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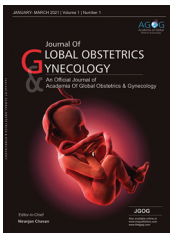

Acute Hepatic Failure in Pregnancy: An Overview on Causes, Management, and Challenges

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ABSTRACT

Aim: The etiologies of acute liver failure (ALF) during pregnancy include causes that occur in the general population as well as pregnancy-specific disorders. Acute fatty liver of pregnancy (AFLP) is a rare and fatal complication that can only be treated by terminating the pregnancy. **Methods:** This article will focus on the etiology, presentation, and management of ALF by providing a narrative review of the existing literature and discussing controversies regarding the optimal management of the disease. **Results:** Following the termination of a pregnancy, supportive care for AFLP should be offered, albeit liver transplantation (LT) may be required. Other etiologies for ALF include viral infections, drug-induced hepatitis, and autoimmune hepatitis as well as idiopathic causes. Although maternal outcome is prioritized, managing ALF during pregnancy is challenging since both maternal and fetal well-being must be considered. There have been reports of ALF during pregnancy for causes other than AFLP, and some of these cases have been managed based on the underlying cause, while others have resulted in LT. The overall outcome is determined by the etiology of liver failure, timely diagnosis, and prompt treatment in a well-equipped multidisciplinary center. **Conclusions:** This review explores the uncertainties surrounding interventions in the management of ALF and whether pregnancy should be terminated in specific circumstances.

Key words: Disease management, Hepatic failure, Hepatitis, Liver failure, Pregnancy

INTRODUCTION

The liver is the second largest organ in the body and serves various functions. The following are some of the key functions of the liver: (1) Bilirubin conjugation and clearance, (2) Bile production, which aids in the removal of waste and the breakdown of lipids in the small intestine, (3) Synthesis of the majority of plasma proteins and amino acids, the building blocks of the proteins, (4) Production of cholesterol and specific proteins to aid in the transport of lipids throughout the body, (5) Conversion of surplus glucose to glycogen for storage as well as synthesis of glucose itself, (6) Processing of hemoglobin (Hgb) for use of its iron content (the liver stores iron), (7) Conversion of poisonous ammonia to urea, (8) Clearing the drugs and toxins, (9) Regulating blood coagulation, and (10) Facilitating antibacterial immune responses by the production of complement system factors. As a corollary when liver dysfunction occurs, the following presentations may arise: hypoglycemia, hypocholesterolemia, hypoalbuminemia, anemia, thrombocytopenia, and coagulation disorders. Albumin serves several functions in the body, acting as an oncotic (50–60% of total blood protein) protein with considerable binding capacity, and anti-oxidant and anti-inflammatory properties. Albumin also has a role in hemostasis, vasodilation, and acid-base hemostasis. Given these important roles, low albumin is a prognostic factor in hepatic failure. In the liver dysfunction, in addition to reducing the amount of albumin, its quality also decreases due to oxidation. Changes that occur in the coagulation system include thrombocytopenia and impaired production of coagulation factors. Both the platelet count decreases and its function is impaired. Thrombocytopenia is mild-to-moderate and platelet count rarely plummets below 30,000/mcl. Causes of thrombocytopenia are splenomegaly secondary to portal hypertension, bone marrow (BM) suppression due to folate deficiency or alcohol consumption

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in patients with liver dysfunction, impaired hepatic production of thrombopoietin (TPO), platelet activation, and increase in consumption. TPO is a glycoprotein hormone produced by the liver and kidney which regulates the production of platelets. In hepatic failure, factor VIII and Von Willebrand factor (VWF) increase due to decreased clearance by the liver, and dysfunction of platelets is due to high VWF. Other coagulation factors (I, II, V, IX, X, XI, factor C, S, and anti-thrombin) are decreased due to impaired production of them by the liver. In addition to reducing factor I (fibrinogen), there is also a fibrinogen dysfunction (dysfibrinogenemia) due to its abnormal production. Vitamin K-dependent coagulation factors include factors II, VII, IX, and X. Decreased bile flow decreases absorption of Vitamin K in the small bowel and leads to coagulopathy. Gamma-glutamyl transpeptidase (GGT) is a transport molecule that is concentrated in liver cell membranes and microsomes and has a significant role in helping the liver to metabolize drugs and other toxins and increases liver damage.

There are two types of liver failure: Acute and chronic. The acute type occurs within days to weeks and early symptoms include nausea, vomiting, diarrhea, and loss of appetite, but as liver failure progresses, the symptoms become more serious (jaundice, bleeding tendency, mental confusion, etc.). Some causes of acute liver failure (ALF) include Acetaminophen overdose, viruses including hepatitis A, B, and E, Epstein–Barr virus (EBV), cytomegalovirus, herpes simplex virus (HSV), herbal medications, autoimmune hepatitis, Wilson's disease (WD), septic shock, Budd–Chiari syndrome (BCS), toxins, and acute fatty liver of pregnancy (AFLP). In some cases, no cause is determined. Here, we will discuss more about the acute causes of liver failure. Moreover, we need to know the liver changes in pregnancy.

EFFECTS OF PREGNANCY ON LIVER

Progressive increases in estrogen and progesterone in pregnancy have effects on hepatic metabolic, synthesis, and excretory functions: Increased synthesis of clotting factors, decreased biliary excretion in late pregnancy, and decreased serum level of proteins due to hemodilution. Albumin is decreased due to hemodilution as early as the first trimester. The decrement becomes more accentuated as the pregnancy advances. The liver enzymes, total bile acids, lactate dehydrogenase (LDH), prothrombin time (PT), international normalized ratio (INR), and partial thromboplastin time (PTT) in pregnant women do not change compared to non-pregnant women. Bilirubin and GGT decrease during pregnancy, but alkaline phosphatase (ALP) and fibrinogen increase during pregnancy. Hence, increased liver enzymes, bilirubin, bile acids, GGT, PT, and PTT, and decreased fibrinogen are pathologic in pregnancy.

The reference range of liver tests in pregnancy: (1) Albumin: First trimester (3.1–5.1 g/dl), second trimester (2.6–4.5 g/dl), and third trimester (2.3–4.2 g/dl), (2) AST, ALT: 7–32 IU/L, (3) ALP: 38–229 U/L, (4) PT: 11–13.7 s, (5) PTT: 30–40 s, (6) LDH: 80–524 U/L, (7) Total bilirubin: 0–1 mg/dl, (8) direct bilirubin: 0–0.4 mg/dl, (9) fibrinogen: 373–619 mg/dl, (10) GGT: 5–36 IU/L 11- Amonia: <30 μ/L.[1,2]

LABORATORY CHANGES IN HEPATIC FAILURE

Laboratory changes in liver dysfunction include: Hypoalbuminemia (<3.1 g/dl in the first trimester, <2.6 g/dl in the second trimester, and <2.3 g/dl in the third trimester of pregnancy), hypoglycemia (blood sugar <55 mg/dl), hypolipidemia (total cholesterol <120 mg/dl or LDL <50 mg/dl), hyperbilirubinemia (unconjugated bilirubin >1 mg/dl, conjugated hyperbilirubinemia is defined as a measure of direct bilirubin >1 mg/dl if the total bilirubin <5 mg/dl or more than 20% of total serum bilirubin, and jaundice detected clinically in bilirubin above 2 mg/dl), thrombocytopenia (platelet count <150,000/mcl), anemia (hemoglobin <11 g/dl), leukopenia (<4.4 * 10^9 cells/L) or leukocytosis (>15,000 cells/L), hyperamonemia (>30 μ/L), coagulopathy (high INR and low fibrinogen) (INR > 1.1, fibrinogen <150 mg/dl), and increased creatinine (Cr > 0.9 mg/dl) due to hepatorenal syndrome.

Some liver diseases are specific to pregnancy such as intrahepatic cholestasis of pregnancy and AFLP, some are multi-systemic diseases with hepatic manifestations such as pre-eclampsia (PE), and some diseases are not related to pregnancy but can initially present in pregnancy or may be worsened by pregnancy. The cause that is specific to pregnancy and can lead to liver failure is AFLP. In this article, we review and discuss various causes of ALF, related and unrelated to pregnancy and their management. The challenge is that any hepatic failure in pregnancy should be terminated.

Causes of ALF in pregnancy:

1. Conditions unique to pregnancy: AFLP, PE
2. Conditions unrelated to pregnancy: Drug-induced, toxins, shock, trauma, and decompensation of preexisting liver disease.
3. Conditions exacerbated by pregnancy: Viral hepatitis, BCS
4. We will discuss AFLP and then other causes of ALF in pregnancy.

DISCUSSION

Because ALF in pregnancy is rare, especially for causes other than AFLP, we have little information about how to properly manage their pregnancy. Perhaps, because AFLP is fatal and a medical emergency, we terminate all ALF pregnancies because it is difficult to differentiate it from other causes. Another reason is that the opportunity for treatment may be lost until the results of specialized tests become ready. Many cases that have other causes for liver failure are identified in post-termination evaluations or post-mortem autopsies. Differentiation of AFLP from other causes of ALF unrelated to pregnancy is especially important in cases that occur at early gestational age or lab tests are not completely typical of ALF or our clinical suspicion is high for these causes such as hepatitis E in endemic areas or a case with history of autoimmune hepatitis. In these cases, a good history and physical examination are very important and helpful. The majority of causes of ALF

during pregnancy requiring liver transplantation are reported to be unknown.[3] The question is whether all pregnancies with ALF for any reason should be terminated? Do they benefit from termination of pregnancy? Or is it different depending on the cause and gestational age of presentation? Is the self-limited course of the underlying disease important in our decision-making? For example in hepatitis E. Another issue is with liver transplantation (LT) during pregnancy, can post-transplantation medications can be used during pregnancy? It is clear that ALF due to pregnancy-related causes benefits from termination of pregnancy, as well as curable non-pregnancy-related causes also don't benefit from termination of pregnancy. The biggest challenge is when there are incurable causes that lead to LT or causes that get worse with pregnancy.

Causes that lead to ALF and are curable in some situations: Hepatitis E virus (HEV) (it may be self-limited with supportive care), Acetaminophen overdose (ALF prevented by administration of N-acetylcysteine [NAC]), HSV (treatment with acyclovir) and autoimmune hepatitis (AIH) (treatment with corticosteroids [CSs]), BCS (treatment with anticoagulants and radiological interventions), Willson's disease (WD) (copper chelation medications in some cases).

AFLP

AFLP is a rare and catastrophic obstetric emergency characterized by maternal liver dysfunction that can lead to maternal and fetal complications. It affects women in the third trimester of pregnancy or the postpartum period. It is associated with a high mortality rate due to rapid progression to death, so early diagnosis and prompt delivery to improve prognosis is necessary. The prevalence is now estimated to be 1–3 cases/10,000 deliveries.[4] It is characterized by micro-vesicular fatty infiltration of the liver. It can cause multi-organ failure and is an obstetric emergency. The pathogenesis is unclear, but there is evidence of the genetic basis where defective mitochondrial fatty acid beta-oxidation in the fetus is implicated in some cases of AFLP.[5] Potential risk factors are nulliparity, low body mass index (BMI), male fetal sex, multiple gestation, and prior episodes of AFLP. Symptoms of this disease are quite vague and its diagnosis requires strong clinical suspicion. The symptoms are non-specific and include: Nausea, vomiting, feeling unwell (malaise), abdominal pain, anorexia, confusion, and jaundice. Signs and symptoms of AFLP, including jaundice, ascites, encephalopathy, disseminated intravascular coagulopathy, hypoglycemia, renal failure (RF), and finally multi-organ failure rapidly develop.[6] Hepatorenal syndrome is a kind of RF in liver failure patients whose kidney function reduces without intrinsic kidney disease such as hematuria, proteinuria, or abnormal kidney ultrasound. It results from functional changes in the renal circulation and vasoconstriction. It presents with oliguria, decreased glomerular filtration rate, and increased Cr. transient central diabetes insipidus (DI) is another complication of AFLP. It is characterized by polyuria, polydipsia, and dehydration and leads to electrolyte imbalance. The changes in the laboratory tests are the same as those mentioned above in hepatic failure. Furthermore, all women with AFLP have elevations in liver enzymes (AST and ALT), usually ranging from 5 to 10 times the upper limit of normal. Liver ultrasound is not diagnostic for AFLP. It is important to differentiate this disease from other diagnoses. The most common differentials are severe PE, HELLP, and other causes of ALF other than AFLP (causes that are unrelated to pregnancy), each of which will be explained separately. Hypertension is present in up to 50% of patients with AFLP,[7] so it can be difficult to differentiate AFLP from severe PE, and the two may coexist. The main treatment is termination of pregnancy regardless of gestational age, followed by supportive care and if necessary, LT. The recognition of milder presentations, early delivery, and maternal supportive care have likely contributed to a decreased maternal mortality rate.

Viral Hepatitis

HEV is the most common cause of ALF in endemic areas such as India and Africa. It is associated with a high rate of maternal and neonatal death. Management is supportive and termination of pregnancy is not recommended as a general rule and it does not improve maternal outcomes.[8] HEV etiology is associated with a better prognosis than other causes of acute hepatic failure.[9] Hepatitis A, B, C, and HSV can also lead to ALF in rare cases. They are associated with marked elevation of AST and ALT. Treatment with acyclovir should be considered in HSV hepatitis. The course of most viral infections is unaffected by pregnancy, however, a more severe course of the disease has been observed in patients with hepatitis E.[10] Despite the worsening course of hepatitis E in pregnancy, termination of pregnancy has not been shown to improve maternal outcomes in a study of 42 pregnant women by Banait *et al.*[11]

Autoimmune Hepatitis (AIH)

AIH is a rare diagnosis in pregnancy, especially in the setting of ALF. Furthermore, ALF as the first presentation of AIH is very rare and there is very limited data on them in the literature. The important point is that patients with AIH may diagnosed in pregnancy by flare and may seem perfectly healthy but had compensated cirrhosis before pregnancy. The diagnosis is based on the presence of autoantibodies, elevated IgG levels, exclusion of other causes, and compatible liver histology.[12] The main treatment is immunosuppressant and the first choice is CSs. We have to keep in mind that we are facing two groups of patients: the group that responds to CSs and the group that may not respond. One of the challenges is how to recognize early on that our patient may not respond to CSs. All responders to corticosteroids[13] had Model Foe End-Stage Liver Disease score <28 at admission or either improvement or stabilization in bilirubin and INR within 3–4 days of initiation of CS therapy.[13] The diagnosis and management are challenging in these cases. About one-third respond to CS therapy and the majority need liver LT.[14] Should the pregnancy be terminated if the patient does not respond to CS therapy and a LT is needed? There have been reports of LT during pregnancy after which the continuation of pregnancy has been successful and the maternal and fetal outcomes have been good.[15-17] Therefore,

the need for a LT is not a definite indication for termination of pregnancy. Sajja *et al.*,[18] reported a pregnant case with ALF in the 17th week of pregnancy that was confirmed by liver biopsy and treated successfully with corticosteroids. Finally, the pregnancy continued to 37 weeks of gestation and resulted in the birth of a healthy baby.

BCS

BCS is a rare syndrome caused by hepatic venous outflow obstruction mainly by thrombosis and resulting hepatic dysfunction due to sinusoidal congestion, ischemic injury to the liver, and portal hypertension. One of the most important risk factors is thrombophilia. The prevalence of pregnancy-related BCS is 6.8%, suggesting that pregnancy might be a relatively common etiology of BCS.[19] Most commonly, the clinical presentation of BCS associated with pregnancy is acute.[20] Therefore, we should consider this diagnosis in cases of ALF, and Doppler ultrasound can be helpful in the diagnosis. The management of BCS is largely successful with anticoagulants, interventional angioplasty, or transjugular intrahepatic portosystemic shunting (TIPS) and LT is needed in cases with failure of these treatments.[21] TIPS procedure has a risk of radiation to the fetus. The accepted safe cumulative dose of ionizing radiation during pregnancy is fim rad and the maximum risk is between 8 and 25 weeks.[22] TIPS procedure lasts about 45 min and the exposure of the fetus is above 5 rad during this procedure.[23] Therefore, when performing this procedure, the gestational age should be taken into consideration and parents should be given detailed counseling. There are reports of cases in which the BCS develops at 18 weeks and is treated during pregnancy and the pregnancy continued after LT with a therapeutic dose of anticoagulants and finally terminated at 31 weeks.[22] Therefore, although the pregnancy itself is a risk factor for BCS, it is not a definitive indication of pregnancy termination.

Systemic Lupus Erythematosus (SLE), Antiphospholipid Antibody Syndrome (APS)

SLE is a multi-systemic autoimmune disease and its spectrum of hepatic involvement ranges from abnormalities in LFT to fulminant hepatic failure. Liver involvement is not common in the early disease course, especially as the primary presentation. SLE can be associated with other autoimmune liver diseases such as AIH and primary biliary cirrhosis (PBC) (overlap syndrome).[24] AIH-SLE overlap syndrome is not distinguishable from lupus hepatitis because the clinical and biochemical features are very similar.[25] The most common pathological finding found in liver histology of SLE patients is fatty liver.[26] Moreover, Takahasi *et al.*[27] reported that 59.7% of SLE cases had liver dysfunction, 30.9% of 123 patients with SLE and liver dysfunction induced by drug, 28.5% caused by SLE itself, 17.9% due to fatty liver, AIH in 4.9%, PBC in 2.4%, cholangitis in 1.6%, alcohol in 1.6%, and viral hepatitis in 0.8% of cases and liver dysfunction usually is mild, except in AIH cases. Increased risk of thrombosis in SLE patients as well as its association with the APS can be involved in the development of portal vein, hepatic artery, splachnic vasculature thrombosis, and BCS and finally lead to liver dysfunction.[28] Mustafa *et al.*[29] reported a case of ALF as the first feature of SLE who presented with abdominal pain. The treatment of this disease is CSs. The problems we face in pregnancy are flare-ups and complications of PE. Differentiating PE from lupus flare can be challenging. It seems that in SLE, similar to AIH, treatment with CSs should be tried, and on the other hand, care should be taken to differentiate PE and HELLP correctly from the adverse effects of lupus. So far, no case of ALF due to SLE has been reported in pregnancy, after considering the mentioned aspects in these patients, it will be very difficult to decide whether to terminate the pregnancy or not. There have also been reports of BCS following APS.[30,31] Therefore, in cases of ALF secondary to BCS, the patient should also be evaluated for APS.

WD

WD is an autosomal recessive disorder of copper metabolism and it also is an uncommon cause of ALF. It can cause ALF due to hepatic copper overload and then hepatic cell necrosis. There have been reports that ALF was the first presentation of WD.[32] Diagnosis is based on high clinical suspicion, the presence of Kayser–Fleischer rings, and reduced serum ceruloplasmin concentration. Main therapies include trientine, penicillamine, and zinc but in cases with liver failure, LT is lifesaving.[33] Liver injury may gradually recover after copper chelation treatment.[34] LT is indicated in end-stage liver disease refractory to medical therapy. Copper chelation medications are contraindicated in pregnancy and it is a major challenge for pregnant women with WD. But in a case series by Malik *et al.*[35] in four cases, they reported successful pregnancy outcomes, all treated with zinc. Furthermore, there are some case reports of normal infants that delivered in cases of pregnant WD who were on penicillamine during pregnancy,[36] but parents' counseling is important in these cases. In normal pregnancy as early as 4–6th week of gestation, the levels of copper and ceruloplasmin start rising. The lower limit in the first trimester is 25 mg/dl, in the second trimester is 30 mg/dl, and in the third trimester is 40 mg/dl.[1] Therefore, it is important to pay attention to these laboratory changes in pregnancy to the diagnosis of WD. There are reports of ALF in pregnancy due to WD.[37] ALF in WD cases alone is not an indication for termination of pregnancy.

Acetaminophen Overdose

It is a common cause of ALF, the most common drug overdose in pregnancy[38] and has a 66% chance of recovery with NAC treatment and supportive care.[39] Acetaminophen crosses the placenta and in toxic doses can cause fetal hepatocyte damage. NAC is safe in pregnancy and can cross the placenta and by binding to toxic metabolites prevents fetal liver damage. The only important point in these patients is a good history and starting treatment with NAC early to reduce the rate of ALF and LT and fetal damage especially when it started before 16 h of ingestion.[38] Rigges *et al.*,[40] evaluated 60 pregnant women with acetaminophen overdose. Of these, 19 women were in the

first trimester of pregnancy, 22 were in the second trimester, and 19 were in the third trimester of pregnancy at the time of overdose. They showed a significant correlation between the time of loading dose of NAC and pregnancy outcome, with an increase in the incidence of spontaneous abortion or fetal death when treatment was begun late. In a study by McElhatton *et al.*,[41] they followed 48 cases of acetaminophen overdose in pregnancy. GourtrBs cases had been exposed in the first trimester of pregnancy, none of the mothers died, and there were 39 live-born infants and two spontaneous abortions after 2 weeks of overdose in the first trimester. They concluded that acetaminophen overdose is not necessarily an indication for termination of pregnancy. Maternal ALF and the need for LT alone is not an indication for pregnancy termination, although in these cases fetal liver damage may lead to intrauterine death and the risk of preterm delivery is higher.[42]

COVID-19 Infection

Mild liver enzyme elevation is common in COVID-19 infection but ALF is a rare event and typically occurs later in the course of the disease.[43] The mechanism of injury is not clear and data is limited about it, but direct viral injury due to ACE2 receptors on hepatocytes surface, immune-mediated inflammatory process, hypoxemia, and drug-induced injury may be involved.[44] When ALF occurs in COVID-19 patients, the prognosis is poor and usually associated with multi-organ damage (lungs, kidneys, heart, and hematologic disorders). Differentiation of changes in liver enzymes and platelet count due to this infection from PE and AFLP may be difficult. Therefore, the decision to terminate a pregnancy will be made based on our clinical judgment.

CONCLUSION

Prompt diagnosis of non-obstetrical causes of ALF in pregnancy is critical to providing the appropriate therapy to achieve optimal pregnancy outcomes. Besides the high maternal mortality rate, the main fetal adverse outcomes are fetal malformations, preterm labor, abortion, and stillbirth.[45] Prospective multicenter studies are needed to address this critical and complex issue. During LT of a pregnant woman, a multidisciplinary approach with hepatologist, transplant surgeon, perinatologist, and anesthesiologist is needed. Furthermore, hemodynamic and volume management is necessary to prevent fetal ischemic damage. Immunosuppressive drugs that can be used in pregnancy after LT are CSs, tacrolimus, cyclosporine, and azathioprine, but mycophenolate mofetil should be avoided.

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DISCLOSURE STATEMENT

The authors declare no conflicts of interest.

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