Chapter 5
Acute Fatty Liver of Pregnancy

David B. Nelson, John J. Byrne, and F. Gary Cunningham

Introduction

Acute liver failure was first described in pregnancy by Tarnier in 1857 as microvesicular fatty infiltration of the liver [1]. Evidence regarding this link was further described by Lomer in 1884, at which time he described 30 cases of fatty liver during pregnancy at time of autopsy [2]. J. Whitridge Williams termed this *acute yellow atrophy* in the first edition of his textbook and stated that pregnancy appeared to be a predisposing factor [3]. Over the next few decades, there were sporadic case reports of women who died near term from acute liver failure with fatty infiltration; however, elucidation of its etiopathogenesis remained obscure [4].

Major progress in understanding the cause of acute liver failure in pregnancy was reported by Sheehan in 1940 [5]. At that time, he concluded that the majority of maternal deaths secondary to fatty liver were related to the common use of chloroform anesthesia which was popular from the mid-1800s through 1940. After excluding cases attributed to hepatotoxins, such as chloroform, and from infectious etiologies, he termed the remaining cases as *obstetric acute yellow atrophy*. During the late 1940s, however there were still case reports reviewing the difficulty of differentiation between end-stage hepatitis and acute fatty liver of pregnancy [6, 7]. But while fulminant viral hepatitis does have clinical similarities with acute fatty liver of pregnancy, the two appear to be distinctly different histologically [8].

In 1982, Burroughs and colleagues [9] described the clinicopathological findings of idiopathic fatty liver of pregnancy, more contemporaneously known as acute fatty liver of pregnancy (AFLP). They described 12 women who were admitted to the Liver Unit at the Royal Free Hospital in London. Importantly, none of these women

D. B. Nelson (✉) · J. J. Byrne · F. G. Cunningham
Department of Obstetrics and Gynecology, University of Texas Southwestern Medical Center, Parkland Health and Hospital Systems, Dallas, TX, USA
e-mail: DavidB.Nelson@utsouthwestern.edu; John.Byrne@utsouthwestern.edu; Gary.Cunningham@utsouthwestern.edu

© Springer Nature Switzerland AG 2021

C. Montufar et al. (eds.), *Obstetric Catastrophes*,
https://doi.org/10.1007/978-3-030-70034-8_5

had been exposed to chloroform, tetracycline, or other hepatotoxic agents. Indeed, the diagnosis in all but one case was biopsy proven. These investigators carefully characterized symptomatology, laboratory findings, light- and electron-microscopic histopathology, pregnancy outcomes, and complications. They reported that these women had characteristic clinical findings of acute liver failure to include encephalopathy and severe metabolic acidosis. The biopsy findings disclosed widespread microvesicular fat infiltration with swollen hepatocytes, minimal necrosis, and cholestasis. They also reported that acute kidney injury was common, and three women required dialysis. Another recognized manifestation was coagulopathy; however, it was reported as seldom clinically significant and infrequent. Common hematological findings included thrombocytopenia and hemolysis.

Epidemiology

The incidence of acute fatty liver of pregnancy varies depending on diagnostic criteria and population studied and ranges from 1 in 7000 to 1 in 20,000 pregnancies [10–13]. There does not appear to be geographic or ethnic differences in the severity or incidence of the disease; however there are limited population-specific data [14]. Although there are a few cases reported in the second trimester, most develop in the late third trimester [12, 15].

AFLP has a number of associated risk factors. Fetal acid oxidation disorders, multifetal gestation, and male fetuses all have been reported to predispose a woman to develop AFLP [12, 16, 17]. Lesser reported risk factors include metabolic disorders, obesity, and hepatic disorders such as intrahepatic cholestasis of pregnancy [12, 14, 18]. Preeclampsia syndrome is also a well-known association; however, cause-and-effect with AFLP are uncertain.

Pathophysiology

An important finding regarding the pathogenesis of fatty liver disease of pregnancy was provided by Reye and colleagues [19], who described a similar syndrome in children. Subsequent research suggested that microvesicular fatty hepatocyte infiltration was caused by deficiency of one or more of the mitochondrial fatty-acid oxidative enzymes or fetal fatty acid oxidation defects [20]. In this scheme, the fetal-placental unit metabolizes free fatty acids for growth and development during pregnancy, and the placenta contains enzymes involved in the fatty acid metabolism pathway. Placental enzymes metabolize triglycerides into free fatty acids which enter the fetal compartment. Because the products of this metabolism are transferred to the fetus, defects in the fatty acid oxidation pathway of the fetal-placental unit result in accumulation of intermediate products of fatty acids in the maternal circulation. These metabolites are taken up by the maternal liver along with reactive

oxygen species that activate inflammatory processes and cause cellular hepatic necrosis [20, 21].

To date, there have been a number of mutations reported for genes that encode for enzymes in this pathway [21]. Of all of these oxidation disorders, maternal deficiency of long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) has been most strongly linked with pregnancy-associated fatty liver disease [22, 23]. Other, less common, fatty acid oxidation defects have been associated with AFLP, such as medium-chain acyl CoA dehydrogenase (MCAD) deficiency, very long-chain acyl-CoA dehydrogenase (VLCAD) deficiency, and carnitine palmitoyltransferase 1 (CPT1) deficiency [24, 25].

LCHAD deficiency is caused by a defect in the mitochondrial trifunctional protein along the inner mitochondrial membrane, specifically on the C-terminal protein of the alpha subunit. The most common defect seen in LCHAD deficiency is a 1528 G-to-C nucleotide change in exon 15 of the alpha subunit, which causes a change of glutamate-to-glutamine [26]. Because the third step in the oxidation of long-chain fatty acids is catalyzed by LCHAD, a buildup of intermediate products of metabolism is seen in individuals with LCHAD deficiency.

There are two proposed scenarios wherein accumulation of fatty acids and metabolites can accrue within the maternal compartment. In the first, a homozygous enzymatic defect is shared by the fetus and placenta. In the second, a heterozygous mother has decreased ability to perform fatty acid oxidation in late pregnancy. As seen in Fig. 5.1, homozygous enzymatic defects in the fetal-placental fatty acid oxidation pathway lead to an accumulation of fatty acid metabolites that are transferred to a heterozygous mother.

Clinical Presentation

The woman with acute fatty liver will typically present in late pregnancy with a variety of nonspecific symptoms, such as persistent anorexia, nausea, vomiting, and abdominal pain. Some will have findings of encephalopathy or polydipsia and polyuria [10, 12, 27]. Nelson and colleagues [10] described 51 women with AFLP who presented to Parkland Hospital at a mean gestational age of 37 weeks. Most of these had a variety of the symptoms mentioned above; however, approximately 10% were asymptomatic. Almost half of the women had associated hypertension, with or without proteinuria. In some of these women, these clinical findings progressed to liver failure with associated renal failure, coagulopathy, and hypoglycemia. Figure 5.2 demonstrates the spectrum of clinical consequence to this disorder.

Classically, the initial laboratory findings in AFLP depend on the degree of hepatic dysfunction. Some of these abnormalities include elevated levels of hepatic transaminases, creatinine, bilirubin, ammonia, and uric acid, along with hypoglycemia. There can also be associated coagulopathy [28]. This dysfunction can be profound and typically manifests as a prolonged prothrombin time and international normalized ratio (INR) with varying degrees of hypofibrinogenemia and elevated

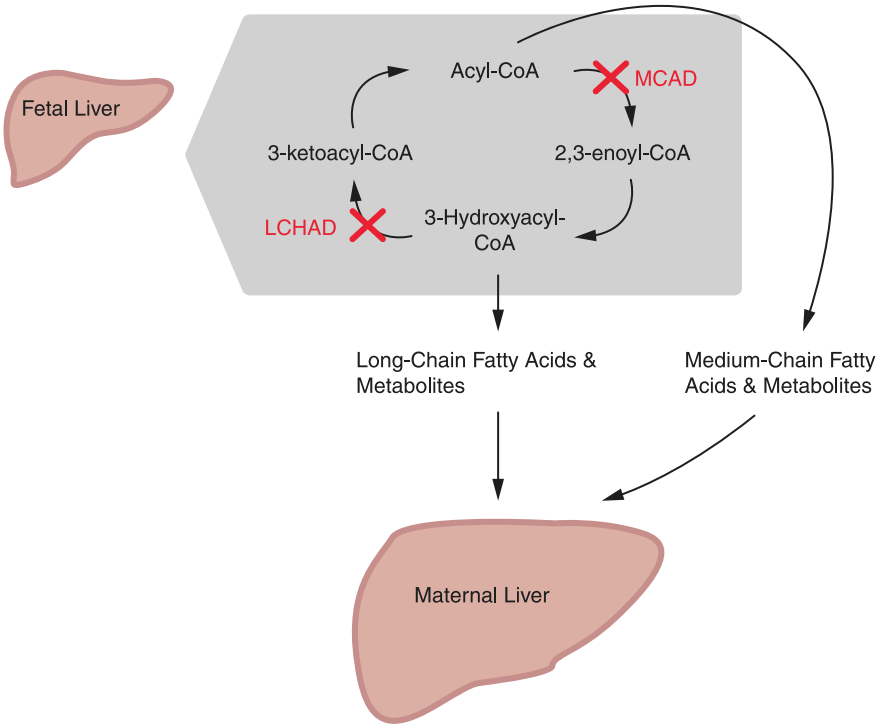

Fig. 5.1 Organ-specific effects of acute fatty liver of pregnancy. (Adapted from Nelson et al. [63])

D-dimer levels [10, 27–30]. There is also usually some degree of hypocholesterolemia concordant with hepatic dysfunction, and antithrombin III levels are also decreased [10, 31]. The peripheral smear shows echinocytosis caused by hypocholesterolemia [32], and there is typically a modest leukocytosis. Hemolysis with reticulocytosis and nucleated erythrocytes are also frequently seen [10].

Hemoconcentration is caused by endothelial cell activation with capillary leakage. There may be polycythemia, but with concomitant hemolysis, the hematocrit may be normal or even low. This "endotheliopathy" ultimately results in prerenal azotemia, compounding acute kidney injury. Intravascular volume depletion can be further intensified by associated ascites [33]. Hypovolemia combined with metabolic acidosis from liver injury can cause a reduction in uteroplacental perfusion that can have profound adverse fetal affects to include death.

Diagnosis

For clinical diagnosis, some recommend application of the Swansea criteria, as described by Ch'ng and colleagues (Table 5.1) [29]. These diagnostic criteria have since been validated by Knight and colleagues [12], and when six of these criteria are

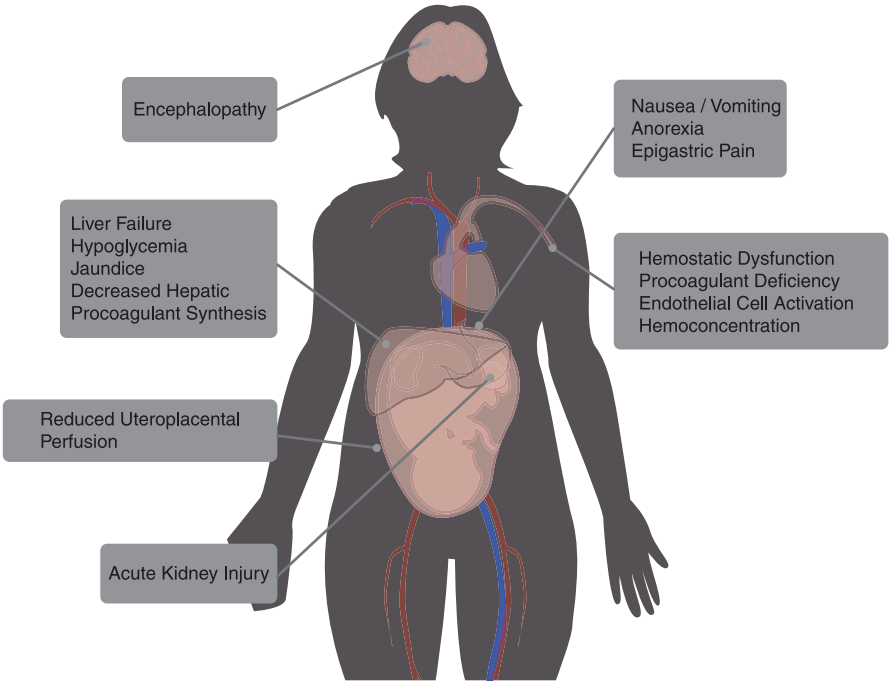

Fig. 5.2 Pathophysiology of acute fatty liver of pregnancy. The oxidation of long-chain fatty acids is catalyzed by long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) and medium-chain acyl CoA dehydrogenase (MCAD). When a homozygous enzymatic defect occurs in the fetal/placental fatty acid oxidation pathway, this leads to an accumulation of intermediate products of metabolism that are transferred to a heterozygous mother

Table 5.1 Diagnostic criteria using the Swansea criteria – six of these criteria satisfy the diagnosis of AFLP

Swansea criteria	Vomiting Encephalopathy Abdominal pain Ascites Polydipsia/polyuria Bilirubin >0.8 mg/dL Hypoglycemia <72 mg/dL White blood cell count >11 × 10^9/l Elevated urea >340 μmol/L ALT >42 U/L AKI or Cr >1.7 mg/dl Ammonia >47 μmol/L Coagulopathy or PT >14s Echogenic liver on ultrasound Microvesicular steatosis on liver biopsy

identified, the diagnosis of AFLP is suggested. These criteria are helpful because diagnosis may not be readily apparent, because of the previously described vague symptomatology. For the woman who presents with persistent nausea and vomiting, abdominal pain and jaundice and encephalopathy, the diagnosis is seemingly more straightforward. But for most women the differential diagnosis is wide. Specifically, AFLP is frequently confused with the more commonly associated obstetric conditions [34]. One of the most difficult conditions to distinguish is hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, which is considered an "imitator" [34].

To establish the diagnosis of AFLP, both clinical findings and laboratory evaluation are essential. Shown in Fig. 5.3 is a suggested testing algorithm. Initially, serum creatinine and hepatic transaminase levels are measured along with a hemogram with platelet quantification. With evidence of liver failure and laboratory abnormalities, these women should undergo further workup to differentiate between related disorders such as acetaminophen toxicity and hepatitis – as discussed in Differential Diagnosis. If abnormal laboratory values are identified, then targeted studies are performed including evaluation for hepatic function and disordered coagulation. Serum cholesterol and plasma fibrinogen levels can be a good measure of liver function. It is important to consider that both of these analytes are markedly influenced by the physiologic changes of normal pregnancy and increase substantially above nonpregnant values. Thus, these analytes can be dramatically abnormal when

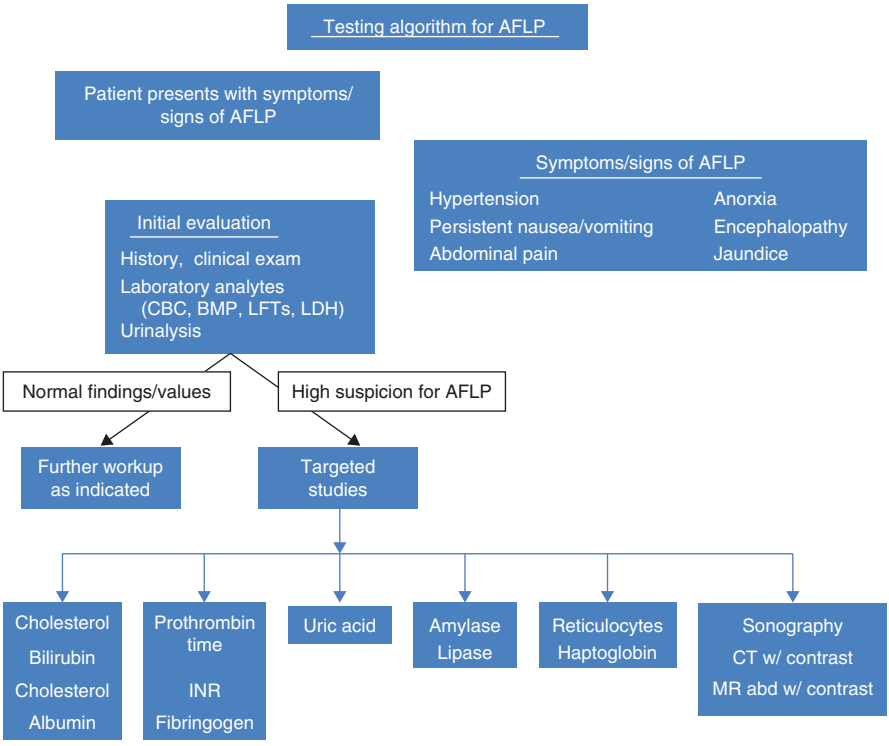

Fig. 5.3 Algorithm to identify acute fatty liver of pregnancy. (Adapted from Nelson et al. [63])

considered in the context of the third trimester of pregnancy. For example, plasma fibrinogen levels in nonpregnant women range from 233 to 496 mg/dL; however, in the third trimester these range between 373 and 619 mg/dL [35].

Although imaging studies are recommended by some [14], in our experience, these are of limited value in the diagnosis of AFLP [10]. For example, although sonographic findings are one element of the Swansea criteria, only a fourth of women had the classic ultrasound findings in a prospective evaluation [12]. Using computed tomography, sonography, and magnetic resonance imaging, Castro and colleagues [11] attempted to confirm the diagnosis; however, they were only able to do so in 30% of patients. The highest yield was 50% with computed tomography [11].

In the past, liver biopsy was considered necessary to confirm the diagnosis of AFLP; however, it is now accepted that it is not the case if characteristic clinical and laboratory findings are present. In women in whom the diagnosis is uncertain, liver biopsy may still be beneficial. As described by Sheehan, pathognomonic histopathologic findings include swollen hepatocytes with central nuclei along with microvesicular fatty infiltration of hepatocytes [5]. In some cases, fat droplets may not be easily identified on hematoxylin and eosin staining; thus a special *oil-red-O stain* must be performed on specimens [36].

Differential Diagnosis

A number of general as well as pregnancy-related disorders may initially be confused with AFLP. In addition to the HELLP syndrome already mentioned, consideration is given to viral hepatitis, acetaminophen toxicity, thrombotic microangiopathies, preeclampsia, and exacerbation of systemic lupus erythematosus [34]. HELLP syndrome is by far the most common disorder that may be mistaken for AFLP and vice versa. The two disorders are characterized by a constellation of similar symptoms and laboratory values; however, there are a number of significant – albeit sometimes subtle – differences. As initially reported by Vigil-de Gracia et al. [37], hepatic, renal, and hemostatic dysfunction is more severe in AFLP. Recent observations by Byrne and colleagues [38, 39] showed that women with AFLP were more likely than those with HELLP syndrome to have hypofibrinogemia, acute kidney injury, hyperbilirubinemia, hypoglycemia, and hypocholesterolemia at the time of admission (Table 5.2). Although initial management is similar and both conditions warrant delivery, the recovery and associated morbidity can be substantially different.

Management

Clinical management may vary because AFLP manifests as a spectrum from mild metabolic and coagulopathic disturbances to overt liver failure and hepatic encephalopathy. The cornerstone of management of AFLP includes (1) prompt recognition

Table 5.2 Most abnormal laboratory findings among women from Parkland Hospital with AFLP and HELLP syndrome

Analyte	AFLP *N* = 67	HELLP *N* = 67
Fibrinogen (mg/dL)	158 [87, 245]	422 [342, 482]
AST (U/L)	278 [146, 564]	135 [77, 250]
Creatinine (mg/dL)	2 [1, 2]	1 [1,1]
Cholesterol (mg/dL)	88 [70, 122]	168 [137, 227]
Total bilirubin (mg/dL)	5 [2, 8]	1 [1,2]
Platelets (/μL)	106,000 [57, 137]	44,000 [33, 63]
LDH (U/L)	512 [398, 865]	678 [530, 850]
Glucose (mg/dL)	88 [70, 122]	98 [137, 227]
White blood cell count ($\times 10^3/mm^3$)	23 [18, 28]	16 [13, 20]

Data are presented as median [Q_1, Q_3]
Data from Byrne et al. [37, 38]

and evaluation of mother and fetus; (2) plan for supportive care such as reversal of coagulopathy; (3) preparation for delivery as soon as feasible; (4) and postpartum supportive care. Until the fetus is delivered, it is thought that the ongoing liver failure will continue with its attendant constellation of abnormalities. After delivery, there is a slow return to metabolic normalcy that frequently requires considerable supportive care for days and even weeks.

Thus, the clinical course of women with AFLP may be characterized by subacute or acute changes in either the maternal or fetal condition. Therefore, women who present with symptoms concerning for AFLP should be admitted to the labor and delivery unit of a hospital with the ability to transition care to an intensive care unit [40]. While evaluating the maternal status, the fetus should undergo fetal heart rate monitoring. Given the proclivity for maternal lactic acidosis with diminished uteroplacental blood flow in the setting AFLP, fetal condition may be nonreassuring. Indeed, fetal jeopardy accounts for the high rate of cesarean delivery. Although the definitive treatment is delivery, AFLP, per se, is not an indication for cesarean delivery, and vaginal delivery is preferable considering the sometimes profound coagulopathy that accompanies the syndrome. In the setting of a vaginal delivery, care is taken to prevent vaginal trauma and lacerations – including episiotomy – given these bleeding risks.

A number of preparations are carried out quickly and as simultaneously as possible. Among these is consultation with anesthesiology colleagues. If the woman is obtunded, airway protection is paramount. Because of vomiting, consideration is given to a nasogastric tube with antacids to neutralize gastric contents. And for the woman with obvious hepatic encephalopathy, tracheal intubation should be considered. Two large-bore intravenous catheters are placed in anticipation of severe hemorrhage. As indicated above, continuous fetal monitoring is performed. Magnesium sulfate infusion is begun for neuroprophylaxis for those women who have evidence for preeclampsia which is seen in up to 70%. Finally, antihypertensive agents are given to treat dangerously high blood pressure levels [41].

Delivery

Although vaginal delivery is preferred, the majority of these women will undergo cesarean delivery because of the high incidence of nonreassuring fetal status associated with maternal acidosis and decreased blood volume due to the endotheliopathy. We prefer a midline skin incision because there is less subcutaneous bleeding than with a Pfannenstiel incision. Some prefer to use a drain such as a Blake or Jackson-Pratt device given the possibility of ascitic fluid and bleeding. At Parkland Hospital, routine draine placement is not our practice.

Given the high risk of coagulopathy at time of delivery, preparations need to be made regarding the potential for massive hemorrhage [42, 43]. Restoration of procoagulants and improvement of hypovolemia are integral especially if cesarean delivery is indicated. Because whole blood is not available in most institutions, resuscitation is done with packed red cells and fresh frozen plasma. Again, especially with operative delivery, maintenance of plasma fibrinogen levels >150 mg/dL is important [42]. Finally, platelet transfusions may be necessary if there is severe thrombocytopenia [43].

Analgesia and Anesthesia

The choice of analgesia depends on the degree of hepatic dysfunction and coagulopathy, especially with consideration for cerebral edema and intracranial hypertension [30]. Cited again is the high incidence of cesarean delivery. For the majority of women who have a limited coagulopathy and only moderate thrombocytopenia, it is reasonable to place neuraxial analgesia with the proviso that the nadir of some of the analytes, vis-à-vis platelets, may not recover until several days postpartum. In other cases, the use of general anesthesia may be necessitated by profound coagulopathy with severe thrombocytopenia, serious hemorrhage, or fetal compromise mandating emergency cesarean delivery.

Postpartum Course

After delivery, even though the AFLP pathophysiology begins to reverse, there will be continuation of the changes for periods up to 7–10 days. Because these women have a high incidence of postpartum hemorrhage, disseminated intravascular coagulopathy, acute renal failure, and gastrointestinal bleeding, continued care is necessary in an acute care unit [40]. Serial measurements of hematologic, hepatic, and renal function is performed every 6 h within the first 1–2 days [10]. Anemia is common from brisk hemolysis, and multiple transfusions are usually required. If there is a recent surgical incision, then clotting function is monitored and transfusion with

fresh-frozen plasma, cryoprecipitate, or platelets may be indicated. Given the risk of hypoglycemia, serial blood glucose levels are monitored every 2–3 h, and if these are less than 60 mg/dL, then an infusion with 10% glucose is begun.

In most women, evidence of liver failure will begin to improve 2–3 days after delivery. Typically, hepatic transaminase values decline in a linear fashion to values at or below 100 IU/L after which values plateau for several weeks [10]. Other markers of liver failure, specifically total bilirubin and cholesterol levels, will start to improve after 3–4 days [44]. Acute kidney injury results from both prerenal and intrinsic pathology. The prerenal component can be seen in the swift decline in serum creatinine values after delivery, recovering to within a normal range within 7–10 days; however, the intrinsic kidney injury component is evidenced by the persistence of elevated serum creatinine for several weeks.

There are also two associated conditions that may be identified in the postpartum period – transient diabetes insipidus and acute pancreatitis. As many as a fourth of women develop diabetes insipidus, which is thought to be from elevated vasopressinase concentrations stemming from diminished hepatic production of its inactivating enzyme. Also, acute pancreatitis develops in up to 20% of the women [45].

More recently, postpartum artificial liver support therapy (ALST) has been described [46]. This includes plasma exchange which removes toxic metabolites, improves electrolyte management and acid-base balance, and supports coagulation factors [47, 48]. While plasmapheresis may result in an improvement of oxidative stress markers and hasten hepatic function recovery, there has not been an improvement in mortality [48, 49]. And although the data are limited, continuous renal replacement therapy (CRRT) along with plasma exchange has been shown to improve clinical symptoms and laboratory analyte recovery [50].

For the woman with persistent profound hepatic failure with hypotension and acidosis, liver transplantation must be considered [51]. Usually, the need for transplantation is typically later in the recovery period remote from delivery. Of the 51 women whom we previously described at Parkland Hospital, only two were considered candidates for transplantation. One woman died from intractable liver failure, and the other survived after a long hospital course with application of CRRT.

Experimental Treatment

One proposed treatment with possible benefits in AFLP is molecular absorbent recirculating system therapy [52, 53]. This system functionally replaces the liver in removing albumin-bound toxic metabolites from the blood via albumin dialysis, which results in stabilization of liver function and improvement in the hyperbilirubinemia. However, there has been no clear mortality benefit. This modality can be considered in patients with acute liver failure who are awaiting liver transplantation.

Maternal and Perinatal Outcomes

Since there has been broad acceptance for relatively uniform criteria for diagnosis, there are at least 10 reports that are listed in Table 5.3 and that include 18 or more pregnancies complicated by acute fatty liver [11, 27, 54–59]. The largest was a multicenter cohort study that identified 133 cases from four tertiary hospitals in China from January 2009 to April 2014 [59]. The single-center studies from Taiwan and California hospitals each reported an incidence of about 1:7000 deliveries in contrast to that of 1:20,000 from the UK nationwide audit [11, 12, 54]. It seems likely that these higher reported incidences result from regional referrals. Uniform to all 12 reports are three major causes of maternal morbidity and mortality, including various combinations and severities of liver failure, renal failure, and hemorrhage. These reports stress that delivery is necessary to reverse ongoing organ dysfunction, but also recognize that cesarean delivery is more likely performed because of associated fetal compromise and that operative delivery has more hemorrhagic complications.

These reports also cite maternal and perinatal survival rates that are much improved compared with earlier reports. In fact, maternal mortality rates in women with AFLP have improved dramatically over the last several decades. In the 1980s, the maternal mortality rate was as high as 80–90%, but this is now below 10% in the most recent literature [12, 59–61]. Many of these cases will trigger as a severe maternal morbidity ("SMM") event, given their increased risk of acute kidney injury, ICU admission, and need for blood and component transfusions. Early diagnosis, prompt delivery, and improved supportive care have led to this improvement in severe morbidity and mortality over time. Although maternal mortality rates have improved over the last several decades, perinatal mortality rates continue to remain substantively increased. As seen in Table 5.3, perinatal mortality over a 20-year period was about 20%. Furthermore, there is still substantive maternal morbidity.

Subsequent Pregnancy

Reports of AFLP recurrence in subsequent pregnancies are unusual [62]. In the setting of women who are heterozygous or carriers of the long chain 3-hydroxyacyconezyme A dehydrogenase mutation, the risk of recurrence is increased. This is contingent upon the fetus being affected during that subsequent pregnancy. If a woman has developed AFLP in a previous pregnancy, it is prudent to screen the fetus for fatty acid oxidation disorder, specifically LCHAD deficiency. At this time, there have only been case reports of recurrent AFLP outside of this proposed pathogenesis [16].

Disclosure Statement The authors report no conflict of interest.

Table 5.3 Selected maternal and perinatal outcomes in women with acute fatty liver of pregnancy

		Diagnosis		Liver failure	Renal failure[a]	Coagulopathy	CD rate	Maternal	Perinatal
Investigator	N	AP	PP	(encephalopathy)				deaths	deaths[b]
Castro (1999) Los Angeles	28	10	18	21%	NS	100%	50%	0	2/30
Knight (2008) UK	57	42	15	9%	14%	52%	74%	1	7/67
Lau (2010) Taipei, Taiwan	18	6	12	11%	83%	61%	72%	2	3/22
Vigil-De Gracia (2011) Panama	35	NS	NS	40%	94%	77%	89%	4	4/39
Mellouli (2012) Tunisia	19	19	0	11%	63%	58%	79%	2	4/22
Nelson (2013) Dallas	51	NS	NS	16%	4%	80%	49%	2	7/58
Cheng (2014) China	32	NS	NS	53%	81%	16%	69%	14	8/41
Zhang (2016) China	56	NS	NS	20%	39%	54%	80%	4	10/61
Gao (2018) China	133	120	13	33%	10%	86%	85%	22	36/161
Ilham (2019) Indonesia	18	16	2	61%	83%	72%	50%	12	11/19
Estimated average	*447*						*298/447 (67%)*	*63/447 (14%)*	*92/520 (18%)[c]*

AP antepartum, *NS* not stated, *PP* postpartum
Adapted from Nelson et al. [63]
[a]Renal failure is variably defined
[b]Fetal demise or neonatal death <28 days
[c]Total 520 includes 92 multifetal pregnancies

References

1. Tarnier. Note sur l'etat graisseux du foie dans la fievre peurperale. C R Soc Biol. 1857;3:209–14.
2. Lomer O. Ueber die Bedeutung des Icterus gravidarum, etc. Zeitschr f Geb u Gyn. 1886;xiii:169–85.
3. Williams JW. Obstetrics: a textbook for students and practitioners. London: D Appelton and Company; 1903. p. 444.
4. Stander H, Cadden B. Acute yellow atrophy of the liver in pregnancy. Am J Obstet Gynecol. 1934;28:61–9.
5. Sheehan HL. The pathology of acute yellow atrophy and delayed chloroform poisoning. J Obstet Gynecol. 1940;47:49–62.
6. Lucke B. the pathology of fatal epidemic hepatitis. Am J Pathol. 1944;20:471–593.
7. Zondek B, Bromberg YM. Infectious hepatitis in pregnancy. J Mt Sinai Hosp N Y. 1947;14:222–43.
8. Sherlock S. Acute fatty liver of pregnancy and the microvesicular fat diseases. Gut. 1983;24:265–9.
9. Burroughs AK, Seong NH, Dojcinov DM, et al. Idiopathic acute fatty liver of pregnancy in 12 patients. Q J Med. 1982;51:481–97.
10. Nelson DB, Yost NP, Cunningham FG. Acute fatty liver of pregnancy: clinical outcomes and expected duration of recovery. Am J Obstet Gynecol. 2013;209:456, e1–7.
11. Castro MA, Fassett MJ, Reynolds TB, et al. Reversible peripartum liver failure: a new perspective on the diagnosis, treatment, and cause of acute fatty liver of pregnancy, based on 28 consecutive cases. Am J Obstet Gynecol. 1999;18:389–95.
12. Knight M, Nelson-Piercy C, Kurinczuk JJ, et al. A prospective national study of acute fatty liver of pregnancy in the UK. Gut. 2008;57:951–6.
13. Reyes H, Sandoval L, Wainstein A, et al. Acute fatty liver of pregnancy: a clinical study of 12 episodes in 11 patients. Gut. 1994;35:101–6.
14. Lui J, Ghaziani TT, Wolf JL. Acute fatty liver disease of pregnancy: updates in pathogenesis, diagnosis, and management. Am J Gastroenterol. 2017;112:838–46.
15. Monga M, Katz AR. Acute fatty liver in the second trimester. Obstet Gynecol. 1999;93:811–3.
16. Bacq Y. Liver disease unique to pregnancy: a 2010 update. Clin Res Hepatol Gastroenterol. 2011;35:182–93.
17. Davidson KM, Simpson LL, Knox TA, et al. Acute fatty liver of pregnancy in triplet gestation. Obstet Gynecol. 1998;91:806–8.
18. Chen H, Yuan L, Tan J, et al. Severe liver disease in pregnancy. Int J Gynaecol Obstet. 2008;101:277–80.
19. Reye RD, Morgan G, Baral J. Encephalopathy and fatty degeneration of the viscera. A disease entity in childhood. Lancet. 1963;2:749–52.
20. Strauss AW, Bennett MJ, Rinaldo P, et al. Inherited long –chain 3-hydroxyacyl-CoA dehydrogenase deficiency and a fetal-maternal interaction cause maternal liver disease and other pregnancy complications. Semin Perinatol. 1999;23:100–12.
21. Browning MF, Levy HL, Wilkins-Haug LE, et al. Fetal fatty acid oxidation defects and maternal liver disease in pregnancy. Obstet Gynecol. 2006;107:115–20.
22. Ibdah JA, Bennett MJ, Rinaldo P, et al. A fetal fatty-acid oxidation disorder as a cause of liver disease in pregnant women. N Engl J Med. 1999;340:1723–31.
23. Tyni T, Ekholm E, Pihko H. Pregnancy complications are frequent in long-chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency. Am J Obstet Gynecol. 1998;178:603–8.
24. Santos L, Patterson A, Moreea SM, et al. Acute liver failure in pregnancy associated with maternal MCAD deficiency. J Inhert Metab Dis. 2007;30:103.
25. Ylitalo K, Vanttinen T, Halmesmaki E, et al. Serious pregnancy complications in a patient with previously undiagnosed carnitine palmitoyltransferase 1 deficiency. Am J Obstet Gynecol. 2005;193:2060–2.

26. Sims HF, Brackett JC, Powell CK, et al. The molecular basis of pediatric long chain 3-hydroxyacyl-Co-A dehydrogenase deficiency associated with maternal acute fatty liver of pregnancy. Proc Natl Acad Sci U S A. 1995;92:841–5.
27. Vigil-de Gracia P, Montufar-Rueda C. Acute fatty liver of pregnancy: diagnosis, treatment, and outcome based on 35 consecutive cases. J Matern Fetal Neonatal Med. 2011;24:1143–6.
28. Nelson DB, Yost NP, Cunningham FG. Hemostatic dysfunction with acute fatty liver of pregnancy. Obstet Gynecol. 2014;124:40–6.
29. Ch'ng CL, Morgan M, Hainsworth I, et al. Prospective study of liver dysfunction in pregnancy in Southwester Wales. Gut. 2002;51:876–80.
30. Naoum EE, Leffert LR, Chitilian HV, et al. Acute fatty liver of pregnancy. Anesthesiology. 2019;130:446–61.
31. Kerr R, Newsome P, Germain L, et al. Effects of acute liver injury on blood coagulation. J Thromb Haemost. 2003;1:754–9.
32. Cunningham FG, Lowe T, Guss S, et al. Erythrocyte morphology in women with severe preeclampsia and eclampsia. Preliminary observations with scanning electron microscopy. Am J Obstet Gynecol. 1985;153:358–63.
33. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013;369:2525–34.
34. Sibai BM. Imitators of severe preeclampsia. Obstet Gyncol. 2007;109:956–66.
35. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. Obstet Gynecol. 2009;114:1326–31.
36. Mabie WC. Acute fatty liver of pregnancy. Crit Care Clin. 1991;7:799–808.
37. Vigil-De Gracia P. Acute fatty liver and HELLP syndrome: two distinct pregnancy disorders. Int J Gynecol Obstet. 2001;73:215–20.
38. Byrne JJ, Seasely A, McIntire DD, Nelson DB, Cunningham FG. Pragmatic acute fatty liver of pregnancy and HELLP syndrome on admission. Am J Obstet Gynecol. 2019;220:863.
39. Byrne JJ, Seasely A, McIntire DD, Nelson DB, Cunningham FG. AFLP versus HELLP syndrome: pregnancy outcomes and recovery. Am J Obstet Gynecol. 2019;220:563.
40. ACOG Practice Bulletin No. 211: Critical care in Pregnancy. Obstet Gynecol. 2019;133:e303–19.
41. American College of Obstetricians and Gynecologists: Hypertension in pregnancy. Report of the American college of obstetricians and gynecologists' task force on hypertension in pregnancy. Obstet Gynecol. 2013;122:1122–31.
42. Alexander JM, Sarode R, McIntire DD, et al. Use of whole blood in the management of hypovolemia due to obstetric hemorrhage. Obstet Gynecol. 2009;113:1320–6.
43. Kenny L, McCrae K, Cunningham FG. Platelets, coagulation, and the liver. In: Taylor R, Roberts JM, Cunningham FG, editors. Chesley's hypertension in pregnancy. 4th ed. Amsterdam: Academic Press; 2015.
44. Rolfes DB, Ishak KG. Acute fatty liver of pregnancy: a clinicopathologic study of 35 cases. Hepatology. 1985;5:1149–58.
45. Moldenhauer JS, O'brien JM, Barton JR, et al. Acute fatty liver of pregnancy with pancreatitis: a life-threatening complication. Am J Obstet Gynecol. 2004;190:502–5.
46. Wu Z, Huang P, Gong Y, et al. Treating acute fatty liver of pregnancy with artificial liver support therapy: systematic review. Medicine (Baltimore). 2018;97:e12473. https://doi.org/10.1097/MD.0000000000012473.
47. Martin JN, Briery NM, Rose CH, et al. Postpartum plasma exchange as adjunctive therapy for severe acute fatty liver of pregnancy. J Clin Apher. 2008;47:113–5.
48. Yu CB, Chen JJ, Du WB, et al. Effects of plasma exchange combined with continuous renal replacement therapy on acute fatty liver of pregnancy. Hepatobiliary Pancreat Dis Int. 2014;13:179–83.
49. Tang W, Huang Z, Wang Y, et al. Effect of plasma exchange on hepatocyte oxidative stress, mitochondria function, and apoptosis in patients with acute fatty liver of pregnancy. Artif Organs. 2012;36:E39–47.

50. Ding J, Han LP, Lou XP, et al. Effectiveness of combining plasma exchange with plasma perfusion in acute fatty liver of pregnancy: a retrospective analysis. Gynecol Obstet Investig. 2015;79:97–100.
51. Kushner T, Tholey D, Dodge J, et al. Outcomes of liver transplantation for acute fatty liver disease of pregnancy. Am J Transplant. 2019;19:2101–7.
52. de Naeyer S, Ysebaert D, van Utterbeeck M, et al. Acute fatty liver of pregnancy and molecular absorbent recirculating system (MARS)- therapy: a case report. J Matern Fetal Neonatal Med. 2008;21:587–9.
53. Saliba F. The molecular absorbent recirculating system (MARS) in the intensive care unit: a rescue therapy for patients with hepatic failure. Crit Care. 2006;10:118.
54. Lau HH, Chen YY, Huang JP, et al. Acute fatty liver of pregnancy in a Taiwanese tertiary care center: a retrospective review. Taiwan J Obstet Gynecol. 2010;49:156–9.
55. Mellouli MM, Amara FB, Maghrebi H, et al. Acute fatty liver of pregnancy over a 10-year period at a Tunisian tertiary care center. Int J Gynaecol Obstet. 2012;117:88–9.
56. Cheng N, Xiang T, Wu X, et al. Acute fatty liver of pregnancy: a retrospective study of 32 cases in South China. J Matern Fetal Neonatal Med. 2014;27:1693–7.
57. Zhang YP, Kong WQ, Zhou SP, et al. Acute fatty liver of pregnancy: a retrospective analysis of 56 cases. Chin Med J. 2016;129:1208–14.
58. Aldika Akbar MI, Mayang Sari I, Aditiawarman DEG, Dekker G. Clinical characteristics of acute fatty liver of pregnancy in a tertiary Indonesian hospital. J Matern Fetal Neonatal Med. 2019;32:826–32.
59. Gao Q, Qu X, Chen X, et al. Outcomes and risk factors of patients with acute fatty liver of pregnancy: a multicenter retrospective study. Singap Med J. 2018;59:425–30.
60. Varner M, Rinderknecht NK. Acute fatty metamorphosis of pregnancy. A maternal mortality and literature review. J Reprod Med. 1980;24:177–80.
61. den Boer ME, Wanders RJ, Morris AA, et al. Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency: clinical presentation and follow-up of 50 patients. Pediatrics. 2002;109:99–104.
62. Usta IM, Barton JR, Amon EA, et al. Acute fatty liver of pregnancy: an experience in diagnosis and management of fourteen cases. Am J Obstet Gynecol. 1994;171:1342–7.
63. Nelson DB, Byrne JJ, Cunningham FG. Acute fatty liver of pregnancy. Clin Obstet Gynecol. 2020;63(1):152–64.