in literature, and the final consensus statements were formulated according to both scientific evidence and clinical expertise of the involved physicians. Only those statements that were unanimously approved by most members of the taskforce were accepted. Each statement of the guideline was graded according to the Grading of Recommendations Assessment Development and Evaluation (GRADE) system with minor modifications.[1] The strength of recommendations (strong or weak) thus reflects the quality (grade) of underlying evidence (I, II-1, II-2, II-3, and III) (Table 1).

The primary objective of this document is to present the consensus statements approved jointly by the INASL and FOGSI for diagnosing and managing pregnant women with liver diseases. This article provides an overview of liver diseases occurring in pregnancy, an update on the key mechanisms involved in its pathogenesis, and the recommended treatment options.

NORMAL AND ABNORMAL LFTS DURING PREGNANCY

The gastrointestinal tract and liver, similar to other organs, undergo various physiological and anatomical changes during pregnancy. An understanding of these changes can help one to differentiate the physiological changes from the pathological ones. Elevated levels of hormones, such as progesterone, contribute to delayed gastric emptying. Gastric acidity is increased because of the higher production of gastrin by the placenta.[2,3] Among the physical findings, spider angiomata and palmer erythema can be seen especially in the later half of the pregnancy.[4] Pregnancy is characterized by a hemodilution state induced by volume expansion due to retention of salt and water.[2] Hemodilution results in the decrease in hemoglobin and serum albumin that worsens as pregnancy progresses. Most of the liver biochemical tests remain within normal limits during pregnancy with a few exceptions. Serum alkaline phosphate (ALP) increases markedly (up to four times the normal) in the third trimester which results from the increased levels of placental isoenzyme of ALP. Conjugate increase in serum gamma-glutamyl transpeptidase (GGT) along with serum ALP usually indicates a pathological process as the level of serum GGT is usually normal or slightly reduced during normal pregnancy. Other liver biochemical tests such as serum alanine transferase (ALT), aspartate aminotransferase (AST), and prothrombin time (PT) typically remain within normal limits, and any increased value should be considered pathologic and warrant further evaluation. Moreover, total

Table 1 Modified Grading of Recommendations, Assessment, Development and Evaluation (GRADE).

Quality of evidence	Criteria
I	Randomized controlled trials
II-1	Controlled trials without randomization
II-2	Cohort or case-control analytical studies
II-3	Multiple time series, dramatic uncontrolled experiments
III	Opinions of respected authorities, descriptive epidemiology
Strength of recommendations	**Criteria**
Strong	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost
Weak	Variability in preferences and values or more uncertainty. Recommendation is made with less certainty and higher cost or resource consumption

bilirubin concentrations are decreased during all three trimesters of pregnancy. Total cholesterol, triglyceride, fibrinogen, and ceruloplasmin are few other laboratory findings that are noticeably augmented during pregnancy. Platelet levels may decrease but usually remain within the normal range. Clotting factor concentrations are affected by pregnancy, with a mild decrease in antithrombin III, protein C, and protein S and an increase in factors I to X, XII, and fibrinogen, which favors a procoagulant state.[2,5]

The most common cause of liver functional derangements in pregnancy is pregnancy-induced liver diseases. Disorders arising in pregnancy, such as preeclampsia and eclampsia, acute fatty liver of pregnancy (AFLP); hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome; cholestasis; hyperemesis gravidarum; and isolated cases of raised liver enzymes can have serious implications. Coincidental diseases, such as acute viral hepatitis, biliary obstruction, etc., may also occur during pregnancy.

Proper interpretation of LFTs at an early stage can lead to timely management and may reduce complications in both mother and fetus. Normal LFTs do not always mean that the liver is normal. A number of pitfalls can be encountered in the interpretation of basic blood LFTs. The commonly used LFTs primarily assess liver injury rather than hepatic function. Abnormal LFTs may indicate that something is wrong with the liver, and they can provide clues to the nature of the problem, but this is not always the case.[6]

Consensus statements on normal and abnormal liver function tests during pregnancy are provided in Table 2.

IMAGING IN PREGNANCY

Ultrasonography and magnetic resonance imaging (MRI) are not associated with risk and are the imaging techniques of choice for the pregnant patient, but they should be used prudently and only when use is expected to answer a relevant clinical question or otherwise provide medical benefit to the patient. Ultrasonography examination of the liver during normal pregnancy usually reveals a normal biliary tree. The only striking ultrasonographic findings are increased fasting gallbladder volume and residual volume after contraction.[4]

The use of diagnostic radiological procedures in pregnancy should be justified by a careful and thoughtful assessment of the benefit of prompt and early diagnosis that should substantially outweigh the small but finite risk of exposing the developing fetus to radiation, particularly when the fetus is in view. The most radiation to the developing fetus from a diagnostic examination results from a computerized tomography (CT) scan of the abdomen and pelvis. Whenever feasible, initial or exclusive use of modalities, such as sonography or MRI, that do not use ionizing radiation is warranted. However, a CT scan of the pregnant abdomen may be indicated in clinical situations where a prompt and accurate diagnosis is needed and where modalities that do not use ionizing radiation may be unhelpful or unavailable. In these instances, to provide clear and clinically pertinent information to the patient and clinician, it is imperative for the supervising radiologist to have a thorough and adequate understanding of the issues involved in exposing the fetus to ionizing radiation resulting from radiological procedures performed.[7] With few exceptions, radiation exposure through radiography, CT scan, or nuclear medicine imaging techniques is at a dose much lower than the exposure associated with fetal harm. If these techniques are necessary in addition to ultrasonography or MRI or are more readily available for the diagnosis in question, they should not be withheld from a pregnant patient.

MRI is considered safe during pregnancy because magnetic energy has been shown not to be harmful for the developing fetus.[8] However, most radiology service providers consider gadolinium-based contrast agents for MRI (e.g., gadopentetate, gadodiamide, gadolinium diethylenetriamine pentaacetic acid, gadoterate meglumine) to be relatively or absolutely contraindicated during pregnancy; these paramagnetic agents are not recommended by the FDA because they cross the placenta and their long-term effects are unknown.[9] Nevertheless, the European Society of Radiology has issued a guideline discussing gadolinium use during pregnancy.[10] They conclude that gadolinium is probably safe during pregnancy because excessive quantities are not expected to cross the placenta or to be toxic to the fetus if they do. These guidelines also state that given that gadolinium is mainly distributed

Table 2 Consensus Statements on Normal and Abnormal Liver Function Tests During Pregnancy.

- Serum ALT and AST activity levels do not change during pregnancy or remain within the normal limits established in nonpregnant women (level of evidence, II-3).
- Serum AST or ALT activity values above the upper normal limit before labor should be considered pathologic (level of evidence, II-3).
- The serum ALP level rises during the 3rd trimester of pregnancy because of placental isoenzyme (level of evidence, II-3).
- Total bilirubin concentrations are decreased during all three trimesters of pregnancy (level of evidence, II-3).
- Serum GGT activity usually remains normal during pregnancy (level of evidence, II-3).
- The most common cause of liver functional derangements in pregnancy is pregnancy-induced liver diseases (level of evidence, II-3; strength of recommendation, strong).
- Coincidental diseases may also occur during pregnancy (level of evidence, II-3; strength of recommendation, strong).

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase.

in extracellular water and rapidly eliminated by the kidney, in the unlikely event that some gadolinium reached the baby, it would be rapidly eliminated via urine.[10] The INASL and FOGSI advise that the use of gadolinium should be limited; it may be used as a contrast agent in a pregnant woman only if it significantly improves diagnostic performance and is expected to improve fetal or maternal outcomes. Breastfeeding should not be interrupted after gadolinium administration.

Consensus statements on imaging in pregnancy are provided in Table 3.

ENDOSCOPY IN PREGNANCY

Gastrointestinal (GI) endoscopy has a major diagnostic and therapeutic role in most GI disorders; however, limited information is available about clinical efficacy and safety in pregnant patients. Endoscopic procedures during pregnancy may include upper GI endoscopy, percutaneous endoscopic gastrostomy, sigmoidoscopy, colonoscopy, enteroscopy of the small bowel or video capsule endoscopy, endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasonography. The major risks of endoscopy during pregnancy include potential harm to the fetus because of hypoxia, premature labor, trauma, and teratogenesis.[11,12]

Upper gastrointestinal endoscopy seems to be relatively safe for the fetus and may be performed when strongly indicated during pregnancy. Despite limited clinical data, endoscopic banding of esophageal varices and endoscopic hemostasis of nonvariceal upper GI bleeding seem justifiable during pregnancy. Flexible sigmoidoscopy during pregnancy also appears to be relatively safe for the fetus and may be performed when strongly indicated. Colonoscopy may be considered in pregnant patients during the second trimester if there is a strong indication. Data on colonoscopy during the other trimesters are limited. Although therapeutic ERCP may be considered during pregnancy, this procedure should be performed only for strong indications, and attempts should be made to minimize radiation exposure.[11,12]

Unless emergency or urgent indications are present, endoscopic procedures may be postponed until after delivery. When these indications are present, endoscopic procedures may be considered with utmost precautions. All GI endoscopic procedures in pregnant patients should be performed in hospitals by expert endoscopists, and an obstetrician should be informed about all endoscopic procedures. Fetal risks from endoscopic medications are minimized by avoiding FDA category D drugs, minimizing endoscopic medications, and anesthesiologist attendance at endoscopy. FDA category B drugs may be used in low doses. A multidisciplinary team should assist with management, including determination of the degree of maternal and fetal monitoring. Endoscopic procedures involving mild to moderate sedation during pregnancy may require midazolam. If deeper sedation is required, propofol is the preferred agent provided by an anesthetist. When electrocautery is required, bipolar electrocautery can be used. If monopolar electrocautery must be used, the grounding pad should be placed to minimize flow of electrical current through the amniotic fluid. In late pregnancy, women

Table 3 Consensus Statements on Imaging in Pregnancy.

- Ultrasonography and magnetic resonance imaging (MRI) are not associated with risk and are the imaging techniques of choice for the pregnant patient, but they should be used prudently and only when use is expected to answer a relevant clinical question or otherwise provide medical benefit to the patient (level of evidence, II-2; strength of recommendation, strong).
- With few exceptions, radiation exposure through radiography, computed tomography (CT) scan, or nuclear medicine imaging techniques is at a dose much lower than the exposure associated with fetal harm (level of evidence, II-2; strength of recommendation, strong)
- If these techniques are necessary in addition to ultrasonography or MRI or are more readily available for the diagnosis in question, they should not be withheld from a pregnant patient (level of evidence, II-3; strength of recommendation, strong).
- The use of gadolinium contrast with MRI should be limited; it may be used as a contrast agent in a pregnant woman only if it significantly improves diagnostic performance and is expected to improve fetal or maternal outcomes (level of evidence, II-3; strength of recommendation, strong).
- Breastfeeding should not be interrupted after gadolinium administration (level of evidence, II-3; strength of recommendation, strong).

should be in the lateral decubitus position before, during, and after the procedure.

Consensus statements on endoscopy in pregnancy are provided in Table 4.

Table 4 Consensus Statements on Endoscopy in Pregnancy.

• Endoscopy is safe in pregnancy; however, it should be performed only when there is a strong indication and should be postponed to the second trimester whenever possible (level of evidence, II-2; strength of recommendation, strong).
• Multidisciplinary team to assist with management, including determination of the degree of maternal and fetal monitoring (level of evidence, II-3; strength of recommendation, strong).
• Endoscopic procedures involving mild to moderate sedation during pregnancy may require midazolam (level of evidence, III; strength of recommendation, weak).
• If deeper sedation is required, propofol is the preferred agent provided by an anesthetist (level of evidence, III; strength of recommendation, strong).
• Therapeutic ERCP is generally safe in pregnancy. We recommend that care be taken to minimize radiation exposure to the fetus and risks to the mother (level of evidence, II-2; strength of recommendation, strong).
• When electrocautery is required, bipolar electrocautery can be used. If monopolar electrocautery must be used, the grounding pad should be placed to minimize flow of electrical current through the amniotic fluid (level of evidence, II-3; strength of recommendation, weak).
• In late pregnancy, women should be in the lateral decubitus position before, during, and after the procedure (level of evidence, II-3; strength of recommendation, strong).

ERCP, endoscopic retrograde cholangiopancreatography.

SAFETY OF PRESCRIPTION DRUGS IN PREGNANCY

The differentiation of fetal organs takes place during the early weeks of pregnancy, whereby it is imperative that the mother's medication be revised already when planning a pregnancy.[13]

In many cases, the decisions on medications during pregnancy have to be made without evidence-based information about the effectiveness and safety of the treatment. Although few drugs are known with certainty to be harmful for fetal development, the evidence for evaluating harm to the fetus is insufficient for most drugs. A drug should primarily be chosen, for which experience has accumulated about its use during pregnancy and is not suspected or known to be associated with adverse effects.[13]

In 2015, the FDA replaced the former pregnancy risk letter categories (Table 5) on prescription and biological drug labeling with new information to make them more meaningful to both patients and healthcare providers.[14] The new drug information has descriptive subsections for pregnancy exposure and risk, lactation, and effects to reproductive potential for women and men. Labeling changes from this rule began on June 30, 2015, with all submissions for prescription drugs and biological agents using the labeling changes immediately. The new labeling system allows better patient-specific counseling and informed decision-making for pregnant women seeking medication therapies. While the new labeling improves the old format, it still does not provide a definitive "yes" or "no" answer in most cases. Clinical interpretation is still required on a case-by-case basis. The rule does not affect the labeling of over-the-counter drugs.

COMMON BILIARY AND PANCREATIC DISEASES IN PREGNANCY

Pregnancy can cause an increase in cholesterol level and decrease in bile acids and phosphatidylcholine level. In addition, there is decrease in motility of gallbladder mediated by progesterone. Gallbladder contains progesterone receptors, which are susceptible to circulating hormonal conditions and which have a regulatory effect on gallbladder contractility.[15] All these factors act together to reduce the solubility of cholesterol, thus leading to formation of cholesterol microcrystals that may act as a nidus for stone formation. The risk gallstone formation remains elevated for five years after pregnancy and then returns to baseline.[16–19] In a study from South India that screened 500 pregnant women, it was found that one percent of pregnant women have asymptomatic gallstones and most of them, if not all, continue to be asymptomatic during the first year postpartum.[20] Decrease in gallbladder ejection fraction is the most significant risk factor for newly developed gallstone and sludge in pregnant women, whereas multiple childbirth is the other but less important risk factor.[21] In a patient with symptomatic gallstones or gallstone pancreatitis, laparoscopic cholecystectomy should preferably be performed in the 2nd trimester. There is no role of any intervention in asymptomatic gallstones in pregnancy. During postpartum period, patients should be observed for 3 months for spontaneous dissolution of gallstones.

The incidence of acute cholecystitis in pregnancy is reported in approximately 0.2–0.5 per 1000 pregnancies.[22] Depending on gestational age and symptoms, different methods of management have been reported, ranging from supportive care, antibiotics, percutaneous transhepatic gallbladder drainage, ERCP, laparoscopic cholecystectomy, and open cholecystectomy. Previously, it was recommended that surgical intervention of a patient in the first trimester be deferred until the second trimester and that of a patient in the third trimester be delayed until after parturition. During the second trimester, fetal organogenesis is complete, the size of the gravid uterus allows relatively good operative field visualization,

Table 5 FDA Pregnancy Categories.

Pregnancy category	Description
A	*No risk in controlled human studies:* Adequate and well-controlled human studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	*No risk in other studies:* Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women OR Animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus in any trimester.
C	*Risk not ruled out:* Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D	*Positive evidence of risk:* There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	*Contraindicated in pregnancy:* Studies in animals or humans have demonstrated fetal abnormalities, and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.
N	The FDA has not yet classified the drug into a specified pregnancy category.

FDA, Food and Drug Administration.

and possible injury to the gravid uterus is diminished compared with that during the third trimester. However, recent trends indicate that with newer instrumentation and skilled personnel, laparoscopic cholecystectomy should be performed at the time of diagnosis in any trimester.[23]

Consensus statements on common biliary and pancreatic diseases in pregnancy are provided in Table 6.

HEPATITIS B VIRUS INFECTION IN PREGNANCY

The prevalence of chronic hepatitis B in general population India is between 1.4% and 2.7%.[24] Although the predominant mode of hepatitis B virus (HBV) transmission in India is horizontal, vertical transmission from their mothers (mother-to-child transmission [MTCT]) is also common.[24] Most vertically acquired infection results into chronic infection, due to induction of an immune-tolerant state. Hence, management of chronic HBV infection during pregnancy and strategies to prevent MTCT would go a long way in global control of HBV infection and the morbidity and mortality associated with it.[25]

All HBV-positive women of childbearing age should be counseled about implications of pregnancy, the risk of MTCT of HBV, and safety of HBV drugs during pregnancy and lactation. A woman of childbearing age with chronic hepatitis B, who plans pregnancy in the near future, should be treated with antiviral agents that belong to pregnancy category B drugs, preferably tenofovir disoproxil fumarate (TDF), although pegylated interferon (PegIFN)-α has an advantage in female patients who are planning pregnancy due to its finite treatment duration. However, the side effects pertaining to fetal malformations make PegIFN-α treatment contraindicated during pregnancy, and it should be recommended only in combination with contraception.[24]

The prevalence of hepatitis B surface antigen (HBsAg) positivity among asymptomatic pregnant women in North India is 1.1%, with 71% having high HBV DNA levels.[26] These women may have a high risk of transmitting infection to their newborns. Hence, screening for HBsAg in the first trimester of pregnancy is strongly recommended.[24]

In women who are already on nucleos(t)ide analog (NA) therapy for HBV infection or HIV started before pregnancy, TDF appeared to be safe during pregnancy.[27] Hence, in pregnant women already on NA therapy, TDF should be continued, whereas entecavir (ETV) or other NA should be switched to TDF.[24]

If no immunoprophylaxis is given after delivery, depending on the maternal status for hepatitis B envelope antigen (HBeAg), about 30–42% of the infants born to HBV-infected mothers may become infected in utero, during delivery, or in infancy because of close contact with mother.[28] Universal immunization against HBV, starting at birth with the administration of at least three doses of vaccine by 6 months of age, has reduced the prevalence of HBV infection.[29] The additional administration of hepatitis B immune globulin (HBIG) at birth to infants born to HBV-infected mothers further reduces the risk of MTCT.[30,31] Hence, the INASL recommends that newborns of HBV-infected mothers who are HBeAg positive (or unknown HBeAg status) should receive HBIG and hepatitis B vaccine at delivery and complete the recommended vaccination series. In full-term neonates born to mothers who are HBsAg positive and HBeAg negative, protection against perinatally acquired HBV infection may not be significantly improved by the addition of HBIG to

Table 6 Consensus Statements on Common Biliary and Pancreatic Diseases in Pregnancy.

- There is no role of any intervention in asymptomatic gallstones in pregnancy (level of evidence, II-2; strength of recommendation, strong).
- In a patient with symptomatic gallstones or gallstone pancreatitis, laparoscopic cholecystectomy should preferably be performed in the 2nd trimester (level of evidence, II-2; strength of recommendation, strong).
- Laparoscopic cholecystectomy is recommended in acute cholecystitis in any trimester (level of evidence, II-2; strength of recommendation, strong).
- During the postpartum period, patients should be observed for 3 months for spontaneous dissolution of gallstones (level of evidence, II-3; strength of recommendation, weak).

hepatitis B vaccine, and hence, its use in these neonates has questionable benefit.[32] However, MTCT can still occur in neonates born to women with HBeAg positivity or with a high HBV viral load (>10^5 IU/ml).[33,34] Hence, women with these risk factors may require additional measures to block this MTCT. According to a recent trial, in a setting in which the rate of mother-to-child HBV transmission was low with the administration of HBIG and hepatitis B vaccine in infants born to HBeAg-positive mothers, the additional maternal use of TDF did not result in a significantly lower rate of transmission.[34] However, in this trial, the percentage of HBV-infected infants in the placebo group (2%) was lower than was originally assumed (12%), hence the negative results of the trial. In a previous meta-analysis, it was shown that for pregnant women with high HBV DNA levels, TDF administration in the second or third trimester prevented MTCT when combined with HBIG and the HBV vaccine.[35] Hence, it is recommended that in all pregnant women with high HBV DNA levels (>200,000 IU/ml), antiviral prophylaxis with TDF should start at week 24–28 of gestation and continue for up to 12 weeks after delivery.

Under the recommended prophylaxis, breastfeeding is not a risk factor for MTCT of HBV.[36] Therefore, clinicians should encourage HBV-infected mothers to breastfeed their infants. Breastfeeding, even by mothers with high infectivity, is not associated with demonstrable risk of infantile chronic hepatitis B (CHB) infection, provided that the infants have been vaccinated against HBV at birth.[37] In mothers on TDF during lactation, TDF was detectable at low concentrations in breast milk, but was not measurable in any of the breastfeeding infants sampled.[38] Hence, TDF appears to be safe during lactation. Thus, the INASL-FOGSI recommends that breastfeeding be not contraindicated in HBsAg-positive untreated women or on TDF-based treatment or prophylaxis.

Consensus statements on HBV infection in pregnancy are provided in Table 7.

HEPATITIS C VIRUS INFECTION IN PREGNANCY

The estimated prevalence of hepatitis C virus (HCV) in India is between 0.5 and 1.5%, with higher prevalence in the northeast, in tribal populations, and in Punjab and a lower prevalence in western India and Eastern India.[39] HCV can be transmitted to the fetus of an infected mother by intrauterine, intrapartum, or postnatal routes. Risk factors for higher MTCT of HCV include high HCV RNA viral load; HIV coinfection; premature rupture of membranes; and fetal exposure to maternal infected blood by interventions such as amniocentesis, episiotomy, and invasive fetal monitoring.[40] No specific interventions during pregnancy are currently recommended to decrease the risk of vertical transmission, except for suppression of HIV replication in HIV/HCV coinfection.

For women of childbearing age with HCV infection, antiviral therapy should be given before planning pregnancy to reduce the risk of transmission of HCV to the child. The FDA classified ribavirin in pregnancy category X because of its embryocidal and teratogenic effects. Therefore, ribavirin is absolutely contraindicated for both HCV-infected childbearing women and HCV-infected male partners of pregnant women unless they take effective contraceptive measures. In addition, because ribavirin-induced spermatogenic abnormalities (cell toxicity, mutagenicity, and a decreased epididymal sperm count) revert only many months after treatment withdrawal, women are advised to avoid pregnancy for at least 6 months after their male partners stop taking ribavirin treatment. Thus, the INASL-FOGSI recommends that if HCV therapy of the woman or the male partner includes ribavirin, pregnancy should be avoided for 6 months after ribavirin cessation.[41,42]

Any woman with a diagnosis of HCV infection during pregnancy should be referred to a hepatologist so that long-term care can be established. Monitoring of HCV-infected women during pregnancy should include LFT, International normalized ratio (INR), platelet counts, ultrasonography of liver, and HCV-RNA. In most cases, the initiation of treatment for chronic hepatitis C should be delayed until after pregnancy. Hepatitis C should not be treated in pregnancy outside of a research protocol because of unknown risk without demonstrated benefit.[41] Given the lack of human studies, no direct-acting antivirals (DAAs) have yet been approved for use in pregnancy or during breastfeeding.[42] Therefore, DAA therapy is not recommended during pregnancy. After delivery, mother should be evaluated with HCV-RNA at 9–12 months to assess for spontaneous clearance before starting therapy.

Breastfeeding is not associated with increased risk of transmission unless done in the presence of cracked or bleeding nipples; hence, breastfeeding is not contraindicated.[40]

Table 7 Consensus Statements on HBV Infection in Pregnancy.

• All HBV-positive women of childbearing age should be counseled about implications of pregnancy, the risk of mother-to-child transmission of HBV, and safety of HBV drugs during pregnancy and lactation (level of evidence, I; strength of recommendation, strong).
• A woman of childbearing age with hepatitis B infection, who plans pregnancy in the near future, should be treated with antiviral agents that belong to pregnancy category B drugs (preferably TDF) (level of evidence, I; strength of recommendation, strong).
• Screening for HBsAg in the first trimester of pregnancy is strongly recommended (level of evidence, I; strength of recommendation, strong).
• In pregnant women already on NA therapy, TDF should be continued and ETV or other NA should be switched to TDF (level of evidence, I; strength of recommendation, strong).
• In all pregnant women with high HBV DNA levels (>200,000 IU/ml), antiviral prophylaxis with TDF should start at week 24–28 of gestation and continue for up to 12 weeks after delivery (level of evidence, I; strength of recommendation, strong).
• Newborns of HBV-infected mothers who are HBeAg positive (or unknown HBeAg status) should receive HBIG plus hepatitis B vaccine at delivery and complete the recommended vaccination series (level of evidence, I; strength of recommendation, strong).
• Role of HBIG in neonates born of HBeAg-negative women is unclear. Hence, these neonates should receive only hepatitis B vaccine at delivery and complete the recommended vaccination series (level of evidence, I; strength of recommendation, strong).
• Breastfeeding is not contraindicated in HBsAg-positive untreated women or those on TDF-based treatment or prophylaxis (level of evidence, I; strength of recommendation, strong).

HBV, hepatitis B virus; TDF, tenofovir disoproxil fumarate; HBsAg, hepatitis B surface antigen; NA, nucleos(t)ide analog; HBIG, hepatitis B immune globulin; HBeAg, hepatitis B envelope antigen; ETV, Entecavir.

Children who have acquired hepatitis C via vertical transmission can clear the infection, have persistent asymptomatic mild liver disease, or develop end-stage liver disease. The rate of spontaneous clearance of the infection is reportedly between 11% and 25%.[40,43] The child should be evaluated with anti-HCV at or after 18 months of age, and if anti-HCV positive, HCV-RNA should be tested after three years of age.

Consensus statements on HCV in pregnancy are provided in Table 8.

HBV-HIV AND HCV-HIV COINFECTION IN PREGNANCY

HBV or HCV infections occur frequently in HIV-infected persons because the three viruses share common routes of transmission. For both hepatitis viruses, coinfection with HIV is associated with accelerated liver disease progression. Estimates of HCV and HBV prevalence in HIV-infected pregnant women are scarce. In a French cohort of 4236 HIV-infected pregnant women, the prevalence of HBV (by HBsAg) and HCV (by HCV-RNA) were 6.2% and 1.7%, respectively.[44] Given this high prevalence, it is recommended that all pregnant women living with HIV should be screened during the current pregnancy for HBV and HCV infection. All pregnant women living with HIV who screen negative for HBV (i.e., HBV surface antigen negative and HBV surface antibody negative) should receive the HBV vaccine series.

Most studies on HBV or HCV coinfection in HIV-infected pregnant women have focused primarily on MTCT because several studies have reported an increase rate of HBV/HCV transmission, mostly due to higher hepatitis viral load.[44–46] The potential impact of maternal HBV/HCV chronic infection on the risk of adverse pregnancy outcomes and maternal health during pregnancy is also an important issue.

All pregnant and postpartum women with HIV/HBV coinfection should receive antiretroviral therapy (ART). Antepartum ART in pregnant women with HIV/HBV coinfection should include TDF plus lamivudine or emtricitabine. If women with HIV/HBV infection are virally suppressed on a tenofovir alafenamide (TAF) plus lamivudine- or emtricitabine-based ART and become pregnant, they can be offered the choice of continuing that ART regimen or switching TAF to TDF in their ART regimen. Women with chronic HBV infection should be counseled on the importance of continuing anti-HBV medications indefinitely, both during and after pregnancy. If ART drugs that include anti-HBV activity are discontinued in women with HIV/HBV coinfection, frequent monitoring of LFTs for potential exacerbation of HBV infection is recommended with a prompt reinitiation of treatment for HBV flare if detected. Pregnant women with HIV/HBV coinfection receiving ART drugs should also be counseled about signs and symptoms of liver toxicity. Liver transaminases should be assessed 1 month after initiation of ART drugs and at least every 3 months thereafter during pregnancy.

Decisions concerning mode of delivery in pregnant women with HIV/HBV coinfection should be based on standard obstetric and HIV-related indications alone. HIV/HBV coinfection does not necessitate cesarean delivery, if not otherwise indicated. Within 12 h of birth, infants born to women with HBV infection should receive HBIG and the first dose of the HBV vaccine series.

All pregnant and postpartum women with HIV/HCV coinfection should receive ART. No specific anti-HCV interventions during pregnancy are currently recommended except for suppression of HIV replication in HIV/HCV coinfection. The management of HCV in pregnant women with HCV-HIV coinfection is the same as management of HCV in pregnant women without HIV coinfection.

Table 8 Consensus Statements on HCV in Pregnancy.

• For women of childbearing age with HCV infection, antiviral therapy should be given before pregnancy to reduce risk of transmission to child. In case HCV therapy of the woman or the male partner includes ribavirin, pregnancy should be avoided for at least 6 months after ribavirin cessation (level of evidence, II-2; strength of recommendation, strong).
• Monitoring of HCV-infected women during pregnancy should include LFT, INR, platelet count, ultrasonography of liver, and HCV-RNA (level of evidence, III; strength of recommendation, weak).
• DAA therapy is not recommended during pregnancy due to lack of safety and efficacy data (level of evidence, I; strength of recommendation, strong).
• Breastfeeding by HCV-infected mothers is not contraindicated (level of evidence, II-3; strength of recommendation, strong).
• After delivery, mother should be evaluated with HCV-RNA at 9–12 months to assess for spontaneous clearance before starting therapy (level of evidence, II-3; strength of recommendation, strong).
• The child should be evaluated with anti-HCV at or after 18 months of age, and if anti-HCV positive, HCV-RNA should be tested after three years of age (level of evidence, II-3; strength of recommendation, weak).

HCV, hepatitis C virus; LFT, liver function test; DAA, direct-acting antiviral; INR, International normalized ratio.

Consensus statements on HBV-HIV and HCV-HIV coinfection in pregnancy are provided in Table 9.

MANAGEMENT OF ACUTE LIVER FAILURE DURING PREGNANCY

Acute liver failure (ALF) in pregnancy is rare, but it negatively affects both maternal and fetal outcomes and has the potential for fetal loss and maternal morbidity and mortality. Because early diagnosis of ALF is of vital importance, a high index of suspicion should be kept for pregnant women presenting with altered mental status, deranged LFTs, and coagulopathy. Once ALF or impending ALF is diagnosed, determining the etiology of ALF becomes a major challenge because multiple conditions can result in similar changes in laboratory parameters during pregnancy. The clinician must evaluate for pregnancy-related as well as non–pregnancy-related causes for ALF in pregnancy (Table 10). For those women with pregnancy-related liver failure, delivery may allow for quicker recovery and improved survival of both mother and infant.[47,48] For the liver failure due to non–pregnancy-related causes, the management remains the same as management of ALF in nonpregnant state. The diagnostic or therapeutic interventions must ensure the safety of both mother and fetus.[47]

The overall outcome of ALF in pregnancy depends not only on severity and etiology of ALF but also on timely diagnosis, immediate management, and early referral to a center equipped in managing medical or obstetric complication. The fetal outcome is affected by the stage of pregnancy in which the mother developed the ALF, with a worst prognosis associated with the first- or second-trimester ALF[47,48,48a].

Optimal management of ALF in pregnancy begins with early recognition and accurate diagnosis of the underlying etiology. There are few evidence-based recommendations for managing the pregnant women with ALF. Therefore, management of ALF should broadly be guided by the same principles followed for the management of nonpregnant patients with ALF. The maternal outcome should take precedent over fetal well-being; and no therapy that is considered lifesaving should be withheld from a patient with ALF simply for reason of pregnancy status because the risks of untreated or fulminant ALF are generally higher than the fetal risk from therapy. Intensive care management of a patient with ALF should be focused on the diagnosis and etiology-specific treatment. Management protocol should be individualized for each case, keeping in mind the risk versus benefit to both mother and fetus. Management of ALF in pregnancy requires a combined and coordinated effort by the obstetrician, intensivist,

Table 9 Consensus Statements on HBV-HIV and HCV-HIV Coinfection in Pregnancy.

• All pregnant women living with HIV should be screened during the current pregnancy for hepatitis B virus (HBV) and hepatitis C virus (HCV) infection (level of evidence, II-1; strength of recommendation, strong).
• All pregnant women living with HIV who screen negative for HBV (i.e., HBV surface antigen–negative and HBV surface antibody–negative) should receive the HBV vaccine series (level of evidence, II-3; strength of recommendation, strong).
• Pregnant women with HIV/HBV coinfection receiving antiretroviral (ARV) drugs should be counseled about signs and symptoms of liver toxicity (level of evidence, II-3; strength of recommendation, strong).
• Liver transaminases should be assessed 1 month after initiation of ARV drugs and at least every 3 months thereafter during pregnancy (level of evidence, II-3; strength of recommendation, weak).
• Decisions concerning mode of delivery in pregnant women with HIV/HBV coinfection should be based on standard obstetric and HIV-related indications alone. HIV/HBV coinfection does not necessitate cesarean delivery, if not otherwise indicated (level of evidence, II-3; strength of recommendation, strong).
• Within 12 h of birth, infants born to women with HBV infection should receive hepatitis B immune globulin and the first dose of the HBV vaccine series (level of evidence, I; strength of recommendation, strong).
• The management HCV in pregnant women with HCV-HIV coinfection is the same as management of HCV in pregnant women without HIV coinfection (level of evidence, III; strength of recommendation, weak)

Table 10 Causes of ALF in Pregnancy.[48]

Category	Causes
Pregnancy-associated acute liver disease	• Preeclampsia/eclampsia with liver infarction • Syndrome of hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome) • Acute hepatic rupture • Acute fatty liver of pregnancy (AFLP).
Unrelated to pregnant state	• Viral hepatitis • Drug-induced liver disease • Toxins/mushroom poisoning • Budd-Chiari syndrome (BCS) • Shock

ALF, acute liver failure.

hepatologist, neonatologist, and, if necessary, the liver transplant surgeon.[47]

In circumstances when ALF is not likely to recover, liver transplantation is the only viable option.[48] It is difficult to predict which patients will require liver transplantation among those with ALF. Similar to other diseases of pregnancy, resolution after delivery is common. Therefore, delivery and supportive care may improve liver function and allow avoidance of transplant. For the patient with ALF not recovering, a liver transplant may be essential. The evaluation and determination of the need for liver transplantation is generally made according to criteria similar to those for the nonpregnant patient. Delivery before transplant is likely to be recommended regardless of gestational age because fetal loss during liver transplantation is high.[47,48]

Consensus statements on management of ALF during pregnancy are provided on Table 11.

SYSTEMIC DISEASES AFFECTING THE LIVER AND PREGNANCY

The liver might be affected in many systemic diseases such as diabetes mellitus, systemic lupus erythematosus, hypercoagulable disorders, amyloidosis, etc. However, there is insufficient information on hepatic affliction in these systemic diseases during pregnancy, and hence, no robust recommendations can be made in this regard. In the event of hepatic imaging or functional alterations in a pregnant patient with a systemic disease, management should involve a multidisciplinary approach involving the obstetrician, rheumatologist, and hepatologist.

Consensus statements on systemic diseases affecting the liver and pregnancy are provided in Table 12.

PREGNANCY WITH CIRRHOSIS

In general, in women with cirrhosis, infertility is expected because of altered endocrine metabolism, anovulatory cycles, and hepatocellular damage. However, pregnancy can still occur in cirrhotics. The estimated prevalence of cirrhosis is 1 in 5950 pregnancies.[49] The normal physiological changes that occur in pregnancy, such as progressive increase in circulating blood volume and elevation of portal pressure, may prove too challenging for the compromised cirrhotic liver. Maternal morbidity and mortality is high during pregnancy in patients with cirrhosis, and the prognosis depends on the degree of hepatic dysfunction and portal hypertension. Hepatic decompensation occurs in 15%, including ascites in 11% and variceal hemorrhage in 5%. In women with decompensation, maternal and fetal mortality are 6 and 12%, respectively.[50] Maternal deaths are due primarily to GI bleeding from varices. The rates of spontaneous abortion, premature birth, and perinatal death are all increased in women with cirrhosis. Infants born alive, however, generally are normal and do well.[49,51,52]

In women with cirrhosis, an assessment of the presence of portal hypertension is mandatory, and the diagnosis of portal hypertension can be made by the presence of indirect evidence, such as the presence of esophageal varices, abdominal collateral veins, hypersplenism, or ascites. In cases of decompensated cirrhosis with pregnancy, the decision to terminate pregnancy must be individualized depending on the severity of liver disease and stage of pregnancy. Assisted vaginal delivery may be preferred to shorten the second stage of labor.

Consensus statements on pregnancy with cirrhosis are provided in Table 13.

MANAGEMENT OF PORTAL HYPERTENSIVE BLEED IN PREGNANCY

Portal hypertension may occur in the setting of cirrhosis, or it may occur in various noncirrhotic vascular liver

Table 11 Consensus Statements on Management of Acute Liver Failure During Pregnancy.

• ALF in pregnancy is a medical emergency because it negatively affects both maternal and fetal outcomes with a potential for fetal loss and maternal morbidity and mortality (level of evidence, II-3; strength of recommendation, strong).
• Every effort should be made to determine the etiology of ALF because the management of ALF is etiology specific. For pregnancy-related ALF, delivery may allow for quicker recovery and improved survival of both the mother and infant. For the liver failure due to non–pregnancy-related causes, the management remains the same as the management of ALF in nonpregnant state (level of evidence, II-3; strength of recommendation, strong).
• No therapy that is considered lifesaving should be withheld from a patient with ALF simply for reason of pregnancy status because the risks of untreated or fulminant ALF are generally higher than the fetal risk from therapy (level of evidence, II-3; strength of recommendation, strong).
• For pregnant women with ALF, not recovering by conservative treatment, a liver transplant may be essential (level of evidence, II-3; strength of recommendation, strong).

ALF, acute liver failure.

Table 12 Consensus Statements on Systemic Diseases Affecting Liver and Pregnancy.

• In the event of hepatic imaging or functional alterations in a pregnant patient with a systemic disease, the management should involve a multidisciplinary approach involving the obstetrician, rheumatologist, and hepatologist (level of evidence, III; strength of recommendation, strong).

diseases such as noncirrhotic portal fibrosis, extrahepatic portal vein obstruction, or Budd-Chiari syndrome (BCS), when it is termed as noncirrhotic portal hypertension. Pregnancy is rare with cirrhosis but is common in the setting of noncirrhotic portal hypertension because liver function is preserved.[53] With advancement in the medical field, pregnancy is not contraindicated in these women, as was previously believed. However, pregnancy in these women presents a special challenge to the obstetrician because the physiological hemodynamic changes associated with pregnancy worsen the portal hypertension, thereby putting mother at risk of potentially life-threatening complications such as acute variceal hemorrhage. Risks of variceal bleed and hepatic decompensation increase manifold during pregnancy. In pregnancies with portal hypertension, 30%–50% of pregnancies suffer from portal hypertension–associated complications, resulting mainly because of variceal bleed and hepatic failure.[53,54]

Optimal management revolves around diagnosing and managing portal hypertension and its complications. Extensive and detailed preconceptional counseling, evaluation, and antenatal and perinatal monitoring are needed in patients with portal hypertension with or without cirrhosis planning for pregnancy.[53] Before conception, all patients with cirrhosis should be screened for esophageal and gastric varices. If the patient has not been screened before pregnancy, a screening endoscopy may be performed at 20 weeks. If detected, primary prophylaxis in the form of endoscopic variceal ligation (EVL) to eradicate high-risk esophageal varices or cyanoacrylate glue to obliterate high-risk gastric varices is recommended. If patient is on beta-blockers, it may be continued, although caution is advised about its effects on mother and baby. The principal risk of using them in pregnancy is fetal growth restriction and fetal bradycardia.

Acute variceal bleeding is managed endoscopically, as in the nonpregnant, with EVL or sclerotherapy, although terlipressin use is not recommended because of arteriolar vasospasm and an increased risk of placental abruption, myocardial infarction, peripheral ischemia, and hypertension. Octreotide, category B by the FDA, is often used to treat acute variceal bleeding, although its safety has not been well studied in pregnant patients.

Consensus statements on management of portal hypertensive bleed in pregnancy are provided in Table 14.

PREGNANCY WITH WILSONS'S DISEASE

Wilson's disease is an autosomal recessive genetic disorder affecting copper transport, leading to hepatic and/or neuropsychiatric manifestations. Because it is an inherited disease, patients with Wilson's disease should be offered genetic counseling before planning pregnancy.

Although there are numerous reports of successful pregnancies in Wilson's disease, fetal demise and maternal death from liver disease have also been described. In a retrospective, multicenter study from Europe, 282 pregnancies in 136 patients with Wilson's disease were reviewed.[55] Worsening of LFTs was evident in 6% of pregnancies and occurred in undiagnosed patients as well as in those under medical treatment. Liver test abnormalities resolved in all cases after delivery. Aggravation of neurological symptoms during pregnancy was rare but tended to persist after delivery. The overall spontaneous abortion rate in the study cohort was 26%. Patients with an established diagnosis of Wilson's disease receiving medical treatment experienced significantly fewer spontaneous abortions than therapy naöve patients. Birth defects occurred in 3% of live births. The authors concluded that pregnancy in women with Wilson's disease on anticopper therapy is safe, and hence, treatment should be maintained during pregnancy and patients should be monitored closely for hepatic and neurological symptoms. However, prevention of overchelation, or overdecoppering, might be achievable by calculated dose adjustments in terms of dose reduction of anticopper drugs during pregnancy.[55,55a]

Consensus statements on pregnancy with Wilsons's disease are provided in Table 15.

PREGNANCY AND BCS

BCS is a rare disorder caused by hepatic venous outflow obstruction and resulting hepatic dysfunction due to sinusoidal congestion, ischemic injury to the liver, and portal

Table 13 Consensus Statements on Pregnancy With Cirrhosis.

• Pregnancy in uncommon in women with cirrhosis. In addition, there are higher abortion rates, prematurity, and perinatal deaths (level of evidence, II-3).
• Maternal prognosis depends on the degree of hepatic dysfunction and portal hypertension (level of evidence, II-3).
• In cases of decompensated cirrhosis with pregnancy, the decision to terminate pregnancy must be individualized depending on severity of liver disease and stage of pregnancy (level of evidence, III; strength of recommendation, weak).
• Cesarean section may be preferred when there are large varices, whereas assisted vaginal delivery with shortened second stage of labor may be preferred when there are small varices (level of evidence, III; strength of recommendation, weak).

Table 14 Consensus Statements on Management of Portal Hypertensive Bleed in Pregnancy.

- Before conception, all patients with cirrhosis should be screened for esophageal and gastric varices. If the patient has not been screened before pregnancy, a screening endoscopy may be performed at 20 weeks (level of evidence, II-3; strength of recommendation, weak).
- If detected, primary prophylaxis in the form of endoscopic variceal ligation (EVL) to eradicate high-risk esophageal varices is recommended (level of evidence, II-3; strength of recommendation, weak).
- If patient is on beta-blockers, it may be continued, although caution is advised about its effects on mother and baby (level of evidence, II-3; strength of recommendation, weak).
- Bleeding from esophageal or gastric varices should be managed as in nonpregnant women, although terlipressin use is not recommended (level of evidence, II-3; strength of recommendation, weak).

hypertension. The main mechanism of BCS is thrombosis of the hepatic veins or the terminal portion of the inferior vena cava. Usually, multiple risk factors for venous thromboembolism are present in patients with BCS. Pregnancy is also considered to be a thrombophilic state because of increased levels of fibrinogen and factor II, VII, VIII, X, and XII; decreased protein C and S levels; increased resistance to activated protein C; elevated plasminogen activation inhibitor-I; and venous stasis due to gravid uterus and reduced venous tone. Pregnancy is a relatively common risk factor for BCS, but there is a huge variation in the prevalence among studies. A systematic review and meta-analysis of twenty studies demonstrated a pooled prevalence of pregnancy-related BCS of 6.8%.[56]

Pregnancy is a hypercoagulable state, and earlier studies had reported that women with BCS could be at risk of developing severe exacerbation of their underlying disease during pregnancy. A recent study from India[57] on 60 women with BCS showed that primary infertility was common and pregnancy outcomes were poor even before the onset of symptoms of BCS. With treatment of BCS, pregnancy is safe for the mother and fetal outcomes are modest with transjugular intrahepatic portosystemic shunt or hepatic vein stenting and/or anticoagulation. A proportion of women with primary infertility and poor pregnancy outcomes can successfully bear children after effective therapy for BCS.[57] Previously, Rautou et al[58] had conducted a study on the outcomes of pregnancy in women with known and treated BCS and concluded that good maternal outcomes could be achieved with current treatment modalities and close surveillance of BCS. Therefore, BCS cannot be considered a contraindication to pregnancy in stable patients with treated and well-controlled disease. If anticoagulation is needed, then low-molecular-weight heparin (LMWH) should be preferred over warfarin.

Consensus statements on pregnancy and BCS are provided in Table 16.

LIVER INVOLVEMENT IN HYPEREMESIS OF PREGNANCY

Nausea and vomiting are the most frequent medical conditions during pregnancy, affecting 50–80% of women. These symptoms begin between the 4th and 6th week, peak at the 8th to 12th, and often cease by the 20th week.[2,59] Hyperemesis gravidarum (HG) is a severe form of nausea and vomiting associated with weight loss of more than 5% of prepregnant weight, dehydration, and electrolyte imbalances. Mild elevations in liver enzymes are common in patients admitted for HG. However, if the bilirubin is > 2 mg/dL and transaminases are >5 × upper limit of normal, these patients should have careful monitoring and evaluation for alternative causes.

HG is a diagnosis of exclusion. The approach to nausea and vomiting entails the exclusion of other causes, especially if these symptoms persist during the second and third trimesters. An objective and validated index of nausea and vomiting such as the Pregnancy-Unique Quantification of Emesis (PUQE) score can be used to classify the severity of nausea and vomiting and to track progress with treatment.[60] Stepwise management of HG with liver involvement remains the same as management of those patients without liver involvement, and management details are beyond the scope of this review.

Consensus statements on liver involvement in hyperemesis of pregnancy are provided in Table 17.

INTRAHEPATIC CHOLESTASIS OF PREGNANCY

Intrahepatic cholestasis of pregnancy (ICP) is a cholestatic liver disorder of late pregnancy characterized by pruritus and elevation of bile acid levels and serum aminotransferases. It is a reversible type of hormonally influenced cholestasis, and spontaneous relief of symptoms usually occurs within 2–3 weeks after delivery or occasionally up to 6–8 weeks.[2,61] ICP tends to occur in older, multiparous women and twin gestations. A previous history of ICP, cholestasis during oral contraceptive therapy, and family

Table 15 Consensus Statements on Pregnancy With Wilsons's Disease.

Pregnancy with Wilsons's disease
• Pregnancy in Wilson's disease may be continued with maintenance of chelation drugs at a reduced dosage (level of evidence, II-2; strength of recommendation, strong).
• Patients with Wilson's disease should be offered genetic counseling before planning pregnancy (level of evidence, III; strength of recommendation, strong).

history of both ICP and contraceptive-induced cholestasis are associated with an increased risk of ICP.[2,62]

The pathogenesis of ICP is not well understood but most likely multifactorial. The hormonal changes, use of high-dose oral contraceptive (high estrogen state causes cholestasis), geographic variability, and genetic susceptibility all likely trigger for alteration of the transport of sex steroids across the canalicular and hepatic membranes and ICP. At least ten different MDR3 mutations have been associated with ICP, of which the ABCB4 variant has been reported to be associated with a severe form of ICP.[4] The pathogenesis of poor fetal outcomes is not completely understood, but it is postulated that higher concentrations of bile acids may be toxic and lead to sudden development of fetal arrhythmia or vasospasm of the placental chorionic surface vessels.[61]

The diagnosis of ICP is based on the presence of pruritus that starts in the palms and soles and usually worsens in the evening. Jaundice may develop within 1–4 weeks after the onset of the pruritus. Steatorrhea can be present, and fat malabsorption can lead to vitamin K deficiency, resulting in prolonged PT and postpartum hemorrhage.[2,62] Laboratory findings are characterized by an increase in total bile acid levels (>10 mmol/L) and a 2- to 10-fold increase in aminotransferases, exceptionally reaching 1000 UI/L. GGT elevation is present in one-third of cases. ALP may also rise up to fourfold, but this is not helpful for the diagnosis because ALP is elevated in pregnancy because of placenta production. Hyperbilirubinemia rarely reaches 6 mg/dL and is found in one quarter of patients.

Although ICP is considered a benign disorder to the mother, it is associated with an increased risk of preterm delivery, meconium staining of amniotic fluid, fetal bradycardia, fetal distress, and fetal death. All these risks are higher with higher bile acid levels (especially >40)[61]. The therapeutic approach to ICP includes relief of maternal symptoms and obstetric management to prevent fetal distress. Team of specialists in a hospital setting should manage these women. Ursodeoxycholic acid (UDCA) is the drug of choice in ICP. UDCA is effective in reducing pruritus, decreasing the total serum bile acid, normalizing LFT, and allowing delivery closer to term. UDCA should be given at 10–15 mg/kg to women with ICP for symptomatic improvement. For severe cholestasis not responding to UDCA alone, rifampicin or cholestyramine can be added. Dexamethasone should not be the first-line therapy for treatment of obstetric cholestasis. Topical emollients are safe, but their efficacy is unknown. Careful fetal monitoring is essential in the management of ICP. Owing to increased risk of fetal complications with IHCP, early delivery at 37 weeks is recommended.[2,63] Women should be informed of the increased risk of perinatal morbidity and maternal morbidity from early intervention (37 + 0 weeks of gestation); that the case for intervention (before 37 + 0 weeks of gestation) may be stronger in those with more severe biochemical abnormality; and of inability to predict stillbirth if pregnancy continues. In some cases with severe symptoms and very high bile acids (>100), delivery earlier than 37 weeks should be considered after counseling the patient and giving steroids for fetal lung maturity. Breastfeeding is safe for babies born of mothers with ICP.

Consensus statements on ICP are provided in Table 18.

Table 16 Consensus Statements on Pregnancy and Budd-Chiari Syndrome.

- In well-compensated patients with Budd-Chiari syndrome and pregnancy, the maternal and fetal outcomes are good. Hence, pregnancy is not a contraindication in these patients (level of evidence, II-3; strength of recommendation, weak).
- If anticoagulation is needed, then LMWH should be preferred over warfarin (level of evidence, II-3; strength of recommendation, strong).

LMWH, low-molecular-weight heparin.

LIVER INVOLVEMENT IN PREGNANCY-INDUCED HYPERTENSION, PREECLAMPSIA, AND ECLAMPSIA

Pregnancy-induced hypertension (PIH) complicates 6–10% of pregnancies.[64] It is defined as systolic blood pressure (SBP) > 140 mmHg and diastolic blood pressure (DBP) > 90 mmHg. PIH refers to one of four conditions: (i) preexisting hypertension, (ii) gestational hypertension and preeclampsia, (iii) preexisting hypertension plus superimposed gestational hypertension with proteinuria, and (iv) unclassifiable hypertension.[64] PIH is a major cause of maternal, fetal, and neonatal morbidity and mortality. Maternal risks include abruptio placentae, cerebrovascular events, disseminated intravascular coagulation, and organ failure. Fetal risks include intrauterine growth retardation, prematurity, and intrauterine death.

LFTs may be abnormal in women with PIH. Although there is considerable overlap of LFT abnormalities between various conditions in pregnancy, interpreting

Table 17 Consensus Statements on Liver Involvement in Hyperemesis of Pregnancy.

- Mild elevations in liver enzymes are common in patients admitted for hyperemesis gravidarum. However, if the bilirubin is > 2 mg/dL and transaminases are >5 × ULN, these patients should have careful monitoring and look for alternative causes (level of evidence, II-2; strength of recommendation, strong).
- Stepwise management of hyperemesis gravidarum with liver involvement remains the same as management of those patients without the liver involvement (level of evidence, II-2; strength of recommendation, strong).

ULN, upper limit of normal.

the pattern of LFTs, timing, association with PIH, and associated clinical features helps reach a diagnosis in most. Presence of PIH and ascites favors pregnancy-induced liver diseases.

Treatment of PIH depends on blood pressure levels, gestational age, and presence of symptoms and associated risk factors. Methyldopa has been the drug of choice for PIH, whereas labetalol has an efficacy comparable to methyldopa. Atenolol and metoprolol also appear to be safe and effective in late pregnancy. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists are contraindicated in pregnancy because of their association with increased risk of fetopathy.

Preeclampsia is defined as PIH with proteinuria of >300 mg/24 h or spot protein–creatinine ratio of 0.3 after 20 weeks of gestation. Severe preeclampsia may be associated with organ dysfunction. Eclampsia occurs when generalized seizures occur in a patient with preeclampsia. The pathophysiology of preeclampsia involves placental and maternal vascular dysfunction characterized by abnormal trophoblast invasion of spiral arteries. The symptoms of preeclampsia include headache, visual disturbances, vomiting, edema, abdominal pain, chest pain, dyspnea, oliguria, and altered mental status. Investigations may reveal acute kidney injury, hyperuricemia, hyperlipidemia, neutrophilia, urinary sediment, and raised hematocrit.[65]

Symptoms of hepatic involvement include epigastric or right upper quadrant pain, likely from hepatomegaly stretching Glisson's capsule. Increase in liver enzymes to twice the normal values classifies preeclampsia into severe form. Typically, clotting studies remain normal unless there is progression to liver failure or placental abruption. Liver injury results as a consequence of vasoconstriction, reduced hepatic flow leading to hepatic ischemia, periportal hemorrhage, endothelial damage, and fibrin precipitation in the liver.[65] Complications of liver involvement can include hematoma below Glisson's capsule and hepatic rupture.[66] HELLP syndrome is a severe and rare variant of preeclampsia characterized by hemolysis, elevated liver enzymes, and low platelet count.

Generally, women with severe preeclampsia should be delivered after 34 completed weeks of gestation after initial stabilization while expectant management should be pursued between 25 and 34 weeks provided the patient is stable with no organ involvement, abruption, or fetal compromise. Antihypertensives such as hydralazine, labetalol, or nifedipine should be given to patients with preeclampsia with severe hypertension (≥160/110 mmHg). LFTs, renal function tests, and full blood count should be monitored at least twice weekly. Successful conservative management could delay elective delivery until after 34 weeks, even for patients with severe hypertension if their blood pressure gets adequately controlled. However, if there is recurrent severe hypertension, abruptio, worsening end-organ dysfunction, eclampsia, or fetal nonassuring heart patterns, termination of pregnancy even before 34 weeks of gestation should be considered after stabilizing the maternal condition. Magnesium sulfate should be given for seizure prophylaxis in severe preeclampsia and for treatment of convulsions in eclampsia. No specific therapy is recommended for liver dysfunction, but the disease as a whole has to be addressed.[67,68] Decisions are not based only on LFTs because severe disease may be present in spite of normal LFTs.

Consensus statements on liver involvement in PIH, preeclampsia, and eclampsia are provided in Table 19.

Table 18 Consensus Statements on Intrahepatic Cholestasis of Pregnancy.

- Intrahepatic cholestasis of pregnancy (ICP) is diagnosed when otherwise-unexplained pruritus occurs in pregnancy; abnormal liver function tests and/or raised bile acids occur in the pregnant woman, and both resolve after delivery. Pruritus that involves the palms and soles of the feet is particularly suggestive (level of evidence, II-2; strength of recommendation, strong).
- Although ICP is considered a benign disorder to the mother, it is associated with an increased risk of preterm delivery, meconium staining of amniotic fluid, fetal bradycardia, fetal distress, and fetal death. All these risks are higher with higher bile acid levels (especially >40) (level of evidence, II-2; strength of recommendation, strong).
- Team of specialists in a hospital setting should manage these women (level of evidence, III; strength of recommendation, strong).
- Ursodeoxycholic acid (UDCA) improves pruritus and liver function in women with obstetric cholestasis. Ursodeoxycholic acid should be given at 10–15 mg/kg to women with ICP for symptomatic improvement (level of evidence, I; strength of recommendation, strong).
- For severe cholestasis not responding to UDCA alone, rifampicin or cholestyramine can be added (level of evidence, II-3; strength of recommendation, weak).
- Careful fetal monitoring is essential in the management of ICP (level of evidence, II-3; strength of recommendation, weak).
- Owing to increased risk of fetal complications with IHCP, early delivery at 37 weeks is recommended (level of evidence, I; strength of recommendation, strong).
- Women should be informed of the increased risk of perinatal morbidity and maternal morbidity from early intervention (at 37 weeks of gestation); that the case for intervention before 37 weeks of gestation may be stronger in those with more severe biochemical abnormality; and of inability to predict stillbirth if pregnancy continues. In some cases with severe symptoms and very high bile acids (>100), delivery earlier than 37 weeks should be considered after counseling the patient and giving steroids for fetal lung maturity (level of evidence, III; strength of recommendation, strong).
- Breastfeeding is safe for babies born of mothers with ICP (level of evidence, III; strength of recommendation, strong).

HELLP SYNDROME

HELLP syndrome is a relatively rare complication of pregnancy. It is a severe and rare variant of preeclampsia, which

Table 19 Consensus Statements on Liver Involvement in Pregnancy-Induced Hypertension, Preeclampsia, and Eclampsia.

- Antihypertensives such as hydralazine, labetalol, or nifedipine should be given to patients with preeclampsia with severe hypertension (a systolic blood pressure of 160 mm of Hg or more and or a diastolic of 110 mm of Hg or more) (level of evidence, II-2; strength of recommendation, strong).
- Women with severe preeclampsia should be delivered after 34 completed weeks of gestation after initial stabilization (level of evidence, II-2; strength of recommendation, strong).
- Expectant management may be pursued between 25 and 34 weeks provided the patient is stable with no organ involvement, abruption, or fetal compromise (level of evidence, II-3; strength of recommendation, strong).
- Terminate at <34 weeks after stabilizing the maternal condition irrespective of gestation if recurrent severe hypertension, abruptio, worsening end-organ dysfunction, eclampsia, or fetal nonassuring heart patterns (level of evidence, II-2; strength of recommendation, strong).
- Magnesium sulfate should be given for seizure prophylaxis in severe preeclampsia and for treatment of convulsions in eclampsia (level of evidence, I; strength of recommendation, strong).

is defined as elevated blood pressure seen after 20 weeks of gestation in the presence of proteinuria or end-organ dysfunction if proteinuria is absent. HELLP syndrome usually develops in the third trimester or after delivery and is associated with increased complications: both maternal (placental abruption, disseminated intravascular coagulation, hepatic hematomas and rupture, and acute kidney injury) and neonatal (prematurity and low birth weight). The clinical presentation of HELLP syndrome is highly variable. The patient might be asymptomatic or may present with symptoms such as right upper quadrant abdominal pain, enlarged liver, nausea, vomiting, jaundice, or confusion.[69]

Although the etiopathogenesis of this condition remains unclear, histopathologic findings in the liver include intravascular fibrin deposits that presumably may lead to hepatic sinusoidal obstruction, intrahepatic vascular congestion, and increased intrahepatic pressure with ensuing hepatic necrosis, intraparenchymal and subcapsular hemorrhage, and eventually capsular rupture.[70]

The laboratory findings are significant for intravascular hemolysis, schistocytes on peripheral smear, elevated LFTs (usually ALT), and low platelet count. Serum aminotransferases are more than ten times elevated, and unconjugated hyperbilirubinemia may be present due to hemolysis. The diagnostic criteria such as Tennessee or Mississippi Classifications should be used to diagnose and to grade HELLP syndrome because it has prognostic value (Table 20). In a large retrospective cohort study comprising 442 pregnancies complicated by the HELLP syndrome, the maternal mortality was 1.1%.[71] Perinatal mortality and morbidity are considerably higher in the HELLP syndrome than those of the mother and are primarily dependent on the gestational age when the condition develops. Similar to ICP, prematurity remains the most common risk associated with fetal outcomes. According to Gul et al,[72] the perinatal mortality was 34% before 32-week gestation and 8% after the 32nd gestational week.

The cornerstone of treatment of HELLP syndrome is early delivery of the fetus; however, the timing of delivery depends on gestational age. At 34-week gestation or later, immediate delivery is the treatment of choice. For management of HELLP syndrome before the gestational age of fetal viability, maternal stabilization should be done followed by delivery. At 27–34 weeks of gestation, cesarean section (CS) delivery within 48 h after evaluation and stabilization of the maternal clinical condition appear appropriate and rational for most cases. Expectant (conservative) management for more than 48–72 h may be considered in pregnant women before 27-week gestation. If gestation age is less than 34 weeks, treatment with steroids for 24–48 h should be considered for fetal maturity before attempting delivery of the fetus. Patients being treated with delayed delivery and expectant management are advised bed rest, magnesium sulfate for 48 h, bolus doses of antihypertensive medications to control blood pressure exceeding 160/110 mmHg, volume expansion, and glucocorticoids such as dexamethasone to promote fetal maturation. Evidence supports the use of $MgSO_4$ as a first-line treatment for seizure prophylaxis. Magnesium sulfate more than halves the risk of eclampsia and probably reduces maternal death.[73]

Consensus statements on HELLP syndrome are provided in Table 21.

ACUTE FATTY LIVER OF PREGNANCY

Acute fatty liver of pregnancy (AFLP) is an obstetric emergency characterized by maternal liver failure and may have complications for mother and fetus, including death. Pathogenesis of this disease has been linked to defects in fatty acid metabolism during pregnancy, especially in the setting of fetal genetic defects in fatty acid oxidation.[74] Distinguishing AFLP from other high-risk liver diseases of pregnancy that have overlap features, such as HELLP and preeclampsia, can be challenging. To enable a rapid diagnosis of "suspected AFLP", it is important to quickly rule out differential diagnosis of AFLP (i.e. causes of acute liver failure that are endemic in the geographic area such as HEV, malaria). Although sensitive diagnostic tools for AFLP such as the Swansea criteria have been developed, further work is needed to diagnose AFLP more quickly. The Swansea criteria (Table 22) to diagnose AFLP refer to meeting ≥6 of 15 criteria, in the absence of alternate explanation occurring in late pregnancy.[75] These criteria have a

Table 20 Diagnosis and Grading of HELLP Syndrome.

Tennessee Classification	Mississippi classification
Complete syndrome	*Class 1*
• Platelets <100,000/L	• Platelets <50,000/L
• AST >70 IU/L	• AST or ALT >70 IU/L
• LDH >600 IU/L	• LDH >600 IU/L
Incomplete syndrome	*Class 2*
• One or two elements of the triad	• Platelets 50,000 to 100,000/L • AST or ALT >70 IU/L • LDH >600 IU/L *Class 3* • Platelets 100,000 to 150,000/L • AST or ALT >40 IU/L • LDH >600 IU/L

HELLP, hemolysis, elevated liver enzymes, low platelet count; AST, aspartate aminotransferase; ALT, alanine transferase; LDH, lactate dehydrogenase.

high degree of agreement with clinical assessment and with hepatic microvesicular steatosis on liver biopsy.[76]

Although survival rates have improved in the past 30 years, delay in diagnosis and treatment of AFLP has life-threatening consequences. Hence, an algorithmic approach to AFLP may be a valuable resource for clinicians.[77] Standard medical treatment as for managing any patient of acute liver failure needs to be followed. A multidisciplinary team of specialists in an intensive care unit (ICU) or high dependency unit (HDU) best manages these patients. Immediate termination of pregnancy leads to improvement in maternal health. In patients with suspected AFLP, CS may be preferred over vaginal delivery.[78] This decision on the mode of delivery is based on clinical assessment of the patient and is best made by the obstetrician, in consultation with an anesthetist and other members of the multidisciplinary team. Baby delivered of mother with AFLP needs to be managed in the neonatal ICU, especially to watch for hypoglycemia or features of fatty acid oxidation defect.

Future epidemiological and long-term studies will improve our prediction of women at risk for developing AFLP and determine the long-term consequences of this condition. The value of screening all patients for these genetic defects remains to be determined.

Consensus statements on AFLP are provided in Table 23.

Table 21 Consensus Statements on HELLP Syndrome.

• Management of HELLP syndrome depends on gestational age: o At gestational age ≥34 weeks: immediate delivery. o At gestation age 27–34 weeks: delay delivery for 24–48 h to allow adequate maternal stabilization. o At gestation age <27 weeks: conservative management for more than 48–72 h, followed by delivery (level of evidence, II-2; strength of recommendation, strong).
• If gestation age is less than 34 weeks, treatment with corticosteroids for 24–48 h should be considered for fetal maturity before attempting delivery of the fetus (level of evidence, II-2; strength of recommendation, strong).
• Specialist multidisciplinary approach would be needed during delivery (level of evidence, III; strength of recommendation, strong).
• Antihypertensive therapy is recommended for treatment of severe hypertension (BP ≥ 160/110) (level of evidence, II-2; strength of recommendation, strong).
• Magnesium sulfate should be administered intrapartum and early postpartum for seizure prophylaxis regardless of blood pressure (level of evidence, II-2; strength of recommendation, strong).

HELLP, hemolysis, elevated liver enzymes, low platelet count; BP, blood pressure.

Table 22 The Swansea Criteria.

A patient positive for at least 6 of the 15 following criteria should be considered for a diagnosis of AFLP.
1 Vomiting
2 Abdominal pain
3 Polydipsia/polyuria
4 Encephalopathy
5 Bilirubin >0.8 mg/dL
6 Hypoglycemia <72 mg/dL
7 Elevated urea >950 mg/dL
8 White blood cell count >11 × 10^9/L
9 Ascites
10 ALT >42 U/L
11 Ammonia >66 μmol/dL
12 AKI or creatinine >1.7 mg/dL
13 Coagulopathy or PT > 14 s
14 "Bright liver" on ultrasound
15 Microvesicular steatosis on liver biopsy

AFLP, acute fatty liver of pregnancy; ALT, alanine aminotransferase; AKI, acute kidney injury; PT, prothrombin time.

PREGNANCY AFTER LIVER TRANSPLANTATION

The success of liver transplantation program has changed the course of events of pregnancy in cirrhosis, and successful pregnancies after liver transplantation are becoming commoner now. However, despite advances in immunosuppressive therapy and increasing experience in the management of these patients, pregnancies in liver transplant recipients are still more risky than in the general population for both mother and fetus.[79] In a cohort of 18 women who had 26 pregnancies after liver transplantation, only 17 pregnancies (65%) ended in a live birth and only 6 pregnancies (23%) had no maternal or fetal complications. The most frequent maternal complication during pregnancy

Table 23 Consensus Statements on Acute Fatty Liver of Pregnancy.

- The Swansea criteria are useful to make a clinical diagnosis of AFLP. These criteria to diagnose AFLP have a high degree of agreement with clinical assessment as well as with hepatic microvesicular steatosis on liver biopsy (level of evidence, II-2; strength of recommendation, strong).
- To enable a rapid diagnosis of "suspected AFLP", it is important to quickly rule out differential diagnosis of AFLP (i.e., causes of acute liver failure that are common in the geographic area such as HEV- and malaria-endemic ones) (level of evidence, III; strength of recommendation, strong).
- Immediate termination of pregnancy leads to improvement in maternal health (level of evidence, II-3; strength of recommendation, strong).
- Patient with AFLP are best managed by a multidisciplinary team of specialists (level of evidence, II-3; strength of recommendation, strong).
- In patients with suspected AFLP, cesarean section may be preferred over vaginal delivery. This decision on the mode of delivery is based on clinical assessment of the patient and is best made by the obstetrician, in consultation with an anesthetist and other members of the multidisciplinary team (level of evidence, II-2; strength of recommendation, weak).
- Standard medical treatment as for managing any patient of acute liver failure needs to be followed. Patient needs specialized intensive care in an ICU or HDU (level of evidence, III; strength of recommendation, strong).
- Baby delivered of mother with AFLP needs to be managed in the neonatal ICU, especially to watch for hypoglycemia or features of fatty acid oxidation defect (level of evidence, III; strength of recommendation, weak).

AFLP, acute fatty liver of pregnancy; HEV, hepatitis E virus; ICU, intensive care unit; HDU, high dependency unit.

was PIH (17%).[79] According to another transplantation registry, the incidence of prematurity, low birth weight, PIH, and cesarean section was higher in these women.[80] The graft rejection is higher if pregnancy occurs within 6 months of transplantation.[81] Hence, pregnancy should be postponed for at least one year after transplantation to ensure adequate graft functioning and lowest doses of immune suppressants and reduced incidence of infections and acute rejection of graft.[53]

The inferior maternal and fetal outcomes in these pregnancies is mainly due to immunosuppressive agents. Mycophenolate has been reported to be associated with first trimester loss and increased congenital malformations.[82] Hence, mycophenolate should be stopped at least 3–6 months before pregnancy is planned. Calcineurin inhibitor (CNI) should be continued during pregnancy. Increased monitoring of tacrolimus and cyclosporine levels is required during pregnancy. Low-dose (trough levels between 3 and 5) tacrolimus should be used in pregnancy.[83] Because tacrolimus is mainly metabolized by cytochrome P450 (CYP) 3A4 and CYP3A5, further reduction in dosage may be warranted as CYP450 is inhibited during pregnancy.[84] Corticosteroids should be continued during pregnancy if the patient is already on them; however, there is higher incidence of gestational diabetes mellitus and hypertension in patients on steroids after liver transplantation.[85] Mammalian target of rapamycin (mTOR) inhibitors are FDA category D drugs and should be discontinued at least 3–6 months before pregnancy is planned.

Breastfeeding is not contraindicated in patients on tacrolimus, cyclosporine, and steroids; however, it is contraindicated in patients on mycophenolate and mTOR inhibitors.

Consensus statements on pregnancy after liver transplantation are provided in Table 24.

IN VITRO FERTILIZATION AND LIVER DISEASE INCLUDING HBV/HCV

Fertility services should not be withheld from individuals with chronic HBV or HCV infection; however, special considerations must be taken when these patients desire to become pregnant.[86] Because the center has to have the necessary resources to provide care to these couples, it is appropriate to refer these couples to a center(s) having such capabilities wherever it is required. Preconception counseling or consultation with fertility specialists is imperative in patients with HBV and HCV infection so that reproductive goals can be addressed and optimized. Options are available to decrease both vertical transmission

Table 24 Consensus Statements on Pregnancy After Liver Transplantation.

- Pregnancy should be postponed for at least one year post-transplant to ensure adequate graft functioning and lowest doses of immune suppressants and reduced incidence of infections and acute rejection of graft. (Level of evidence II-2, Strength of recommendation strong).
- CNIs should be continued during pregnancy; however, increased monitoring of tacrolimus and cyclosporine levels is required during pregnancy (level of evidence, II-2; strength of recommendation, strong).
- Low-dose (trough levels between 3 and 5) tacrolimus should be used in pregnancy. Further reduction in dosage may be warranted because CYP450 is inhibited during pregnancy (level of evidence, II-2; strength of recommendation, strong).
- Corticosteroids should be continued during pregnancy if the patient is already on them; however, there is higher incidence of gestational diabetes mellitus and hypertension in pregnant women on corticosteroids after liver transplant (level of evidence, II-2; strength of recommendation, strong).
- Mycophenolate and mTOR inhibitors should be stopped at least 3–6 months before pregnancy is planned (level of evidence, II-2; strength of recommendation, strong).
- Breastfeeding is not contraindicated in patients on tacrolimus, cyclosporine, and corticosteroids; however, it is contraindicated in patients on mycophenolate and mTOR inhibitors (level of evidence, III; strength of recommendation, strong).

mTOR, mammalian target of rapamycin.

and viral transmission between partners. If one of the partners has HBV infection, vaccination of the uninfected partner is indicated to prevent HBV transmission.[87] To reduce vertical transmission of HBV, newborns of HBV-infected mothers (especially HBeAg positive) should receive HBIG and hepatitis B vaccine at delivery and complete the recommended vaccination series. In case the woman has HCV, because no safe and effective method exists to reduce vertical transmission of HCV once a woman becomes pregnant, HCV should be treated before pregnancy.[86] Similar to HIV-positive patients, in settings in which the male partner is infected with HBV/HCV infection, density gradient sperm washing can be used before intrauterine insemination or in vitro fertilization (IVF) to reduce transmission of HBV/HCV between partners.[87] However, if the female partner has been adequately immunized against HBV, sperm washing solely to reduce HBV transmission from HBV-infected male partner is unnecessary. It is a good clinical and logical practice to store semen and embryos from patients infected with HCV or HBV in separate HCV- or HBV--designated storage tanks because of theoretic risk of transmission.[87] However, there is no sufficient evidence in support of this recommendation and it may not be appropriate to conduct any randomized trials to support this point. In the case of HBV infection of either the male or female partner, the reasonable precaution is to have all laboratory staff vaccinated for HBV.[87]

Consensus statements on IVF and liver disease including HBV/HCV infection are provided in Table 25.

AUTOIMMUNE LIVER DISEASE AND PREGNANCY

Pregnancy in autoimmune hepatitis (AIH) is a complicated clinical state that can generate concerns regarding maternal and fetal tolerance of the disease and its medication. It also is a powerful immune modulatory state that can affect the behavior and outcome of the disease. Maternal and fetal complications are increased in patients with AIH (as in other immunological disorders) during pregnancy, especially in patients with cirrhosis. In pregnant women with AIH, premature birth is a major risk and fetal mortality may be as high as 19%.[88,89] In a Danish cohort, women with AIH had 3-times increased risk of preterm birth and small-for-gestational-age babies, but not of congenital malformations or stillbirth.[90] In another study, the rate of serious maternal complications was 9% and a high rate (52%) of postpartum flares was noted.[91]

In spite of the aforementioned reports, most experiences indicate that both pregnancy and liver disease can be successfully managed.[88] Hence, women with AIH should not be discouraged from pregnancy, but they must know about the increased frequency of prematurity and fetal loss. It is recommended to have a good disease control before conception and to continue maintenance immunosuppression during pregnancy so as to reduce the risk of AIH flare during pregnancy and in postpartum period. Both prednisolone and azathioprine can be used safely for immunosuppression of AIH in pregnancy.

Primary sclerosing cholangitis (PSC) is characterized by progressive inflammation and destruction of bile ducts, finally resulting in liver failure, whereas primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease, characterized by changes in the small-sized bile ducts near portal spaces. Maternal and fetal complications are not increased in patients with PSC or PBC during pregnancy.[92,93] UDCA can be used safely during pregnancy for patients with PSC and PBC.

Consensus statements on autoimmune liver disease and pregnancy are provided in Table 26.

Table 25 Consensus Statements on IVF and Liver Disease Including HBV/HCV.

- Fertility services should not be withheld from individuals with chronic HBV or HCV; however, special considerations must be taken when these patients desire to become pregnant, including referral to centers that have the necessary resources to provide care to these HBV/HCV-infected couples (level of evidence, III; strength of recommendation, strong).
- It is a good clinical and logical practice to store semen and embryos from patients infected with HCV or HBV in separate HCV or HBV-designated storage tanks because of theoretic risk of transmission (level of evidence, III; strength of recommendation, strong).
- When the male partner is HBV- or HCV-infected, sperm washing can reduce viral loads in the insemination specimen. However, if the female partner has been immunized against HBV, sperm washing solely to reduce HBV transmission from HBV-infected male partner is unnecessary (level of evidence, II-2; strength of recommendation, strong).

IVF, in vitro fertilization; HBV, hepatitis B virus; HCV, hepatitis C virus.

HEV OR HEPATITIS A VIRUS DURING PREGNANCY

HEV is transmitted through contaminated water and is associated with large outbreaks of acute viral hepatitis (AVH), affecting hundreds or thousands of people.[94] It is responsible for more than 50% of AVH cases in general population in endemic countries. In India, human HEV infections are caused by genotype 1[95]. Typically, HEV causes an acute, self-limiting AVH, with about 0.2%–1% mortality rate in the general population. However, the course of hepatitis E in pregnancy is different than the mild self-constraining infection described in other populations. HEV as the cause of AVH is significantly higher among pregnant females than in males and nonpregnant females.[96] During pregnancy, HEV infection can take a fulminant course, resulting in fulminant hepatic failure, membrane rupture, spontaneous abortions, and stillbirths.

Table 26 Consensus Statements on Autoimmune Liver Disease and Pregnancy.

- Maternal and fetal complications are increased in patients with AIH (as in other immunological disorders) during pregnancy, especially in patients with cirrhosis (level of evidence, II-2).
- It is recommended to have a good disease control before conception and to continue maintenance immunosuppression during pregnancy so as to reduce the risk of AIH flare during pregnancy and in the postpartum period (level of evidence, II-2; strength of recommendation, strong).
- Both prednisolone and azathioprine can be used safely for immunosuppression of AIH in pregnancy (level of evidence, II-2; strength of recommendation, strong).
- Maternal and fetal complications are not increased in patients with PSC and PBC during pregnancy (level of evidence, II-2).
- Ursodeoxycholic acid (UDCA) can be used safely during pregnancy for patients with PSC and PBC (level of evidence, II-2; strength of recommendation, strong).

AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis.

Studies from India have shown a high incidence of HEV infection in pregnancy, with a significant proportion of pregnant women progressing to fulminant hepatitis with a fatality rate of up to 30%.[94] In a cohort of 220 consecutive pregnant women presenting with jaundice caused by acute viral hepatitis in India, it was found that infection with HEV caused acute viral hepatitis in 60% of included women. Fulminant hepatic failure was 2.7 times more common, and maternal mortality was 6 times greater in HEV-infected women than in non–HEV-infected women. Women with HEV infection were more likely than those with other forms of viral hepatitis to have complications such as antepartum hemorrhage, intrauterine fetal death, preterm delivery, and stillbirth.[97] In India, HEV is the commonest cause of AVH in pregnancy, both in sporadic and epidemic settings.[98] Moreover, frequency of ALF due to HEV is significantly higher in pregnant than in males nonpregnant females with HEV infection.[99] In epidemics, pregnant women in their 2nd and 3rd trimesters get infected by HEV more frequently than men and nonpregnant women. HEV viremia may persist in ALF up to 2 weeks. Mother to child transmission is also seen with HEV, especially in women with ALF.[100]

Currently, there is no established treatment for HEV during pregnancy. The main treatment for HEV infection in pregnant women is merely supportive, making prevention the main goal.[94] AVH-HEV is mostly self-limiting illness; however, vigilance is required for any evidence of ALF. Management of ALF requires same intensive care as ALF due to any other cause.[101] There are little data to support termination of pregnancy in women with ALF due to HEV to improve the maternal outcome of them[101], whereas the decision of termination of pregnancy for improvement of fetal outcomes needs to be individualized.

Unless the mother is critically ill, there is no evidence to support stopping breastfeeding to prevent transmission. The anti-HEV antibody and HEV RNA are present in the colostrum of HEV-infected mothers in significantly lower levels than in the maternal serum.[101] Breastfeeding appears to be safe for these infants. However, if the mother has fulminant hepatic disease or an increased viral load, breastfeeding may be unsafe.

Pregnant women living in or traveling to endemic areas should follow strict food and water precautions such as washing hands frequently, avoiding any water that is not treated, not adding ice cubes to beverages, and eating only those fruits and vegetables that have been thoroughly washed with safe water.[94] Proper sewage disposal, public education, and promotion of awareness regarding hygienic defecation habits are important steps toward prevention of HEV infection. HEV can be easily killed by boiling water at 100 °C or by chlorination.

Hepatitis A virus (HAV) is a single-stranded RNA virus that belongs to the Picornaviridae family.[102] HAV infection is typically self-limited and rarely life-threatening, with an estimated mortality rate of 0.2%–0.6%.[103] HAV infection is infrequently reported among pregnant women; hence, data on the incidence and outcome of HAV infection during pregnancy are scarce.[104] Overall, the available evidence supports that HAV infection during pregnancy is generally not associated with serious maternal or fetal outcomes. One study has reported that preterm labor, increased premature uterine contractions, placental abruption, and premature rupture of membranes may occur, especially if infection occurs in the second or third trimester.[105] Overall, no mortality was reported among mothers and infants exposed to HAV infection, with full resolution of the infection. Mother-to-child HAV infection is very rare, and most infants born to mothers with HAV infection were not affected and had normal antibody and transaminase levels.[104]

Although mothers infected with HAV have anti-HAV antibodies and HAV RNA in their breast milk, there is no evidence that breastfeeding transmits HAV to suckling infants. Therefore, breastfeeding should not be discouraged.[104]

Consensus statements on HEV or HAV during pregnancy are provided in Table 27.

CLINICAL UTILITY OF GENETIC TESTING FOR PREGNANCY-RELATED LIVER DISEASES

Maternal AFLP is highly associated with fetal fatty acid oxidation defects (FAODs), especially homozygous mutation (1528G > C) in the gene that encodes for mitochondrial long-chain hydroxy acyl-CoA dehydrogenase (LCHAD).[106] The mutation in *LCHAD* results in the accumulation of 3-hydroxy fatty acids, such as 3-hydroxy myristic acid, 3-hydroxy palmitic acid, and 3-hydroxy dicarboxylic acid in the placenta, which are then shunted

Table 27 Consensus Statements on HEV or HAV During Pregnancy.

• HEV as the cause of AVH is significantly higher among pregnant females than in males and nonpregnant females. HEV is the commonest cause of AVH in pregnancy, both in sporadic and epidemic settings (level of evidence, I).
• Frequency of ALF due to HEV is significantly higher in pregnant than in males and nonpregnant females with HEV infection (level of evidence, I).
• Maternal mortality and obstetric complications are high in women with HEV in pregnancy compared with other viral hepatitis in pregnancy (level of evidence, I).
• Poor fetal outcomes such as preterm delivery, intrauterine fetal death rate, and stillbirths are more common in pregnant women with HEV than with other viral hepatitis (level of evidence, I).
• Mother-to-child transmission of HEV can occur, especially in cases of ALF (level of evidence, II-3).
• AVH-HEV is mostly a self-limiting illness; however, vigilance is required for any evidence of ALF (level of evidence, II-2; strength of recommendation, strong).
• Management of HEV-ALF requires same intensive care as ALF due to any other cause (level of evidence, II-2; strength of recommendation, strong).
• In HEV-ALF in pregnancy, there are little data to support termination of pregnancy to improve the maternal outcome of the patient (level of evidence, II-2; strength of recommendation, strong).
• The decision of termination of pregnancy for improvement of fetal outcomes needs to be individualized (level of evidence, III; strength of recommendation, weak).
• Breastfeeding is considered safe in asymptomatic women infected with HEV; however, if the mother has fulminant hepatic disease or an increased viral load, breastfeeding may be unsafe (level of evidence, III; strength of recommendation, weak).
• Data on the incidence and outcome of HAV infection during pregnancy are scarce; however, the available evidence supports that HAV infection during pregnancy is generally not associated with serious maternal or fetal outcomes (level of evidence, III).

HEV, hepatitis E virus; HAV, hepatitis A virus; AVH, acute viral hepatitis; ALF, acute liver failure.

Table 28 Consensus Statements on Clinical Utility of Genetic Testing for Pregnancy-Related Liver Diseases.

• There is an association between fetal/neonatal fetal fatty acid oxidation defects (FAODs), especially homozygous mutation in the gene that encodes for mitochondrial long-chain hydroxy acyl-CoA dehydrogenase (LCHAD) with maternal AFLP/HELLP cases (level of evidence, II-2).
• Diagnosing FAODs by public newborn screening program in India is currently not recommended (level of evidence, III; strength of recommendation, strong).
• In mothers with AFLP/HELLP, the neonates should be monitored for clinical features of LCHAD deficiency (level of evidence, II-2; strength of recommendation, strong).
• Screening for LCHAD deficiency should be performed in newborns from mothers with AFLP (level of evidence, II-2; strength of recommendation, strong).
• While the common Caucasian mutation is E474Q, there are inadequate data of Indian mutations. In the absence of known Indian mutations, molecular diagnosis in affected fetus/neonate requires gene sequencing (level of evidence, III; strength of recommendation, strong).
• Prevention by prenatal diagnosis after identification of the mutation in the family is possible by chorionic villus sampling at 11 weeks of gestation (level of evidence, II-2; strength of recommendation, strong).

AFLP, acute fatty liver of pregnancy; HELLP, hemolysis, elevated liver enzymes, low platelet count.

to the maternal circulation, leading to the development of acute liver injury observed in patients with AFLP.[106] A minor fraction of cases with HELLP, hyperemesis gravidarum, and preeclampsia are reported to be associated, to a variable degree, with the genetic defects of LCHAD.[107]

Diagnosing FAODs by public newborn screening program in India is currently not recommended. However, screening for LCHAD deficiency should be performed in newborns from mothers with AFLP.[108] While the common Caucasian mutation is E474Q, there are inadequate data of Indian mutations. In the absence of known Indian mutations, molecular diagnosis in affected fetus/neonate requires gene sequencing. Symptoms of LCHAD deficiency that may not be immediately recognizable in the infant are often triggered by an increased long-chain fatty acid load in the diet or by illness that results in breakdown of endogenous fat.[109] In mothers with AFLP/HELLP, the neonates should be monitored for clinical features of LCHAD deficiency. Prevention by prenatal diagnosis after identification of the mutation in the family is possible by chorionic villus sampling at 11 weeks of gestation.

Consensus statements on clinical utility of genetic testing for pregnancy-related liver diseases are provided in Table 28.

CONFLICTS OF INTEREST

The authors have none to declare.

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