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REVIEW

Acute fatty liver disease of pregnancy

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EPIDEMIOLOGY

Acute fatty liver of pregnancy (AFLP), originally known as "acute yellow atrophy of the liver," is an obstetrical and medical emergency that is characterized by microvesicular fatty infiltration of hepatocytes.[1] AFLP is rare, with studies demonstrating incidences ranging from 1 in 4000 to 1 in 20,000 pregnancies.[2–6] Despite its infrequency, it is critical to be able to diagnose and manage this condition promptly due to its high perinatal and maternal mortality rates.

AFLP is associated with prior AFLP, nulliparity (a pregnancy in a woman that has never given birth), low body mass index, male gender of the fetus, and multiple pregnancies (a pregnancy with more than 1 fetus).[2,6–8] AFLP is strongly linked with fetal fatty acid oxidation defects, though the precise pathophysiology is unknown. Long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency is most commonly associated with AFLP.[9,10] One study showed up to a 50-fold increased risk of maternal liver disease (either AFLP or HELLP [hemolysis, elevated liver enzymes, and low platelets syndrome]) in infants with an LCHAD deficiency.[11] Homozygous LCHAD deficiency in the fetus leads to the inability to perform mitochondrial beta-oxidation of fatty acids, resulting in the accumulation of long-chain 3-hydroxy fatty acids that pass from the fetal to maternal circulation.[12] Maternal factors of heterozygous LCHAD status, the placental release of long-chain 3-hydroxy fatty acids, increased production of fatty acids during pregnancy, and decreased maternal beta-oxidation of fatty acids, especially in the third trimester likely also contribute to the pathogenesis of AFLP.[12,13] Fatty acid accumulation in the hepatocyte mitochondria produces reactive oxygen species and microvesicular steatosis, resulting in maternal hepatotoxicity (Figure 1).[12] This typically presents as AFLP, though HELLP has also been associated with LCHAD deficiencies through a similar mechanism.[11,14] After birth, LCHAD deficiencies in the infant can present as severe hypoglycemia, myopathies, and multiorgan failure. Due to this strong association, it is imperative for infants of mothers with AFLP to be tested for LCHAD deficiencies.[12,13]

NATURAL HISTORY

AFLP typically occurs in the third trimester of pregnancy or postpartum, with a median presentation of 35–37 weeks. However, cases can still manifest before the third trimester.[2,3,6–8,15] The most common presenting symptoms are nausea and emesis, though patients may also experience epigastric pain, malaise, jaundice, polydipsia, polyuria, and in cases that present as acute liver failure (ALF), encephalopathy (Figure 2).[2,6,7,16] Hypertension or preeclampsia can occur concomitantly. For any patient in the third trimester with a new onset of nausea and emesis, AFLP must be considered.[6]

Lab abnormalities are significant for evidence of liver dysfunction and can distinguish AFLP from other liver disorders of pregnancy.[17] Patients with AFLP typically have elevated transaminases (300–1000), bilirubin, lactate dehydrogenase, and prothrombin time, with low platelets, fibrinogen, and antithrombin III.[17,18] Almost all patients present with acute kidney injury (AKI) early in the disease course, which can differentiate AFLP from other

Abbreviations: AFLP, acute fatty liver of pregnancy; AKI, acute kidney injury; ALF, acute liver failure; HELLP, hemolysis, elevated liver enzymes, and low platelets syndrome; LCHAD, Long-chain 3-hydroxyacyl-CoA dehydrogenase.

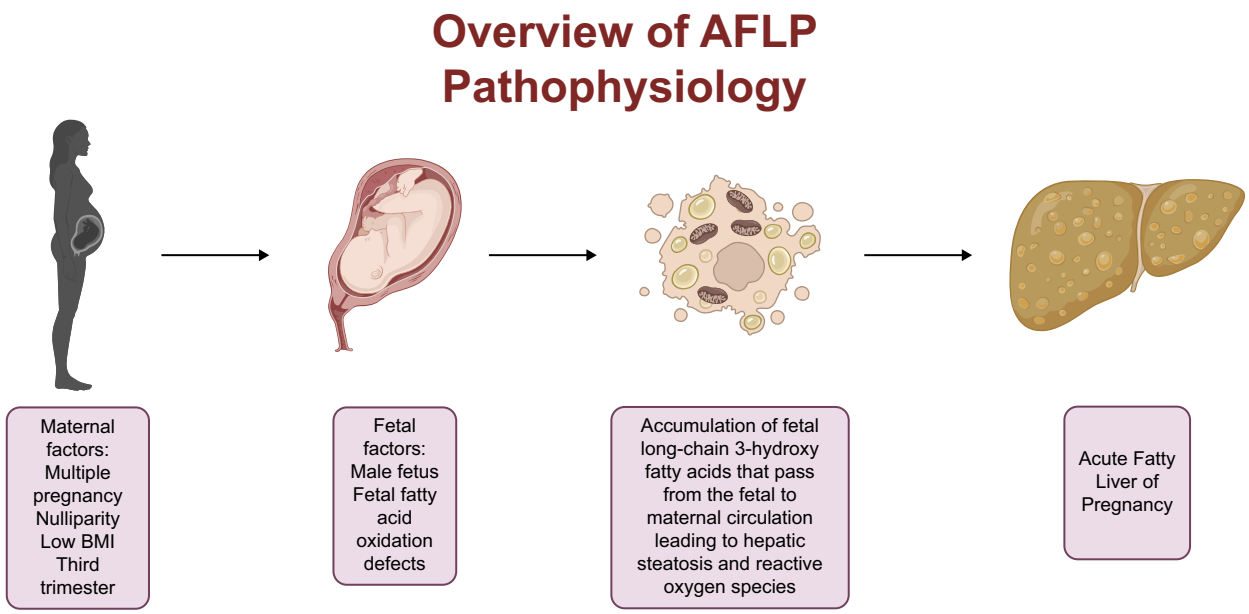

FIGURE 1 Overview of AFLP Pathophysiology. Created with Biorender.com. Abbreviations: AFLP, acute fatty liver of pregnancy; BMI, body mass index.

syndromes. In severe liver dysfunction or ALF, hypoglycemia and severe coagulopathy with complications of disseminated intravascular coagulation can occur.

It is important to be able to distinguish AFLP from preeclampsia/eclampsia and HELLP as immediate delivery is indicated in AFLP, and if progression to ALF occurs, liver transplant must be considered. Maternal mortality rates with AFLP have decreased from 80% to 90% before 1970 to less than 10% more recently due to rapid delivery.[16,19] AFLP and HELLP can present with similar symptoms, including elevated transaminases, preeclampsia/eclampsia, and proteinuria within the same pregnancy time frame (Table 1). One study compared the presentation findings of the syndromes and found that AFLP predominantly presented with nausea, vomiting, jaundice, and AKI, while HELLP initially presented with headache and abdominal pain without AKI.[18] Importantly, coagulopathy is caused by liver dysfunction in AFLP, while in HELLP, it is initially caused by hemolysis, though in rare instances, HELLP can also progress to liver failure.[2] In addition, although both have similar lab findings, patients with AFLP are found to have higher white blood cell count and lower glucose, cholesterol, triglyceride, antithrombin, and fibrinogen levels than patients with HELLP.[6,18,20,21] It is imperative to distinguish between these diseases because initial treatment differs for the 2 syndromes, even though delivery is often the ultimate management for both (Figure 3).

DIAGNOSIS

The Swansea Criteria are used to bring uniformity to the diagnosis of AFLP. They are defined by 6 or more of the following: vomiting, abdominal pain, polydipsia/polyuria, encephalopathy, aspartate transaminase or alanine transaminase $>$ 42 U/L, bilirubin $>$ 0.8 mg/dL, glucose $<$ 72 mg/dL, white blood cell count $>$ 11 $\times$ 10^6/L, uric acid $>$ 5.7 mg/dL, ammonia $>$ 42 IU/L, creatinine $>$ 1.7 mg/dL, prothrombin $>$ 14 sec or partial thromboplastin time $>$ 34 sec, ascites or bright liver on ultrasound, or microvesicular steatosis on biopsy.[4] The criteria have an estimated sensitivity of 100% and a specificity of 57%, with a positive predictive value of 85% and a negative predictive value of 100%, and were validated in a prospective study.[2,22] Notably, the Swansea Criteria seem to be geared towards more critically ill patients, which may correlate to presentations of AFLP later in the disease course. Using these criteria strictly at the initial presentation may, therefore, delay diagnosis.[13] Additionally, 1 study found that the Swansea Criteria were positive for any patient with ALF and were not specific to AFLP.[23] The limitations associated with these criteria are thus important to consider, especially if clinical suspicion is high.

Imaging with ultrasound is not necessary to make a diagnosis of AFLP if the clinical suspicion is high; in fact, studies have shown that imaging is neither sensitive nor specific for AFLP.[2,3] Nonetheless, imaging should be performed to rule out hepatic hemorrhage, infarct, or rupture, and if found, patients should be transferred to a transplant center.[17] Liver biopsy is also not required for diagnosis unless the etiology is unclear and it is necessary for the decision to deliver the fetus (Figure 3).[17] Liver biopsy may also be considered if liver abnormalities do not improve after delivery and another pathology remains a possibility. Liver biopsy in AFLP will reveal microvesicular steatosis with fat droplet deposition.[1]

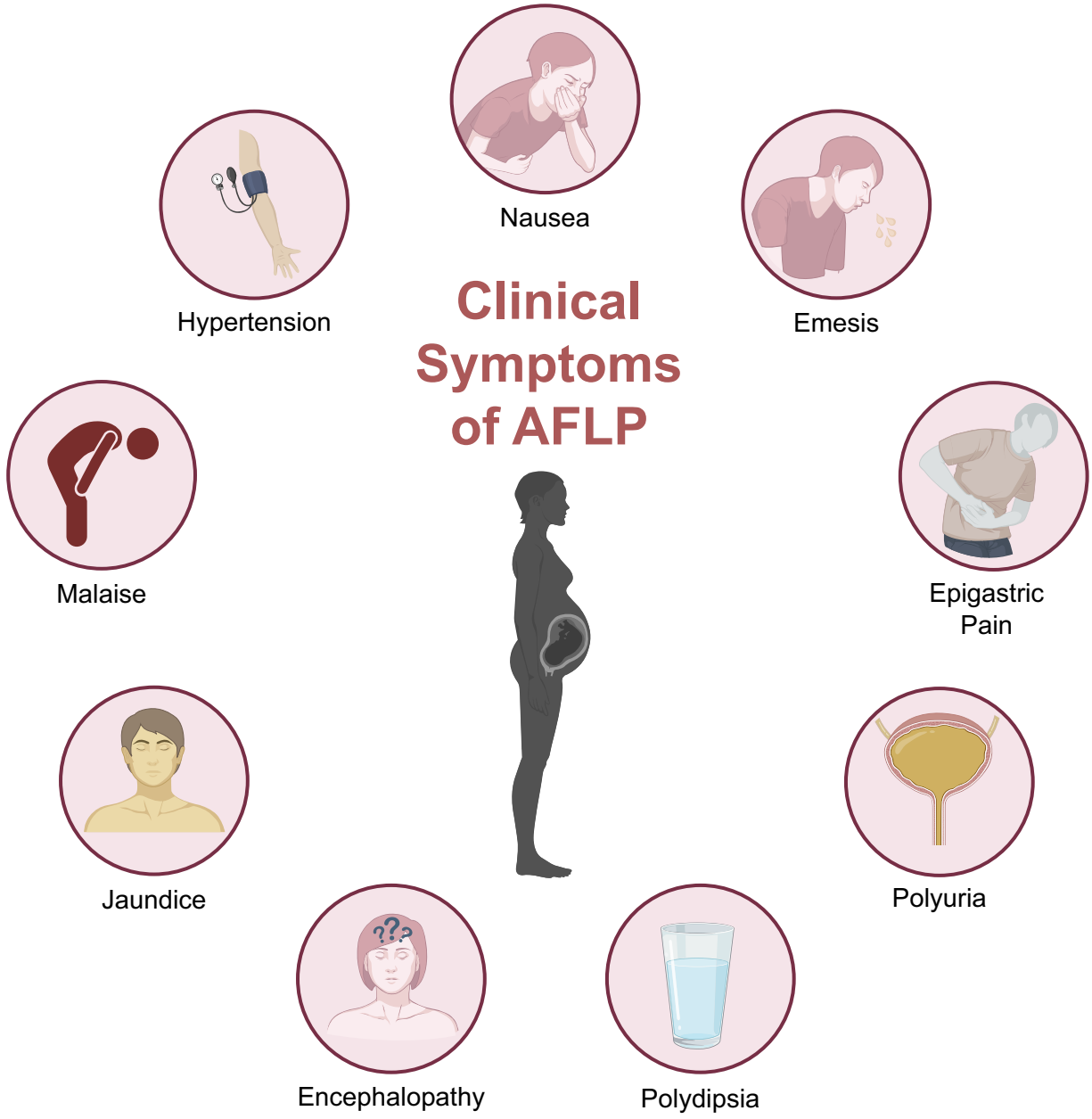

FIGURE 2 Clinical Symptoms of AFLP. Created with Biorender.com. Abbreviation: AFLP, acute fatty liver of pregnancy.

MANAGEMENT

The priority for treatment of AFLP is delivery of the fetus with or without steroids for fetal lung maturation. At this time, there is no consensus on the mode of delivery, though cesarean sections have been more commonly reported. Some studies have proposed that cesarean sections may have lower maternal and fetal mortality rates than vaginal births, though AFLP alone does not provide a sufficient indication for a cesarean.[2,18,21,24,25,26] It is also necessary to take into account that patients who undergo cesarean sections may have higher rates of bleeding complications due to severe coagulopathy that can occur.[6,26]

The treatment of AFLP is otherwise supportive for the mother. Due to the potential for ALF, patients with AFLP can develop complications of ascites, encephalopathy, acute respiratory distress syndrome, renal failure, and bleeding complications from disseminated intravascular coagulation and often need to be admitted to the intensive care unit for frequent monitoring.[27] The most common complications cited are AKI, disseminated intravascular coagulation, and hypoglycemia (Figure 4).[3,6,21,28,29] Patients should be frequently observed for hypoglycemia, as treatment often includes dextrose infusions. In addition, patients should be closely monitored for infections and given broad-spectrum antibiotic coverage if necessary.[3] Pancreatitis has been reported as a potential complication,

TABLE 1 Comparison of AFLP and HELLP

	AFLP	HELLP
Risk factors	Nulliparity, multiple pregnancy, low BMI, male sex of the fetus, prior AFLP	Multiparity, history of diabetes, hypertension, advanced maternal age, and prior HELLP
Trimester presentation	Third trimester and can occur in postpartum	Second or 3rd trimester and can occur in postpartum
Typical clinical symptoms	Nausea, emesis, malaise, epigastric pain, jaundice, and hypertension	Headache, epigastric pain, and hypertension
Initial lab abnormalities	AKI, leukocytosis, thrombocytopenia, elevated AST/ALT, and LDH, prolonged PT, hyperbilirubinemia, hypoglycemia, low fibrinogen, and proteinuria	Proteinuria, leukocytosis, thrombocytopenia, elevated AST/ALT, elevated LDH, and hyperbilirubinemia
Differences in labs abnormalities	AKI, worse leukocytosis and hyperbilirubinemia, prolonged PT, lower fibrinogen and antithrombin	Higher LDH, worse thrombocytopenia, and markers of hemolysis (anemia, low haptoglobin, schistocytes present)
Maternal complications	Ascites, encephalopathy, DIC	AKI, placental abruption, eclampsia
Maternal prognosis	Mortality of 10%–17% or lower with immediate recognition and delivery	Mortality of 1%–2% or lower with immediate recognition and delivery
Fetal prognosis	Estimated up to 20%–25% mortality	Estimated up to 20%–25% mortality
Risk of recurrence	Low but elevated risk of recurrence	Low but elevated risk of recurrence

Abbreviations: AFLP, acute fatty liver of pregnancy; AKI, acute kidney injury; ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver enzymes, and low platelets syndrome; LDH, lactate dehydrogenase; PT, prothrombin.

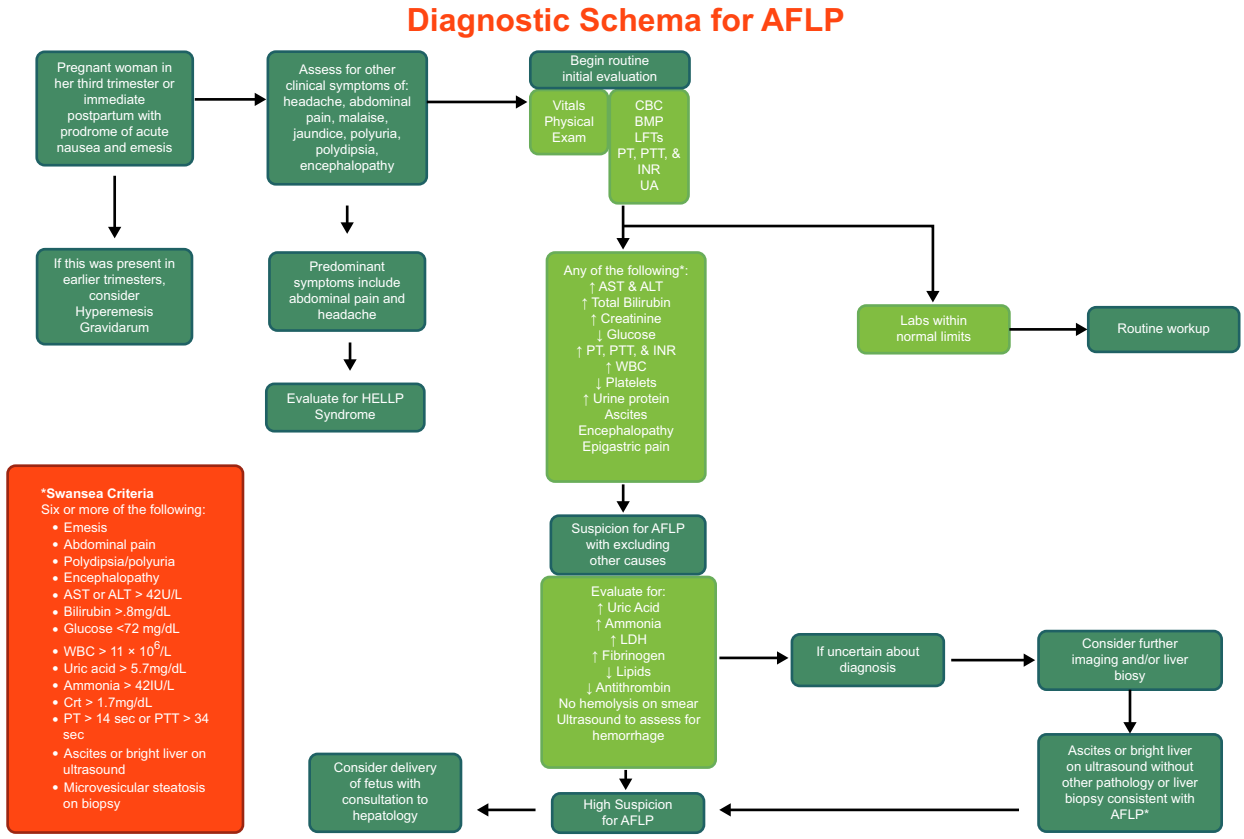

FIGURE 3 Diagnostic Schema for AFLP. Created with Biorender.com. Abbreviations: AFLP, acute fatty liver of pregnancy; ALT, alanine transaminase; AST, aspartate transaminase; BMP, basic metabolic panel; CBC, complete blood count; Crt, creatinine; HELLP, hemolysis, elevated liver enzymes, and low platelets syndrome; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin; PTT, partial thromboplastin time; UA, urinalysis; WBC, white blood cell count.

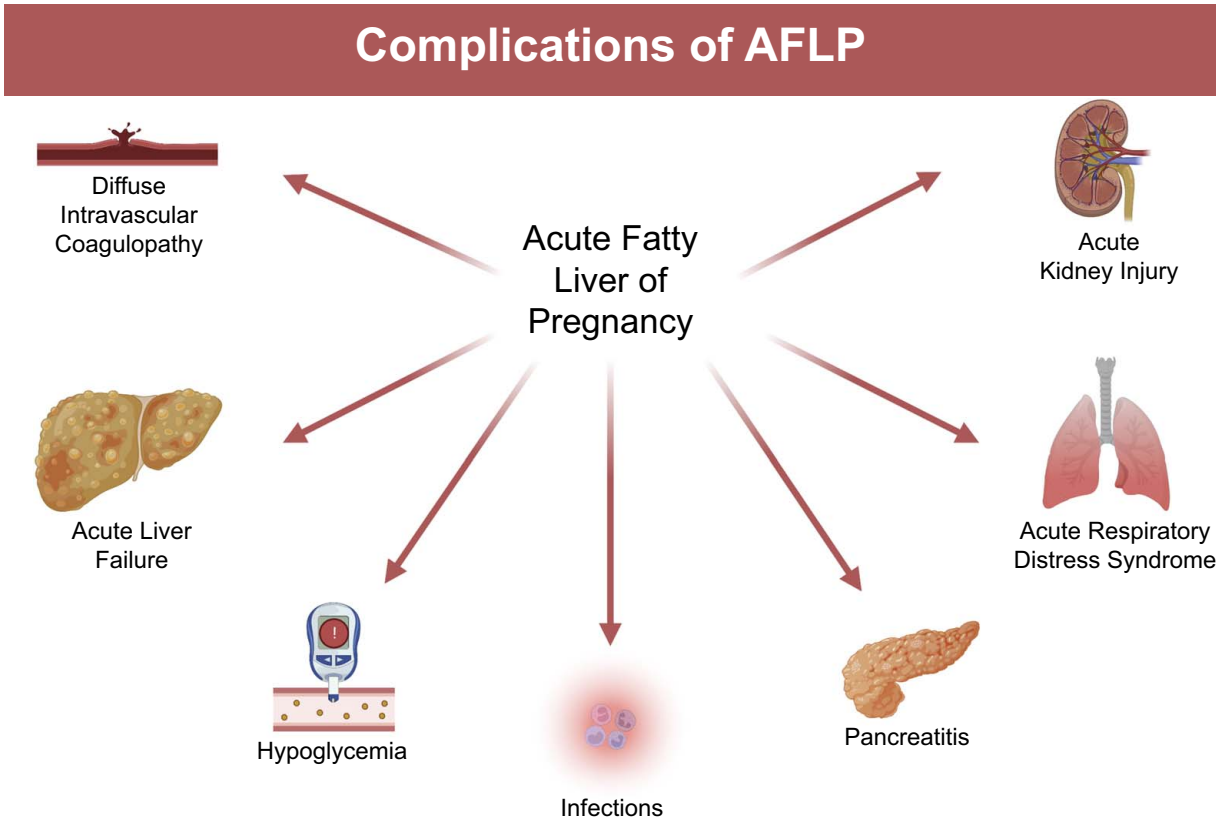

FIGURE 4 Complications of AFLP. Created with Biorender.com. Abbreviation: AFLP, acute fatty liver of pregnancy.

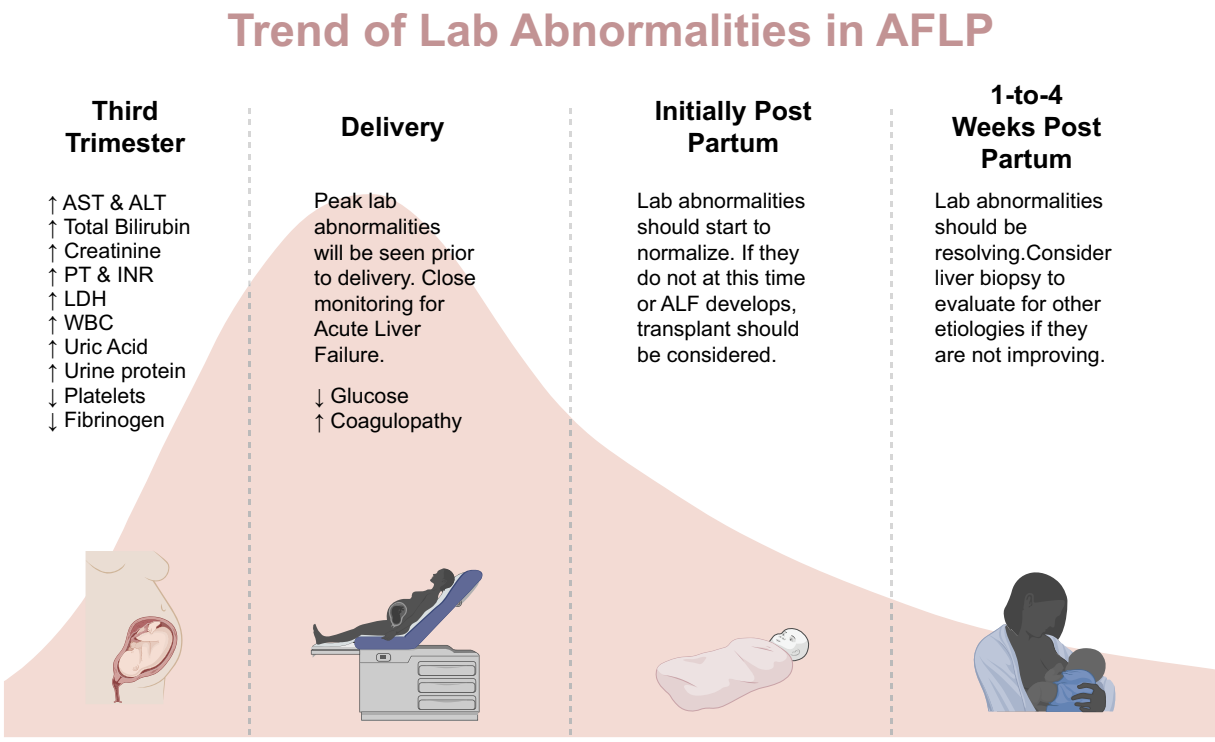

FIGURE 5 Trend of Lab Abnormalities. Created with Biorender.com. Abbreviations: AFLP, acute fatty liver of pregnancy; ALF, acute liver failure; INR, international normalized ratio.

and serum lipase should be monitored if the mother experiences persistent epigastric pain.[6,21,26] Furthermore, coagulation deficits should be corrected, especially if bleeding occurs or a procedure is needed. Plasma exchange and artificial liver support therapy have been trialed as interventions for AFLP, but no randomized controlled trials have been conducted to date. Both therapies have found benefits with shorter hospitalizations and intensive care unit stays but have not affected maternal mortality rates.[29–31]

Once the infant is delivered, maternal improvement should occur. Lab abnormalities and clinical symptoms should normalize within days and sometimes weeks of delivery (Figure 5).[4,6,32] If the mother has not started to improve, other etiologies of liver disease should be investigated. Some predictors of worse outcomes have included the degree of bilirubin and creatinine elevation and the severity of coagulopathy.[7,27,32]

Although ALF is rare in AFLP, it can occur. There are no consensus guidelines on who should be considered for transplant, as AFLP is still regarded as reversible.[13,33] Kushner et al examined transplant outcomes in the National Scientific Registry of Transplant Recipients and found that if patients were listed for transplant, they were less likely to recover without it. They recommended that if a patient does not improve following delivery, they should be considered for transplant. Patients with AFLP who undergo transplant have similar outcomes to other transplant indications. Therefore, it is imperative that any patient diagnosed with AFLP be located to a transplant center.[33]

Maternal mortality for AFLP has improved in recent years and is now estimated to be 10%–17% or lower, compared to prior reports of up to 80%–90%.[2,15,16,18,27,34,35] This is largely due to increased recognition of the condition and prompt delivery. Nevertheless, fetal mortality rates remain elevated, with an estimated rate of 25%.[16,27] Long-term outcomes for the fetus depend heavily on whether fatty acid oxidation defects are identified promptly. Once these are identified, dietary and lifestyle modifications can help reduce morbidity and mortality. Fasting periods should be prevented so that fatty acid oxidation is avoided. A diet that is well-rounded in nutrients with steady carbohydrate intake, adequate medium-chain triglyceride consumption, and lower intake of long-chain fatty acids should be maintained.

CONCLUSION

AFLP is the most feared liver-related disease unique to pregnancy. When it is suspected, it is imperative that clinicians properly differentiate it from other processes that can cause a similar constellation of symptoms and laboratory abnormalities. When there is a high suspicion, urgent delivery of the fetus after maternal stabilization is paramount. Abdominal imaging is indicated to rule out hepatic hemorrhage, infarct, or rupture, and the presence of rupture or ALF should prompt transfer to a transplant center for evaluation. Every newborn of a mother with AFLP needs to be screened for LCHAD deficiency and other fatty acid oxidation defects due to the risk of metabolic crises and death within the first year of life. Newborns can be treated with dietary modifications to reduce morbidity and mortality, and families should be referred for genetic counseling. Mothers who wish to have a subsequent pregnancy after AFLP need to have early co-management with maternal-fetal medicine and hepatology. With prompt diagnosis and treatment, AFLP can go from fatal to treatable with excellent outcomes.

CONFLICTS OF INTEREST

The authors have no conflicts to report.

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