1. Correct answers: 2, 4 and 5

The model for end stage liver disease (MELD) score at time of conception is predictive of outcomes of pregnancy patients with cirrhosis. Patients with a MELD score of ≤ 6 are unlikely to have significant complications while pregnancy should be avoided in patients with MELD score of ≥ 10 .¹ Pregnancy is rare in patients with cirrhosis due to amenorrhea and infertility with the incidence of cirrhosis in pregnancy has been reported as 1 in 5950 pregnancies.² Also, continuation of pregnancy to term is less common with fetal wastage in 10%–66% cases and spontaneous first trimester abortion seen in about 20% cases.³ Conversely, patients with non-cirrhotic portal hypertension (NCPH) have better fertility rates and abortions are seen in 3–6% cases, similar to the general population.⁴ Overall, complications related to portal hypertension and cirrhosis such as variceal bleeding, ascites, splenic artery aneurysm rupture, spontaneous bacterial peritonitis (SBP), postpartum hemorrhage and hepatic encephalopathy occurs in 30–50% pregnancies with portal hypertension.⁵ This is because of additive effects of pregnancy related hemodynamic changes causing exacerbation of portal hypertension related changes, including increased maternal blood volume, decreased systemic vascular resistance and increased cardiac output.⁶

2. Correct answers: 2 and 5

Variceal bleed occurs in 18–32% of pregnancies with cirrhosis, increasing to 50% in patients with known portal hypertension and 75% in patients with documented varices.⁷ Mortality rate in these patients is 18–50% compared to 2–6% for variceal bleed in pregnant patients with NCPH.⁵ Variceal bleeding can occur at any stage of pregnancy but the highest risk is in second and third trimester and second stage of labor. Management is like that in non-pregnant patients with hemodynamic resuscitation and endoscopic band ligation. However, instead of terlipressin which is category D drug, octreotide, a category B drug, should be preferred in pregnant patients. Third generation cephalosporins are used for spontaneous bacterial peritonitis prophylaxis while fluoroquinolones are contra indicated in pregnancy.⁶ Ideally screening and management of esophageal varices should be done prior to conception. However, if it was not done, screening endoscopy should be done in second trimester.⁸

3. Correct answers: 3 and 5

Acute fatty liver of pregnancy (AFLP) is a mitochondrial hepatopathy occurring in the second to third trimester of pregnancy, characterized by diffuse or perivenular microvesicular steatosis in liver biopsy. It is believed to be due to

defect in mitochondrial beta oxidation of fatty acids, such as long chain hydroxyacyl coA dehydrogenase (LCHAD) deficiency, in the mother resulting in mitochondrial toxicity. Co-existing fatty oxidation defects in the fetus leads to increased oxidative stress and fatty acid load to the maternal liver via the placenta resulting in phenotypic manifestation of the disease in pregnancy.⁹ Risk of AFLP in the mother is increased 18 times if the fetus has fatty acid oxidation defects. However, not all mothers with fetus having these defects develop AFLP and not all mothers with AFLP have fatty acid oxidation defects¹⁰ suggesting additional pathological mechanism for AFLP. While liver biopsy is the gold standard to demonstrate microvesicular steatosis and hence AFLP, diagnosis of AFLP is usually based on clinical criteria such as the Swansea criteria in view of coagulopathy and difficulty in obtaining liver biopsy.¹¹ Demonstration of steatosis on ultrasound is neither sensitive nor specific for AFLP. Early recognition of the condition and delivery of the fetus via vaginal route or Caesarean section with adequate correction of coagulopathy is the mainstay of treatment and most patients will recover within days if delivered timely.⁹

4. Correct answers: 1, 3, 4 and 5

Liver dysfunction is seen in upto 50% of patients with pre-eclampsia and portends poor prognosis.^{12,13} A few of these cases have associated hemolysis and low platelet count as a result of endothelial dysfunction and are called as having hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome. HELLP syndrome is almost always associated with pre-eclampsia with the incidence of HELLP syndrome being 11–35% in pregnancies with pre-eclampsia compared to 1–6% for all pregnancies.⁹ HELLP syndrome usually occurs in 3rd trimester of pregnancy but a quarter of patients may present in the immediate postpartum period. Most of these patients will be having pre-eclampsia antenatally.¹⁴ Maternal mortality with HELLP syndrome varies from 0 to 15% and increases significantly if complications like acute renal failure, hepatic infarct, hepatic hematoma, hepatic rupture, disseminated intra-vascular coagulation, postpartum hemorrhage, pulmonary edema or rarely liver cell failure develop. Diagnosis of various pregnancy associated liver diseases overlaps considerably with many patients fulfilling criteria for AFLP, HELLP and pre-eclamptic liver dysfunction simultaneously.¹⁵

5. Correct answers: 2, 4 and 5

Activated stellate cells lose their ability to store vitamin A. Vitamin A deficiency is common in patients with chronic liver disease, seen in upto 50% of patients with alcohol related cirrhosis. It is associated with poor response to treatment for hepatitis C and increased mortality in patients with cirrhosis.^{16–18} Similarly, due to defective hepatic 25-hydroxylation and impaired intake,

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vitamin D deficiency is also common in patients with chronic liver disease, especially those with alcoholic cirrhosis. Low vitamin D levels are correlated to poor response to treatment for hepatitis C, severity of liver dysfunction and increased mortality in patients with cirrhosis.^{19–21} While vitamin E deficiency is well documented in alcoholic liver disease, unlike non-alcoholic steatohepatitis, vitamin E supplementation does not have a role in the treatment of alcohol hepatitis.²² Selenium has been shown to be deficient in patients with chronic liver disease.^{23,24} Selenium deficiency being associated with liver fibrosis in chronic hepatitis C and contributing to insulin resistance.²⁵ Unlike most vitamin and mineral which are deficient in patients with cirrhosis, manganese levels are elevated with selective manganese deposition occurring in the brain.^{26,27} Manganese deposition in the basal ganglia is postulated to be the cause of cirrhosis related Parkinsonism.²⁸

6. Correct answers: 3 and 5

Protein-calorie malnutrition is more prevalent in patients with cirrhosis compared to controls population. Malnutrition is correlated to severity of liver disease and is associated with poor clinical outcome, including death, ascites, renal failure and post operative complications.²⁹ Even patients with Child A cirrhosis with malnutrition are at higher 1-year risk of complications like refractory ascites, HE, variceal bleeding and hepatorenal syndrome and death.³⁰ There is a reduction in branched chain amino acid to aromatic amino acid ratio in plasma and brain in patients with cirrhosis which has been implicated in the pathogenesis of hepatic encephalopathy in patients with cirrhosis.^{31,32} Poor nutritional status is predictive of increased complication after liver transplantation such as increase in operative blood loss, length of stay in the intensive care unit, hospital costs and mortality. There is also an increased rate of postoperative systemic inflammatory response syndrome, multi-organ failure and sepsis in these patients.^{33–35} Obesity is also associated with transplant related complications, with patients with BMI greater than 35 kg/m² having higher intra-operative blood loss, higher risk of multi-organ failure and infections and increased mortality.^{36–38}

7. Correct answers: 1 and 4

With regards to hepatitis C virus (HCV) infection, high prevalence countries are defined as having anti-HCV positivity of >3.5% in the population, moderate prevalence as 1.5%–3.5%, and low prevalence as <1.5%. Anti-HCV positivity in India ranges from 0.5 to 1.5% in various studies.³⁹ There has been a substantial reduction in anti-HCV positivity prevalence in thalassemia patients from 22.5% among those transfused prior to 2001 compared to 13.6% among those who received transfusions only after 2001, when screening for HCV became mandatory in blood

banks in India.⁴⁰ Transfusion related HCV transmission is far from rare even now with a recent study finding that 24.3% of thalassemia patients who were positive for anti-HCV antibodies had been transfused after 2001.⁴¹ Prevalence of HCV in human immunodeficiency virus (HIV) infected patient is higher than the general population and ranges from 1.3 to 4.72%.³⁹ HCV-HIV co-infection is commoner in patients with CD4 counts less than <200/mL.⁴² Overall, genotype 3 is the most common genotype in India with the exception of the northeast where genotype 4 is the most prevalent form.⁴³

8. Correct answers: 2 and 4

Measurement of HCV viral load at baseline and during treatment should be done by quantitative assays using reverse transcriptase-polymerase chain reaction (RT-PCR) with a lower limit of detection of at least 50 IU/mL. These tests also have a broad dynamic range which allows for better quantification of HCV ribonucleic acid (RNA) even at higher levels.⁴⁴ Age >70 years is a relative contraindication for HCV treatment and therapy should be individualized on a case to case basis for elderly patients. As pregnancy is an absolute contraindication for HCV therapy, a negative urine pregnancy test is must in women of child bearing age prior to initiating therapy. Patients must be counseled regarding contraception for the duration of the therapy. IL28B polymorphisms are major pre-treatment determinants of response to treatment. CC genotype at the single nucleotide polymorphism (SNP) rs12979860 and TT genotype at the SNP rs8099917 are associated with sustained virological response (SVR). Indians have a higher frequency of favorable genotype and have better treatment response.⁴⁵ However, due to the significant cost of IL28B polymorphism testing it is not routinely advocated in Indian guidelines as of now and may be performed on a case to case basis for prognostication of treatment response and decide treatment duration.⁴⁴ All patients with genotype 3 infection who do not have contraindication to pegylated interferon (Peg-IFN)/ribavirin (RBV) treatment should be offered therapy, as this combination has 73% SVR rate in India.⁴⁰ However, since SVR rate in genotype 1 infection is only 50–64% in India,^{46–48} it may be appropriate to defer Peg-IFN/RBV therapy and wait for arrival of directly acting agents in patients with no or minimal fibrosis.⁴⁴

9. Correct answers: 2 and 5

NCPH is a relatively common cause of portal hypertension in Asia. NCPH includes a number of diseases classified as prehepatic, intrahepatic or posthepatic based on the site of resistance to portal blood flow. The most common forms of NCPH are the intrahepatic non-cirrhotic portal fibrosis (NCPF) and extrahepatic portal vein obstruction (EHPVO).⁴⁹ Both are common in low socioeconomic

countries like in Asia. Incidence of NCPF is decreasing with NCPF now being responsible for only 5.6% of cases of portal hypertension compared to 23.3% in the 1980s.⁵⁰ On histology NCPF is diagnosed based on demonstration of obliterative portal venopathy involving obliteration of small branches of portal veins, predominantly medium-sized and preterminal veins (0.2–3 mm in diameter).⁵¹ Development of ascites, jaundice, and hepatic encephalopathy is uncommon in NCPF and the prognosis is usually good. However, few patients of NCPF can develop features of hepatocellular failure similar to that seen in cirrhosis of liver, and may progress to requiring liver transplantation.^{52,53} Most cases of EHPVO are diagnosed in childhood and EHPVO is the most common cause of portal hypertension in them accounting for 80–90% of cases.⁵⁴ Portal hypertensive biliopathy is common in EHPVO, seen in 80–100% of patients on imaging. However, only a minority are symptomatic, usually adults who have long standing EHPVO.⁵⁵

10. Correct answers: 3 and 5

Hepatitis B virus (HBV) has been divided into 8 genotypes labeled A to H based on a more than 8% structural variability in the genomic sequence.⁵⁶ Two new genotypes, I and G have been reported recently. Genotypes are typically distributed selectively in different regions of the world and hence direct clinical comparison of all the genotypes is difficult. Most studies have compared the clinical progression of genotype B with C and genotype A with D, as these genotypes are clustered together. Compared with genotype C, genotype B is more likely to have mild disease, more likely to be HBeAg negative and is less likely to develop hepatocellular carcinoma.^{57–59} However, the differences in clinical outcomes are not as clear for genotypes A and D with conflicting results in various studies.⁵⁶ Response to therapy with nucleos(t)ide analogs is not dependent upon genotypes⁶⁰ unlike that seen with interferon therapy. Response to interferon therapy is best with genotype A and worst with genotype D irrespective of HBeAg status.^{61–64}

CONFLICTS OF INTEREST

All authors have none to declare.

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