Review Article

Acute liver failure in pregnancy: Challenges and management

Address for correspondence:
Dr. Chandra Kant Pandey, Department of Anaesthesiology, Institute of Liver and Biliary Sciences, Sector D-1, Vasant Kunj, New Delhi - 110 070, India.
E-mail: ceekeypandey@gmail.com

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Chandra Kant Pandey, Sunaina Tejpal Karna, Vijay Kant Pandey, Manish Tandon
Department of Anaesthesiology, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi, India

ABSTRACT

Acute liver failure (ALF) in pregnancy negatively affects both maternal and foetal outcome. The spectrum of liver disease in pregnancy may range from mild asymptomatic transaminitis to fatal and irreversible deterioration in liver functions leading to significant morbidity and even mortality. In this comprehensive review, we searched articles published as review articles, clinical trials, and case series in the Medline from 1970 to 2012. The overall outcome of ALF in pregnancy depends on the aetiology, timely diagnosis, prompt management, and early referral to a centre equipped in managing medical or obstetric complication. The foetal outcome is affected by the stage of pregnancy in which the mother has a deterioration of the liver function, with a worst prognosis associated with first or second-trimester liver failure. When ALF complicates pregnancy, liver transplantation is the one of the viable options. Management protocols need to be individualised for each case keeping in mind the risk versus benefit to both the mother and the foetus.

Key words: Acute liver failure, pregnancy, liver transplantation,treatment strategies

INTRODUCTION

The spectrum of liver disease in pregnancy may range from mild asymptomatic transaminitis to fatal and irreversible deterioration in liver functions leading to significant morbidity and even mortality. Acute liver failure (ALF) is described as the development of coagulopathy, usually with an international normalized ratio of >1.5, and any degree of mental alteration (encephalopathy) in a patient without pre-existing liver disease and with an illness of <26 weeks' duration.[1] The overall outcome of ALF in pregnancy depends on the aetiology, early diagnosis, prompt management and early referral to a centre equipped in managing medical, obstetric, surgical or neonatal complications. The foetal outcome is most commonly affected by the stage of pregnancy in which the mother has a deterioration of the liver function, with a worst prognosis associated with first or second-trimester liver failure.[2] This review attempts to summarise the common causes of ALF associated and exacerbated during pregnancy, their clinical presentation and management options available including liver transplantation (LT). The literature reviewed included review articles, case reports, case series, and randomised control trials of ALF during pregnancy. We searched articles published as review articles, clinical trials and case series in the Medline from 1970 to 2012 with search words/phrases 'acute liver failure in pregnancy', 'liver transplantation for acute liver failure in pregnancy' and 'treatment strategies for acute liver failure in pregnancy'.

CAUSES OF ACUTE LIVER FAILURE IN PREGNANCY

Pregnancy associated acute liver disease

- Pre-eclampsia/eclampsia with liver infarction
- Syndrome of haemolysis, elevated liver enzymes and low platelets (HELLP syndrome)
- Acute hepatic rupture
- Acute fatty liver of pregnancy (AFLP).

Exacerbated by pregnant state

- Viral hepatitis
- Budd–Chiari syndrome (BCS) with portal vein thrombosis
- Gallstone disease.

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Unrelated to pregnant state

- Drug-induced liver disease
- Toxins/mushroom poisoning
- Shock
- Trauma
- Decompensation of pre-existent liver disease.

GENERAL MANAGEMENT

Management of liver failure in pregnancy requires a combined and coordinated effort by the intensivist, obstetrician, hepatologist, neonatologist, and if necessary, the transplant team. Early diagnosis is of vital importance. A high index of suspicion should be kept for pregnant patients presenting with altered mental status, deranged liver function tests and coagulopathy. However, determining the cause of liver failure is a major challenge because multiple conditions can result in similar changes in laboratory parameters during pregnancy. Thus, it is important to rule out diseases aetiologically associated with pregnancy to expedite the recovery of the patient. The diagnostic or therapeutic intervention must ensure the safety of both the mother and the foetus. The maternal outcome should take precedent over foetal wellbeing in life-threatening situations. Intensive care management of ALF patient should be focused on the diagnosis and aetiology specific treatment.[3]

Aetiology specific treatment

- N acetylcysteine for paracetamol poisoning
- Mushroom poisoning-penicillin G and silymarin
- Herpes virus/varicella zoster-acyclovir
- Autoimmune hepatitis-corticosteroids (prednisone, 40–60 mg/day).

General management

- Prevention/treatment of cerebral oedema/ intra-cranial hypertension
- Surveillance for infections and prompt antimicrobial treatment
- Correction of coagulopathy
- Maintenance of optimum haemodynamics
- Volume replacement
- Vasopressor support
- Renal perfusion.

Correction of metabolic parameters

- Hypoglycaemia
- Dyselectrolytaemia
- Nutrition supplementation.

PREGNANCY ASSOCIATED ACUTE LIVER DISEASES:

Pre-eclampsia/haemolysis, elevated liver enzymes, and low platelets syndrome/liver rupture

Hypertension associated acute liver disease in pregnancy incorporates a wide spectrum of diseases including pre-eclampsia, eclampsia, HELLP syndrome, hepatic infarction and at its most extreme, liver rupture.[4]

Pre-eclampsia is a multisystem disorder which involves endothelial dysfunction and fibrin deposition leading to the development of hypertension, renal failure and hepatic dysfunction. Endothelial dysfunction and fibrin deposition in the sinusoid may cause both hepatic insufficiency and ascites. Eclampsia involves all features of pre-eclampsia and includes neurologic symptoms such as headaches, visual disturbances and seizures or coma. Risk factors for pre-eclampsia and eclampsia include nulliparity, extremes of maternal age, insulin resistance, obesity and infection.[5,6]

HELLP syndrome occurs in approximately 0.5–0.9% of all pregnancies and 10–20% of women with severe pre-eclampsia. The syndrome presents antepartum (most frequently in the third trimester) in 69% and postpartum in 31% of patients.[5] HELLP syndrome is characterised by microangiopathic haemolytic anaemia, hepatic dysfunction and thrombocytopenia. Complications include disseminated intravascular coagulation (DIC), abruptio placentae, acute renal failure, pulmonary oedema, intracerebral haemorrhage, liver haematoma, rupture and ALF.[7] HELLP is easily confused with gastroenteritis, hepatitis or cholelithiasis. On-going haemolysis is suggested by the presence of fragmented or contracted red blood cells with spicula and a low or undetectable haptoglobin levels.[6] Devarbhavi *et al*. reported that hypertension and ascites were predictors of pregnancy associated acute liver disease (PAALD).[8]

Maternal mortality is about 1% with treatment, although complications such as placental abruption, acute renal failure, subcapsular liver haematoma, permanent liver damage and retinal detachment occur in about 25% of women.[9] The increased serum bilirubin and oliguria were the predictors of mortality in PAALD.[8] For foetal outcome, factors such as gestational age are more important than the severity of the syndrome.[10] Infant morbidity and mortality ranges between 10% to 60% depending on the severity of maternal disease.[11] The affected infants

are likely to have intrauterine growth retardation and respiratory distress syndrome.[12] Patients with HELLP syndrome are routinely treated with corticosteroids, but the literature review has found 'no conclusive evidence' supporting corticosteroid therapy either for the mothers or the new-borns.[9]

During the treatment of eclampsia, a systolic and diastolic blood pressure of 90 and 65 mmHg, respectively, should be targeted to maintain cerebral perfusion pressure in patients with ALF.[13] Anaemia and coagulopathy need to be corrected with appropriate transfusion of blood products as guided by laboratory parameters, as well as point of care tests. The recombinant factor VIIa may be safely used to achieve haemostasis in patients with DIC and bleeding as a complication of HELLP syndrome.[14] The optimal treatment for maternal safety is an urgent delivery. If the pregnancy is >34 weeks gestation, immediate induction is recommended. If gestational age is between 24 and 34 weeks, corticosteroids are administered to accelerate foetal lung maturity in preparation for delivery 48 h later.

In 2% cases of the HELLP syndrome, severe spontaneous bleeding into the liver with haemorrhagic liver cell necrosis and rupture of the organ occurs. Despite surgical interventions, HELLP syndrome-associated liver rupture has 39% mortality, with haemorrhagic shock and organ failure being responsible for majority of the deaths.[15] These patients typically present in the third trimester with severe right upper quadrant pain, pyrexia, anaemia, leucocytosis and increased aminotransferase concentrations in excess of 3000 IU/L. Acute complications include acute respiratory distress syndrome, acute kidney injury and hypovolemic shock. Computed tomography (CT) and magnetic resonance imaging help to identify these pathologies.

Management of subcapsular haematoma, haemorrhage and rupture includes interventions such as exploratory laparotomy, packing, haematoma evacuation, hepatic artery embolisation/ligation and laceration suturing.[16] In a retrospective study of 3090 patients undergoing LT, it is reported that about 0.3% transplants were performed for complications of HELLP syndrome. The foetal and early maternal survival rate was 75% and 88%, respectively. In the study, 10 years patient and graft survival rates of 65% and 48%, respectively, supports the lifesaving procedure of LT.[17] Shames *et al*. have also reported a favourable survival rate of 83% in transplants for HELLP syndrome based on their experience and a compilation of total worldwide experience of 17 liver transplants for HELLP syndrome in 2005.[18] The main indications for the liver transplant were liver failure, liver necrosis after rupture, and uncontrollable bleeding. Patients with complicated HELLP syndrome are best managed at a centre with expertise in LT. Literature review suggests an increasing trend toward conserving the pregnancy in contrast to expedite delivery as was practised before. The availability of better intensive care and option for the liver transplant in face of severe and irreversible deterioration of liver functions is one of the main reasons for this changing trend.

Acute fatty liver of pregnancy

Acute fatty liver of pregnancy is a life-threatening condition, frequent in the third trimester or early postpartum, with an incidence of 5/100,000.[19] It is associated with 18% maternal and 23% foetal mortality.[20] Maternal mortality is usually secondary to sepsis, renal failure, circulatory collapse, infection, pancreatitis or gastrointestinal bleeding.[21] Although the exact pathogenesis is unknown, this disease has been linked to an abnormality in foetal fatty acid metabolism.

Early diagnosis of AFLP can be difficult because of an overlap of the clinical and laboratory findings with other common conditions such as pre-eclampsia, viral hepatitis, cholelithiasis and cholestasis of pregnancy. A high index of suspicion with a careful history, physical examination, laboratory and imaging results, are often sufficient to make the diagnosis, and liver biopsy is rarely indicated.[21]

The micro-vesicular infiltration in AFLP substantially decreases the metabolic activity of the liver, thus leading to an increase in the serum bilirubin levels. Severe jaundice, coagulopathy, hepatic encephalopathy, ascites and hypoglycaemia in presence of a normal erythrocyte morphology and haptoglobin levels are pathognomonic of AFLP. Typical laboratory findings are elevated aminotransferases-aspartate transferase (AST) elevation greater than alanine transferase (ALT), both <6 times above upper limit of normal, hyperbilirubinemia, hyperuricemia, high white blood cell (WBC) count (above 15,000 cells/μL), hypoglycaemia, high ammonia and coagulopathy with or without DIC. The symptoms of elevated WBC count in combination with other systemic inflammatory response syndrome criteria like

tachycardia, tachypnoea or fever in combination with encephalopathy, renal and hepatic dysfunction can easily be mistaken for sepsis causing delay in delivery/caesarean section, which is the only therapy in AFLP.[22] Since the patients suffering from ALF due to AFLP have the potential for full recovery, the management and transfer into a tertiary care hospital with the possibility of maximal supportive care is essential to ensure the best possible outcome for mother and child. Before delivery, maternal stabilisation should be achieved, which includes airway management, correction of hypoglycaemia, electrolyte and coagulation abnormalities. Careful maintenance of intravascular volume with appropriate fluids and blood products, frequent maternal vital signs assessment, and evaluation of changes in mental status are crucial. After delivery, an intensive supportive care should be continued. Supportive care and management of complications should be instituted along with the management of ALF. Orthotopic LT (OLT) should be considered for those women with ALF, who manifest signs of irreversible liver failure despite delivery and aggressive supportive care.[23] Successful use of molecular absorbent recirculating system (MARS) in a 31-year-old woman presented with severe AFLP at 32 weeks of gestation is reported.[24] MARS was started on post-operative day 4 of caesarean section as a life-saving measure because of hepatic and renal dysfunction and oedema of the brain. MARS significantly reduced the levels of both water-soluble and albumin-bound substances and also improved the haemodynamics, clotting, hepatic, renal, neural and pulmonary function.[24] However, further randomised, controlled trials are needed before MARS can be properly validated for use in pregnant patients with ALF.

VIRAL HEPATITIS

Pregnant women may be more vulnerable to hepatitis E virus (HEV), particularly from endemic countries like India. It is suggested that diminished cellular immunity and high level of steroid hormones influence viral replication/expression during pregnancy and are responsible for the increased severity of the disease.[25] In a prospective study of 97 pregnant women with jaundice in the third trimester of pregnancy, 45.2% had HEV infection and 9% were complicated by fulminant liver failure. Of these patients with fulminant hepatic failure, HEV was responsible for 81% of the cases.[26] In other prospective studies evaluating pregnant patients with acute hepatitis caused by HEV, progression to ALF has been reported in 15–60% of the patients.[27] The incidence of hepatitis A virus, hepatitis C virus and hepatitis D virus is low in both pregnant and non-pregnant women.

Pregnancy with viral hepatitis usually presents with jaundice and liver test abnormalities without other organ system involvement. Transaminases were elevated to a much higher level (>10 times normal) in viral hepatitis. Hepatitis E in pregnancy is associated with high rates of preterm labour and mortality.[26] The main dangers of fulminant liver failure on foetal outcome are an increased incidence of foetal malformations, preterm labour, abortion, dead foetus in the uterus and stillbirth.[27]

Herpes simplex virus (HSV) hepatitis should also be included in the differential diagnosis for liver failure during pregnancy. The restricted T cell function that occurs in the third trimester in order to prevent rejection of the foetus is thought to allow the development of systemic HSV infection. Features suggestive of HSV hepatitis are an absence of jaundice and a marked elevation of AST and ALT with a very high AST/ALT ratio. Empiric treatment with acyclovir should be considered.[28] In neonates, disseminated HSV infection has a mortality of 29% and is associated with significant long-term sequelae.[29]

Therapeutic termination of pregnancy has not been fully explored in hepatitis. However, in a retrospective study of 42 pregnant women with HEV-induced liver failure, Banait *et al*. found that there was no difference in maternal mortality in pregnant women who delivered and those who did not, questioning the role of therapeutic termination.[30]

BUDD–CHIARI SYNDROME

The most common causes of Budd–Chiari syndrome include myeloproliferative disorders.[31] Hypercoagulability associated with protein C, protein S, antithrombin III deficiency as well as pregnancy itself poses risk factors for the development of this disease.

Ascites may develop rapidly in these patients if the obstruction is large. Workup of this disease includes Doppler ultrasonography of the right upper quadrant of the abdomen, followed by abdominal CT scanning. Venography is the 'gold standard' for diagnosis because it will demonstrate the site of occlusion.

Treatment of BCS in pregnancy is controversial because a balance between maternal health and foetal outcome may be difficult to achieve. Unless contraindicated by bleeding disorders, anticoagulation is advocated.[32] The choice of drug for anticoagulation and prevention of further thrombosis is heparin. Surgical intervention to decompress the liver or transjugular intrahepatic portosystemic shunt placement in the presence of the gravid uterus can be technically difficult. LT has been shown to be effective in up to 88% of patients in combination with anticoagulation.[33]

LIVER TRANSPLANTATION IN ACUTE LIVER FAILURE IN PREGNANCY

Liver transplantation for pregnancy-associated liver failure is uncommon, and information regarding the indications for and outcomes of transplantation is limited for both the patient and the graft.[16] In patients with pregnancy-induced ALF, the King's criteria have not been validated and no patient with pregnancy-associated ALF was included in the original cohort when the criteria were established; thus, application of King's criteria in this individual cohort of patients is questionable.[34] The indications for LT in HELLP syndrome are persistent bleeding despite surgical intervention, extensive liver necrosis or liver failure.[18] Liver transplantation for AFLP is sporadic.[34] Outcomes appear largely favourable. The timing of foetal delivery with respect to the time of OLT in cases in which delivery will not likely contribute to improving the patient's condition is controversial. Previable procedures have variable foetal outcomes.[35] Cases have been reported of previable transplantation that resulted in live-born infants post-viability.[2,36] However, a case of postviable transplant is reported with favourable foetal outcome. The transplant was conducted at 27 weeks for cryptogenic ALF and subsequent delivery of a healthy infant at 39 weeks gestation with caesarean section.[37] There are case reports where postviable OLT was performed between 26 and 27 weeks gestation, associated with neonatal death 2–14 days after transplant.[35] However, successful outcome of combined OLT and caesarean section at 32 weeks' gestation for BCS has also been reported.[38]

ANAESTHESIA CONSIDERATIONS

Anaesthetic plan needs to be modified keeping in view the anticipated problems of coagulopathy, haemodynamic instability and hepatic failure. Regional anaesthesia is contraindicated in view of the inherent coagulopathy associated with ALF. General anaesthesia is administered for LT. The inhaled anaesthetic of choice is isoflurane as it preserves the hepatic arterial buffer response, has fewer effects on hepatic blood flow and has less hepatic metabolism. Sevoflurane and desflurane undergo less hepatic metabolism than halothane or enflurane. Of all the inhaled anaesthetics, halothane is associated with the greatest risk of hepatotoxicity.[39] Among intravenous anaesthetic agents, the negative inotropic and vasodilatory effect with propofol induction may cause transient haemodynamic instability which can be managed with vasopressors. Thiopentone is the agent of choice for induction as its effect is terminated by the biodistribution and not hepatic metabolism. The effects of neuromuscular blocking agents may be prolonged in patients with liver disease because of impaired metabolism. The corticosteroid and magnesium therapy should be taken into consideration in anaesthetic plan as corticosteroid increases blood sugar level requiring aggressive management by insulin infusion whereas magnesium sulphate potentiates and prolongs the effect of muscle relaxants. Atracurium is recommended as the muscle relaxant of choice because of non-hepatic metabolism. Intraoperative and post-operative analgesia may be managed with fentanyl and paracetamol with increased duration between doses.[40]

SUMMARY

The availability of expert care in transplant surgery, hepatology, intensive care medicine, anaesthesiology, interventional radiology and neonatology must be considered when one is presented with a pregnant patient in ALF. Speedy diagnosis and treatment are crucial for management. In case of severe deterioration of hepatocellular function, LT is increasingly being considered as a treatment option especially in PAALD. When ALF complicates pregnancy, mortality approaches 40%, and LT is the only viable alternative. The diagnosis should be considered early with consultation regarding termination of the pregnancy. Management protocols need to be individualised for each case keeping in mind the risk versus benefit to both the mother and the foetus.

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