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Case Report
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Acute Fatty Liver of Pregnancy in the ICU

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Objective: Highlight a less common treatment modality

Background: Acute fatty liver of pregnancy (AFLP) is a rare condition affecting 1 in 7,000 to 16,000 pregnancies in the third trimester of pregnancy. While the primary management remain early diagnosis and expeditious delivery, reported mortality for both mother and fetus remains high, varying from 7 – 85%. AFLP may progress to acute fulminant liver failure requiring transplant. Plasma exchange therapy has, in limited reports, demonstrated decreased mortality and length of ICU stay with postpartum early plasma exchange therapy in severe HELLP syndrome and AFLP. This case report demonstrates a patient diagnosed with AFLP with signs of hepatic encephalopathy who was successfully treated with three rounds of plasma exchange.

Case Report

A 30-year-old Caucasian female who was 32 weeks pregnant with concerns for preeclampsia with severe features (worsening epigastric and right upper quadrant pain, with initial labs notable for a creatinine of 0.238, ALT 389, and AST 186) was admitted to hospital for expectant management. Her past medical history included provoked deep vein thrombosis (DVT) after an ankle fracture, for which she was taking 40mg enoxaparin daily.

After admission, external fetal monitoring showed absent variability with recurrent decelerations. Maternal vitals remained within normal limits. Due to signs of fetal distress in the setting of preeclampsia, the decision was made to perform an urgent Cesarean section delivery. The procedure was started under spinal anesthesia with 12mg bupivacaine and 200 mcg intrathecal morphine. After an inconclusive Alice test, this was converted to general anesthesia via rapid sequence induction using 120mg propofol and 100mg succinylcholine. There were no surgical or airway complications, and she was extubated without incident at the end of the procedure. On postop day (POD) 1, the patient's coagulation studies (PT 30.3, INR 3.0, PTT 71), liver enzymes (ALT 238, AST 120), kidney function (Cr 2.73 mg/dL), and white cell count (WBC 28.62) continued to deteriorate, along with recurrent episodes of hypoglycemia (as low as 30 mg/dL), and afibrinogenemia (fibrinogen < 60 mg/dL). She was subsequently upgraded to the ICU due lab abnormalities concerning for acute liver failure and acute kidney injury. The abnormal coagulation was corrected with 2 units (204 mL) of FFP and 2 units (244 mL) of cryoprecipitate. Duplex ultrasound of the liver and portal vein system showed multiple high intensity transient signals (HITS) in the portal vein, right and mid hepatic veins, and within the inferior vena cava, suggesting multiple microemboli. Hemolysis workup showed elevated LDH (451 u/L) and non-detectable haptoglobin (< 10 mg/dL), suggesting intravascular hemolysis. An initial peripheral smear on POD 1 did not show schistocytes, however these were present on subsequent smears on POD 2 and 4, further indicating hemolysis. The patient's overall laboratory picture of elevated LFTs, elevated bilirubin, coagulopathy, fibrinogenopenia, elevated ammonia (68 umol/L), and lactic acidosis suggested acute liver failure. The patient's MELD score at the time was 37, and her mental status declined over the first few days to a GCS of 12-13 by POD 3. The patient displayed elements of both HELLP (hemolysis, elevated liver enzymes and low platelets (148 K/uL)) and acute fatty liver of pregnancy (AFLP) meeting nine Swansea Criteria. She underwent three plasmapheresis treatments, with subsequent improvement in LFTs, lactate, and coagulopathy. Daily liver duplexes demonstrated improvement in liver perfusion. Patient was downgraded from the ICU on POD 11, and discharged home after 19 days hospitalization.

Table 1: Changes in Laboratory Test Values Before and After the First PEX Treatment with 2,700 mL of FFP.

Parameter	Before first PEX	After first PEX
ALT (U/L)	238	58
AST (U/L)	120	44
TBIL (μmol/L)	8.8	4.4
BUN (mmol/L)	20	22
Cr (μmol/L)	2.73	2.43
PT (s)	30.3	19.2
Fibrinogen	< 60	166
Plt	202	148

Abbreviations: ALT (alanine transaminase); AST (aspartate aminotransferase); TBIL (total bilirubin); BUN (blood urea nitrogen); Cr (creatinine); PT (prothrombin time); ALB (albumin); Plt (platelets); FFP (fresh frozen plasma).

Discussion

Acute fatty liver of pregnancy (AFLP) is an idiopathic microvesicular fatty liver disease that typically occurs in third trimester of pregnancy [1]. It is characterized by abdominal pain, nausea, vomiting, elevated transaminases and bilirubin, and significant coagulopathy, with renal failure, encephalopathy, and DIC being some of the most significant complications [2]. Onset can occur suddenly, with fulminant hepatic failure, hepatic encephalopathy and coagulopathy in women with no prior history of liver disease [3].

HELLP, an acronym for hemolysis, elevated liver enzymes, and low platelets, is a syndrome considered a complication of severe pre-eclampsia [4,5]. Prevalence is estimated to occur in 0.2 – 0.6% of all pregnancies, with a risk of recurrence in later pregnancies from 19 – 27% [6,7]. With significant overlap of symptoms and lab findings of HELLP and AFLP it can sometimes be difficult to distinguish between the two disorders in an individual patient. As such, many consider preeclampsia, HELLP syndrome, and AFLP to be different stages or manifestations of the same disease [1,8]. Patients may even concurrently have AFLP and HELLP or preeclampsia with severe features [9]. That being said, multi-organ involvement (especially renal failure) and severe signs and symptoms of hepatic insufficiency are more consistent with AFLP than HELLP or severe preeclampsia [9]. To diagnose AFLP, at least six of Swansea's criteria must be met: nausea, abdominal pain, polydipsia/polyuria, encephalopathy, hypoglycemia, hyperuricemia, leukocytosis, ascites, increased hepatic aminotransferase, increased bilirubin, increased ammonia, renal failure, coagulopathy with increased prothrombin time, microvesicular steatosis on liver biopsy, metabolic acidosis, or pancreatitis [10].

While the exact cause and pathogenesis are unknown, there is a well-established association between AFLP and inherited defects in beta-oxidation of fatty acids [3]. The body uses several different enzymes to break down fatty acid stores for energy. Defective or deficient enzymes lead to fatty acid oxidation disorders (FAOD). Inability to break down fatty acids in times of energy depletion (such as illness or prolonged fasting) leads to accumulation of intermediate products of metabolism in maternal blood and hepatocytes. Additionally, hormonal changes during pregnancy are associated with decreased oxidation of long- and medium-chain fatty acids, resulting in an increased maternal serum level of fatty acids [11]. In at-risk patients, this may lead to diffuse infiltration of fat in hepatic cells, hepatocyte swelling, slight necrosis and inflammation of hepatic cells [3]. Approximately 20 percent of AFLP cases are associated with LCHAD (long chain 3-hydroxyacyl coenzyme A dehydrogenase) deficiency, an enzyme involved in β-oxidation of fatty acids in mitochondria [1,9]. When the fetus is also affected by fatty acid oxidation disorders, elevated fetal levels of intermediate products of fatty acid metabolism enter the maternal circulation, further contributing to maternal hepatotoxicity and mitochondrial dysfunction [11,12]. A hallmark of AFLP, miscrovesicular fatty steatosis of the liver impairs hepatic production of cholesterol, fibrinogen, and coagulation factors, with decrease in bilirubin conjugation and clearance [11]. Onset of signs and symptoms of acute liver failure, including jaundice, ascites, encephalopathy, DIC, and hypoglycemia typically develop rapidly. Most patients develop acute kidney injury, and often progress to multi-organ failure.

The incidence of AFLP has been reported as affecting 1 in 7,000 to 16,000 pregnancies in the third trimester of pregnancy [3]. Reported mortality of AFLP has varied from 7 to 85%, with maternal mortality in HELLP being 1 – 25% [3,6]. AFLP usually resolves completely after delivery, with return of normal liver function within 7 to 10 days [9]. After pregnancy termination via cesarean or vaginal delivery, the classic treatment has included protective measures such as treatment of anemia and hypoglycemia, electrolyte regulation, acidosis correction, replacement of coagulation factors, sometimes requiring liver transplant [13]. Postpartum plasma exchange (PPEX) therapy has been successfully used in patients with multi-organ failure, DIC, or who are refractory to supportive therapies [6,14]. In several studies, PPEX was initiated 2-8 days following delivery

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and repeated (two to four times, mean=3) at 24-48-h intervals thereafter [15]. Earlier initiation of plasmapheresis has been shown to be associated with better outcomes, reduced duration of hospital stay, and reduced number of plasmapheresis sessions [3,16-18].

Plasma exchange therapy is an extracorporeal treatment in which the patient's blood is passed through an apheresis machine that separates blood components (plasma and/or cellular components) from the patient's blood for the treatment of conditions in which a pathogenic substance in the blood is causing morbidity [19,20]. It is most commonly used for removing antibodies, toxins, or abnormal proteins from the patient's plasma [13,21]. Because a large quantity of plasma must be removed during PEX, it must be replaced with sufficient physiological fluid (FFP or albumin) to maintain the intravascular compartment [21]. While an overall fairly safe procedure, contraindications include: non-availability of central line access or large bore peripheral lines, hemodynamic instability or septicemia, known allergy to fresh frozen plasma or replacement colloid/albumin, known allergy to heparin. Relative contraindications include hypocalcemia (restricts the use of citrate as an anticoagulant during the procedure) and angiotensin-converting enzyme (ACE) inhibitor used in last 24 hours [20,21].

Several suggested mechanisms of PPEX's therapeutic effects include: 1) removal of harmful substances (such as ammonia, endotoxins, bilirubin, and inflammatory cytokines); 2) fresh frozen plasma provided during PPEX replaces coagulation factors, reducing bleeding and incidence of multi-organ dysfunction syndrome, and helping reverse intravascular coagulation; 3) PPEX can remove renin-angiotensin and other vasoactive factors, reducing renal vasoconstriction and increasing renal perfusion; 4) PPEX can supply plasma albumin, opsonin, immunoglobulins, and other biologically active substances to help enhance the body's immune function [23]. PPEX therefore essentially acts as an "artificial liver", protecting liver cells by reducing mitochondrial damage from oxidative stress [24].

In a study with patients with HELLP syndrome, plasma exchange procedure was started within the first two postpartum days, with daily treatments until end goal of platelet counts greater than 100,000/μL and/or normal LDH levels (<500IU) were reached. A median of 4 apheresis procedures were performed (range 1-15), with FFP used for replacement [6]. The maternal mortality rate in this study was 23% (6/26) in the control group, with no deaths in the plasma exchange group [6] who also experienced a shorter length of stay in the ICU.

Conclusion

It is our conclusion, as demonstrated in our case and available literature, that postpartum plasma exchange is an effective treatment in Acute Fatty Liver of Pregnancy. While initial treatments are typically supportive, earlier initiation of plasmapheresis has been shown to decrease mortality, duration of hospital stay, and number of plasmapheresis sessions. We therefore recommend early initiation of plasma exchange in AFLP patients with signs of organ failure, DIC, or conditions refractory to supportive therapies.

Name of Department and Institution where work was done

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