Chapter 19
Pregnancy-Specific Liver Disorders: Acute Fatty Liver

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Patient Questions

1. What is acute fatty liver of pregnancy?

   Acute fatty liver of pregnancy is a rare condition that can occur during the third trimester of pregnancy. Early recognition and prompt management are necessary as both the mother and fetus are at risk for complications.

2. What factors can put me at risk of this disease?

   Low BMI, enzyme deficiencies, multiple pregnancies, and coexisting liver diseases are some of the risk factors which can predispose a pregnant woman to AFLP.

3. What is the cause of this disease?

   While the exact cause of AFLP is unknown, it has been linked mainly to a deficiency in long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD). This enzyme plays a crucial role in fatty acid metabolism. In few of the cases, the deficiency of this enzyme is genetically linked. The deficiency of this enzyme leads to build up of intermediate products which are a cause of AFLP and its complications.

4. What is the usual clinical presentation?

   Patients initially present with malaise, headache, nausea, vomiting, abdominal pain, and anorexia. As the disease progresses, hypoglycemia, encephalopathy, jaundice, and ascites can occur with liver failure at the terminal stage.

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5. How can this disease be diagnosed early in pregnancy to avoid complications?
   Vigilance for symptoms by the care team, especially for those with risk factors for the disease, is important. Using Swansea criteria for screening in suspected cases can also aid in earlier diagnosis.
6. What is the mode of delivery and management?
   Immediate delivery of the fetus through cesarean section is the mainstay of management. Admission to the hospital before delivery with correction of metabolic derangements in the mother and fetus is necessary. Mothers who are critically ill will need intensive care monitoring and management with a small percentage needing support of organ function through dialysis and mechanical ventilation. In very rare cases, liver function does not recover requiring liver transplantation.
7. What are its complications on me and my child?
   Liver injury in the mother is usually reversible, improving after the delivery of the fetus, but can progress to liver failure in a small proportion of cases. In case of the infants, complications such as metabolic derangements, hypotonia, etc. can occur, and hence close follow-up is advised.
8. Will this happen to me in future pregnancies as well?
   Previous episode of AFLP is a risk factor for developing AFLP in future pregnancies, but the recurrence risk is 25% or less.

Introduction

Acute fatty liver of pregnancy (AFLP) is regarded as a rare obstetric emergency with life-threatening complications and poor outcomes for both the mother and the fetus [1]. It usually occurs in the third trimester with a median gestation age being 36 weeks of pregnancy [1–3]. The present chapter will review the epidemiology, pathogenesis, diagnosis, and management strategies as well as identify populations at greater risk for developing AFLP and strategies for preventing long-term maternal and fetal outcomes.

Epidemiology and Risk Factors

AFLP is rare with an incidence of 1 per 7000–16,000 deliveries [4, 5]. Risk factors which predispose to AFLP include low maternal body mass index (BMI <20 kg/m^2) (OR 1.4, 95% CI 0.6–2.9) [6], fetal long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD) (OR 50.0, P = 0.001), short- or medium-chain acyl-CoA dehydrogenase (OR 12.3, P = 0.001) [6, 7], and multiple gestation or twin pregnancy (OR 14.3, 95% CI 6.4–28.6) [8]. Studies note that pregnancies with male infants are also at high risk of AFLP [1, 3, 4]. Furthermore, women with a prior episode of AFLP are also at a risk of developing AFLP in their future pregnancies

[9]. Those with coexisting liver diseases of pregnancy such as preeclampsia or hemolysis, elevated liver enzymes, and a low platelet count syndrome (HELLP syndrome) are thought to have a higher risk of AFLP with 20–40% overlap between the diagnoses [4, 10]. Diabetes type 2 has also been reported as a risk factor for the development of AFLP in a previous case report [11].

Pathophysiology

The exact pathophysiology of AFLP development is unclear, but it has been strongly linked to defects in fatty acid metabolism especially pertaining to long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency [7, 12, 13]. LCHAD (located on the C-terminal portion of the alpha-subunit of the mitochondrial trifunctional protein (MTP) on the inner mitochondrial membrane) catalyzes a step in the beta-oxidation of mitochondrial fatty acids [10]. The fatty acid metabolism is crucial for the growth and development of the fetus. Defects in free fatty acid metabolism during pregnancy produce intermediate products which accumulate and cause complications in both the mother and the fetus [14] (Fig. 19.1).

The carrier frequency of LCHAD deficiency has been reported to be 1 in 675 in the United States, and it is transmitted in an autosomal recessive pattern [15]. When

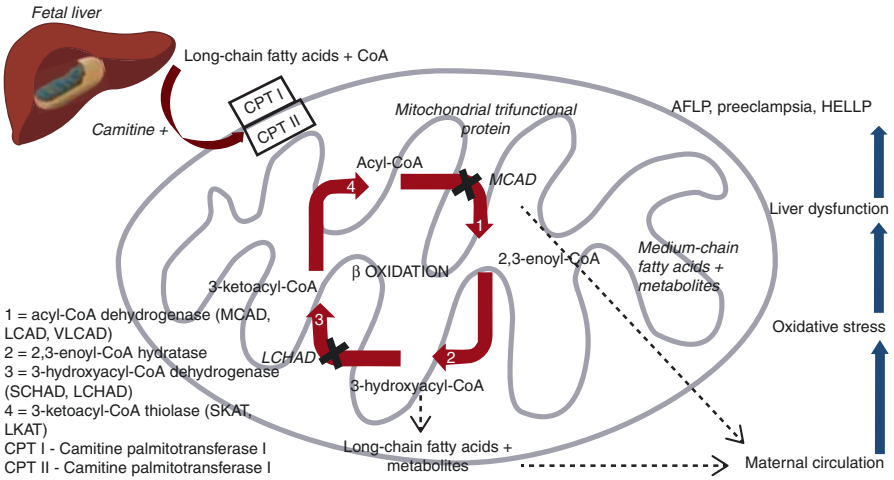

Fig. 19.1 Homozygous defects in the LCHAD and MCAD enzymes in the fetal and placental beta-oxidation of fatty acids lead to the accumulation of fatty acid chains that are transferred to a heterozygous mother producing the clinical symptoms of acute fatty liver of pregnancy [12–14]. Each step of the pathway is catalyzed by homologous enzymes such as LCHAD or MCAD enzyme that creates 2,3-enoyl-CoA. The black "x" depicts the effect of an LCHAD or MCAD enzyme deficiency that leads to the accumulation of fatty acid intermediates that gain entry into the maternal circulation and contribute to the development of acute fatty liver in the mother. (Source: Liu et al. [10])

the mother is heterozygous, there is a reduced capacity of beta-oxidation of fatty acids which is exacerbated during the later stages of pregnancy due to increased demand for fatty acid oxidation contributing to increased stress on the liver. This leads to an increase in the reactive oxygen species and inflammation leading to cellular necrosis, damage, and subsequent liver injury manifesting as AFLP [13, 14]. If the fetus is found to be homozygous for LCHAD deficiency, it is unable to perform the beta-oxidation of fatty acids due to which the level of the intermediate products rises and enters the maternal circulation producing detrimental effects on the maternal hepatocytes [7, 13].

The most common mutation associated with the development of AFLP has been found to be homozygous G1528C mutation (which results in the exchange of glutamic acid for glutamine at amino acid position 474 called the E474Q mutation) which is reported to be seen in around 65–90% of LCHAD patients, while the heterozygous and wild-type genotypes are not [10]. Although LCHAD mutation is strongly linked with AFLP, few cases have been reported where AFLP has occurred even without LCHAD deficiency mutation [10, 14–17]. Previous studies have also found associations of G1528C mutation with hemolysis, elevated liver enzymes, and a low platelet count and preeclampsia during pregnancy, which has overlap in phenotypic features with AFLP [14, 17, 18].

Some more enzyme deficiencies apart from LCHAD have also been found to be associated with AFLP, but they occur less commonly than the G1528C mutation such as carnitine palmitoyl transferase, medium-chain acyl-CoA dehydrogenase (MCAD), and short-chain acyl-CoA dehydrogenase (SCAD) enzyme deficiencies [7, 19–22].

Clinical Presentation

AFLP is usually a diagnosis of the third trimester, but few cases have been reported as early as 22 weeks and as late as 4 days post-delivery [1, 6]. Diagnosis is mainly based on the clinical presentation and the laboratory findings which also help in distinguishing it from other liver diseases of pregnancy. Early in the course of AFLP, a pregnant mother clinically presents with nonspecific signs and symptoms including malaise, headache, nausea, vomiting, abdominal pain, and anorexia [3, 6]. In the case of coexisting liver diseases of pregnancy such as preeclampsia or HELLP syndrome, they can also have signs of hypertension, which may or may not be accompanied by proteinuria [10]. Elevated aminotransferase level (aspartate aminotransferase or alanine aminotransferase), usually ranging from 5 to 10 times the upper limit of normal, but not exceeding 500 IU/L with bilirubin not exceeding 10 mg/dL, is a characteristic lab finding [10] (Table 19.1).

With delayed diagnosis and increased severity of AFLP, pregnant women can also demonstrate signs of jaundice, ascites, hypoglycemia, and encephalopathy and can progress to acute liver failure, disseminated intravascular coagulopathy, and multi-organ failure, while few of them can also progress to acute renal failure [4, 10]. AFLP has also been associated with central diabetes insipidus due to increased

Table 19.1 Features of AFLP (Differentiate from other liver diseases of pregnancy)

Acute fatty liver of pregnancy	
Clinical features	Abdominal pain vomiting, polydipsia/polyuria, encephalopathy
Trimester	Third (less common second and postpartum)
Ascites	+/−
Thrombocytopenia	+/−
Bilirubin	Usually <10 mg/dL (ULN 1.9 mg/dL)
Bile acid elevation	−
Hypoglycemia	+/−
Coagulopathy	+/−
Proteinuria	+/−
Aminotransferases	5–10×
Uric acid elevation	+
Hemolysis	−
Renal dysfunction	+
Histopathology	Microvesicular steatosis
Treatment	Delivery

Source: Adapted and modified from Liu et al. [10]

levels of the vasopressinase enzyme in the setting of impaired liver clearance resulting in decreased levels of vasopressin [23]. Rarely, acute pancreatitis can also be seen with AFLP and acute liver failure during pregnancy [24].

Differential Diagnosis

There is an overlap in clinical presentation among AFLP, HELLP syndrome, and severe preeclampsia, yet differentiating between these entities is critical to timely management. Development of acute liver or kidney failure, encephalopathy, coagulopathy, pancreatitis, pulmonary edema, and adult respiratory distress syndrome aids in the diagnosis of AFLP but occur late in the presentation [25–28]. Earlier in the course, the following points are generally used to differentiate AFLP from other liver diseases of pregnancy (Fig. 19.2):

- Proteinuria which is common with HELLP and preeclampsia but rare with AFLP.
- Ascites and hypoglycemia while absent in other liver diseases of pregnancy suggest, if present, AFLP diagnosis.
- The level of bilirubin in AFLP is usually less than 10 mg/dL as compared to that of other liver diseases of pregnancy.
- The bilirubin level does not rise above 5 mg/dL.
- Also a small rise in aminotransferase level is noted in AFLP compared to that of other liver diseases of pregnancy (5–10× AFLP vs 1–100× HELLP and preeclampsia).

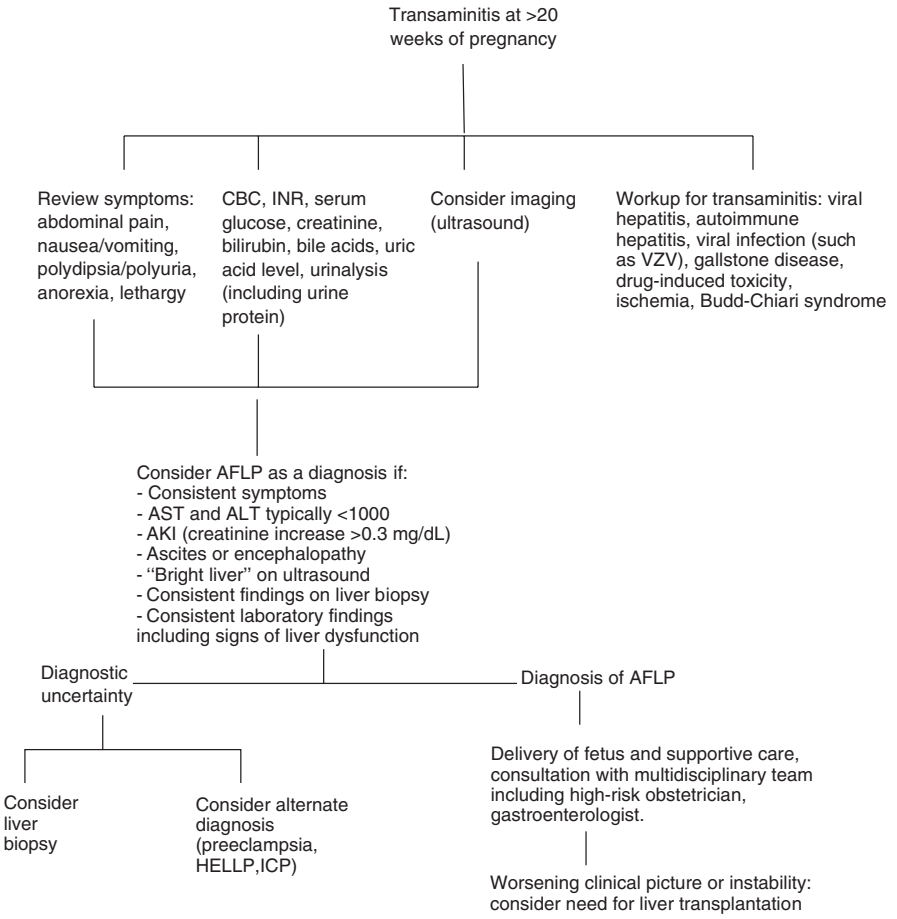

Fig. 19.2 Diagnostic algorithm for AFLP. Algorithm for diagnosis and management of AFLP, highlighting the features of AFLP and differentiation from other liver diseases of pregnancy. (Source: Liu et al. [10])

- Hemolysis is usually a feature of HELLP syndrome but is no present in AFLP.
- Renal failure can occur in AFLP but rare in the course of HELLP syndrome and preeclampsia [10].

Importantly, these diseases can coexist, and eclampsia and HELLP syndrome should be considered after making the diagnosis of AFLP and vice-versa.

The Swansea criteria have been developed and validated for the diagnosis of AFLP [3, 6] (Table 19.2). It is also used for screening the pregnant women for AFLP. It is found to be more accurate if the AFLP is severe, but the accuracy decreases if other pregnancy-associated liver diseases coexist making the diagnosis challenging [10, 29]. Diagnosis of AFLP is considered likely if 6 or more out of 15 criteria are met with a study noting 85% positive predictive value and a 100% negative predictive value in a small group of patients [10].

Table 19.2 Swansea criteria

S.no	Clinical features	Laboratory values	Imaging	Biopsy
1	Vomiting	Bilirubin >14 μmol/L	Bright liver on ultrasound	Microvesicular steatosis
2	Abdominal pain	Hypoglycemia <4 mmol/L		
3	Polydipsia/ polyuria	Elevated urea >340 μmol/L		
4	Encephalopathy	White blood cell count $>11 \times 10^6$ cells/L		
5	Ascites	ALT or AST >42 μmol/L		
6		Ammonia >47 μmol/L		
7		AKI or Creatinine >150 μmol/L		
8		Coagulopathy or PT >14 s or APPT >34 s		

Source: Tran et al. [3]

While considered by some as gold standard, liver biopsy is not typically used for diagnosing AFLP due to risk of complications of the procedure; stabilization and management of the mother and the fetus should not be delayed for liver biopsy if AFLP has already been confirmed clinically [1]. If the liver biopsy is performed, a transjugular approach in lieu of a percutaneous approach is preferred to minimize the risk of bleeding in patients with AFLP. The characteristic histological finding is microvesicular fatty infiltration of the hepatocytes involving the pericentral zone with sparing of the periportal hepatocytes confirmed on the Oil Red O stain which is done on frozen sections [10]. Majority of the cases have reported microvesicular fatty changes, while few cases have also demonstrated the presence of giant mitochondria and lymphocytic infiltration in the hepatocytes in patients with AFLP with some evidence of intrahepatic cholestasis [30]. The histological changes occurring during pregnancy in an AFLP patient have been found to reverse to normal after delivery without progression to cirrhosis [31].

Imaging usually does not aid in the diagnosis of AFLP and is nonspecific showing fatty infiltration or brightness [10, 32]. In a case series of five patients with AFLP, serial magnetic resonance imaging (MRI) showed increased detectable fat that was found to resolve within 2 weeks post-delivery [33].

Management

AFLP is an obstetric emergency and requires a multidisciplinary approach in order to reduce the risk of associated complications. In order to decrease the mortality and morbidity of the patients with AFLP, immediate delivery of the fetus is required irrespective of the gestational age of the patient, and the route of delivery depends on the severity of the disease and maternal and fetal decompensation [10]. Monitoring and correction of metabolic derangements are crucial in case of patients

presenting with thrombocytopenia, hypoglycemia, and altered metabolic panel since they are at a risk of multisystem failure. Both the fetus and the mother should be monitored closely in order to avoid complications. Invasive hemodynamic monitoring should be avoided due to the risk of bleeding. Due to the risk of encephalopathy, regular evaluation of maternal mental status can lead to early identification of a serious complication.

If the disease becomes severe, the patients are shifted to an intensive care unit (ICU) before and after delivery, and close attention is paid to their fluid status as previous cases have been reported to have developed pulmonary edema in the setting of low oncotic pressure [4]. Principles of critical management for acute liver failure are pillars of management of AFLP with frequent assessment of liver function and coagulation by exam and labs (i.e., plasma glucose, platelet count, prothrombin time, fibrinogen) to monitor for progression into DIC and acute liver failure [34, 35]. Similarly, regular monitoring of renal function with creatinine and blood-urea nitrogen for early identification of renal dysfunction is important. In cases of severe renal failure, patients may also require dialysis [10]. Combined plasma exchange with continuous hemodiafiltration has also been shown to be successful in treating terminally ill patients with AFLP [36]. Indications for plasma exchange include severe encephalopathy, liver or renal failure, or patients on mechanical ventilation who rapidly deteriorate and fail to respond to the above management [37–39].

AFLP has been seen to resolve post-delivery with the return of normal liver functions in 7–10 days [4]. In the case of multisystem failure, the patients may have a prolonged course in the hospital requiring supportive care and management [3]. Liver transplantation can be considered if the liver dysfunction persists with evidence of hepatic encephalopathy and lactic acidosis as suggested by previous studies [2, 10, 40]. Less than 0.1% liver transplants performed are due to AFLP but have shown excellent outcomes. Mostly these are performed within 1 week after delivery and have shown to be lifesaving in severe cases of AFLP [41–43]. Currently, there are no guidelines to identify women with AFLP and perform liver transplantation, and the decision to perform liver transplantation is made by worsening or persistence of symptoms or the evidence of hepatic encephalopathy and lactic acidosis [2, 10, 40, 41].

Complications

AFLP is associated with life-threatening conditions such as acute liver and renal failure, encephalopathy, disseminated intravascular coagulation, and gastrointestinal bleeding usually immediately postpartum [44–46]. Few cases have also reported having a hematoma and hepatic rupture with AFLP which are usually seen with preeclampsia or HELLP syndrome in pregnancy [47, 48]. Since women with AFLP are at increased risk for the above complications, they often require admission to ICU for frequent monitoring for coagulopathy, correction of glucose levels due to hypoglycemia, dialysis, and mechanical ventilation in case of acute respiratory distress syndrome (ARDS).

Maternal Outcomes

Earlier diagnosis of AFLP, immediate delivery, and advances in critical care have been successful in decreasing the maternal mortality rate from 75% to less than 10% over the past few years [4, 6, 10, 29, 49]. History of termination of pregnancy (OR 1.958, 95% CI 1.13–3.385), total bilirubin (OR 1.009, 95% CI 1.003–1.014), and serum creatinine (OR 1.010, 95% CI 1.003–1.017) have been identified as potential and independent risk factors for poor maternal outcomes post-delivery [50]. Post-delivery, reversal of histological changes (few cases have reported the persistence of fatty infiltration for up to 5 weeks), normalization of the liver function, and resolution of renal injury within a week are expected [10]. On the other hand, cases of AFLP with pancreatitis can take up to 3 months for resolution [29, 51].

Few studies have demonstrated none to minimal adverse events post-delivery indicating a relatively benign course thereafter [31]. The risk of recurrence is around 25% (fetus is homozygous or compound heterozygous for LCHAD deficiency) in women with prior episode of AFLP during pregnancy, but not many studies support this fact, and recurrence is not definite [9, 52–54]. Hence, expecting mothers should be informed of the risk of AFLP and should be followed up closely during subsequent pregnancies for an earlier diagnosis and prompt management.

Fetal Outcomes

Fetal mortality has been reported to be as high as 50% until 1985 [55]. Advances in critical care have contributed to improved fetal prognosis, but fetal mortality still remains high as compared to the maternal mortality which is attributed to maternal acidosis and prematurity [56]. Concerns regarding fetal outcomes remain high because of LCHAD deficiency, the effects of which can be mild to profound, and hence, close follow-up of the fetus after birth is suggested. Complications such as retinopathy, metabolic derangement, hypotonia, and muscle pain have been identified in a few cases in long-term [57]. Children with no fatty oxidation defect are free from adverse outcomes [57]. Fetal and/or newborn screening has been suggested for fatty acid oxidation deficiency which can help in detecting the disease earlier preventing unforeseen outcomes [17].

Conclusion

Although AFLP is rare, several important studies have enhanced our understanding of AFLP which has led to the decrease in mortality and morbidity due to early recognition, prompt delivery, and management, crucial to the well-being of both the mother and the fetus. The severity of this disease lays importance on the need for

early diagnosis and immediate delivery and management in order to avoid life-threatening complications.

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