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Acute Liver Failure (ALF) in Pregnancy: How Much Is Pregnancy-Related?

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Abstract

Background: Acute liver failure (ALF), characterized by sudden onset of coagulopathy (INR 1.5) and encephalopathy may occur during pregnancy, either as a pregnancy-associated etiology or as an unrelated and co-incidental liver injury. The U.S. Acute Liver Failure Study Group comprised of 33 tertiary care liver centers has enrolled consecutive patients with ALF or acute liver injury (ALI: INR ≥ 2.0 with no encephalopathy), over two decades.

Methods: The etiologies, clinical features and outcomes of 70 of 3,155 patients (2.2%), who developed ALF or ALI during pregnancy were reviewed to determine how many were pregnancy-associated (PAALD) and how many were attributed to other etiologies.

Results: Thirty-five of the 70 were considered PAALD, of whom nearly half were attributed to hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome and half to acute fatty liver of pregnancy (AFLP), although in some instances the distinction was unclear. Virtually all with PAALD had been delivered prior to hepatology referral, mostly by cesarean section. Acetaminophen toxicity accounted for 21 (60% of the remaining cases), with the remainder resulting from a variety of other causes, but not including viral hepatitis A through E. Although recovery with delivery or supportive measures was possible in most cases, 11 of 70 (16%) required liver transplantation and 8 (11%) died. Swansea criteria to diagnose AFLP were met by all patients with PAALD and also by virtually all women with other forms of ALF.

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Conclusions: Only half of those with ALF during pregnancy appeared to have HELLP or AFLP. Morbidity and mortality for mother and fetus are strongly associated with the etiology of liver failure.

Keywords

Fatty liver of pregnancy; HELLP syndrome; eclampsia; LCHAD deficiency; acetaminophen toxicity

Introduction

Acute liver failure (ALF) is a rare condition, affecting approximately 2-3,000 patients annually in the United States (1). ALF occurring in pregnancy is associated with significant maternal and fetal morbidity and mortality (2,3). Certain liver conditions that lead to ALF such as the hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome and acute fatty liver of pregnancy (AFLP) are limited solely to pregnant women, occur during the third trimester, and can be classified as pregnancy-associated liver diseases (PAALD [4-6]). In the obstetrical literature, diagnostic criteria for AFLP known as the Swansea criteria have been proposed as a means to distinguish AFLP from other causes of liver dysfunction including HELLP, but these have not been extensively validated (7,8).

Not all ALF that occurs during pregnancy is directly related to the pregnancy itself. For example, certain viruses occur relatively frequently in the reproductive years; likewise, pregnant women may be more susceptible to conditions not specifically pregnancy-related, such as *Herpes simplex* virus (HSV) infection (9-11). The U.S. Acute Liver Failure Study Group (ALFSG) registry has prospectively collected detailed demographic, clinical and biochemical information on more than 3,100 patients admitted to tertiary care hospitals over two decades, including those presenting with full-blown ALF (defined as any degree of encephalopathy and coagulopathy with INR $\geq$ 1.5) and those with acute liver injury (ALI, severe injury with INR of $\geq$ 2.0, but without encephalopathy) (12). To better understand and manage future pregnant women with ALF/ ALI, the clinical features and outcomes of all pregnant women enrolled in the ALFSG registry that met the standard entry criteria for ALF/ALI were reviewed. The aim of this study was to provide a detailed snapshot of ALF/ALI occurring in North America during pregnancy: both pregnancy-associated conditions and those conditions that may simply occur during an intra-uterine pregnancy. We also evaluated the utility of the Swansea criteria to differentiate AFLP from other causes of liver injury in this relatively large patient cohort.

Patients and Methods

Between January 1998 and November 2017, 3,155 subjects were registered with ALF or ALI, 70 of whom (2.2%) were pregnant or within a week of delivery at the time of initial hospital admission and/or study enrollment. The ALFSG protocols allow ALI patients to consent for themselves, while those with ALF, by definition, are not capable of consent, requiring the signature of next of kin or other legally authorized representative. For all subjects enrolled, de-identified clinical information (as well as serum, plasma, DNA and urine samples) were collected and the data uploaded to an electronic database maintained at

the Medical University of South Carolina (MUSC), Charleston, SC. Data included demographics, etiology, detailed laboratory profiles, imaging and liver biopsy information where available, outcomes at 21 days: death, liver transplant (LT) or 'spontaneous' or transplant-free survival (TFS), and fetal outcomes as well where available. Etiologic diagnosis was initially established by the site principal investigator (PI) and then later confirmed or revised by a causality adjudication committee composed of senior hepatologists. In some instances, the committee had access to additional serological or biochemical data that was not available at the time of initial etiologic diagnosis (13). For example, explant or autopsy histology were sought, testing for acetaminophen (APAP) protein adducts was performed on selected subjects to confirm or deny a suspected diagnosis of APAP overdose (14,15), and further autoimmune serologies were systematically performed. As a secondary analysis, the causality committee reviewed the evidence for PAALD (vs. other etiologies) and determined, where possible, whether specific evidence for AFLP or HELLP was present. We also reviewed all 70 cases, scoring them for the features present that define the Swansea criteria (7,8). Some of the Swansea criteria such as uric acid measurements were not routinely available.

Statistical Analysis

Non-parametric Kruskal-Wallis analysis or Mann-Whitney-U analysis was used for laboratory data and Fisher's Exact test for demographic data across the various etiologic sub-groups using SPSS v25 (IBM – SPSS, Armonk, NY).

Results

Overall Group

Among 3,155 prospectively enrolled subjects, 70 (2.2%) were identified as having ALF or ALI, either during pregnancy or in the immediate post-partum period, defined as within a week of delivery; six were initially classified as ALI including two with PAALD (AFLP), two with APAP and two with Other etiologies. The median age of enrollees was 29; 67.1% were Caucasian, 22.9% African American, 4.3% Asian and 4.3% Hispanic (Table 1). The specific pregnancy-associated acute liver diseases (HELLP or AFLP or features of both) were recognized and confirmed by the adjudication committee in 35 (50%) of the overall group. We initially compared PAALD, acetaminophen (APAP) and the remaining Other groups (Tables 1 and 2). All PAALD patients were enrolled in the study post-partum, since emergent delivery of the infant invariably had occurred once the obstetrical team became aware of a liver-related issue. The median gestational age of the PAALD group was 36 weeks (range 28-39 weeks). PAALD patients were further adjudicated as AFLP (n=14), HELLP (n=16) and those where delineation was uncertain (n=5) (Tables 3 and 4). Acetaminophen toxicity was present in 21 (30% of the overall group, 60% of the remainder). Of these, four were considered intentional (attempted suicidal ingestion), 15 unintentional (without suicidal intent, typically for pain relief) and two were unknown; 11 of the 21 APAP cases had received N-acetylcysteine (NAC), route unspecified but virtually all intravenously, the remaining 10 were unknown with regard to NAC. Ten non-APAP subjects received NAC including three AFLP, two HELLP and 5 Others. The remaining 14 "Other" group was

comprised of many etiologies: autoimmune hepatitis (3), drug-induced liver injury (DILI, 2), HSV (4), cancer (lymphoma, 2; adenocarcinoma, 1), Kikuchi-Fujimoto syndrome (1), and thyrotoxicosis (1). No hepatitis A, B, C or E cases were identified. No patients were considered to have indeterminate etiology. Follow-up antibody testing for hepatitis E was performed on 5 patients, three with PAALD, one with autoimmune hepatitis and one with APAP-induced hepatotoxicity. All were negative for anti-HEV IgM, one (AIH) was positive for anti-HEV IgG.

Subsequent testing for APAP adducts was performed on 23 subjects, including 17 presumed to have APAP toxicity as well as three PAALD and three Others. All APAP adduct levels were confirmed positive in those adjudicated as APAP overdose on clinical grounds; of the 6 remaining patients tested, five had undetectable adducts; however, one subject did test positive for APAP adducts (see below).

Comparison of clinical features and outcomes for the three groups

The median gestational age of presentation by etiology group was PAALD 36 weeks, APAP 30 weeks, and Other/miscellaneous group 30 weeks. The latter two groups included patients from all three trimesters (Table 1). Primiparity was present in ~60% of all three groups (data not shown). Among PAALD patients, 57.1% were primiparas, and more than 2/3 experienced (at least) pre-eclampsia, or eclampsia (68.8% and 15.4% respectively). Pre-eclampsia/eclampsia was infrequently observed in the non-PAALD groups. PAALD patients were at or near term, and generally considered in need of emergency delivery. Thus, 89.3% had undergone Caesarean section, as compared to 44.4% in the APAP group and none in the Other diagnosis group.

Certain laboratory features varied considerably between groups (Table 2): median white blood cell counts, bilirubin and creatinine levels were significantly higher, and platelet counts lower, in the PAALD patients when compared to the other two groups. Hemoglobin, INR, ammonia and lactate values were similar across the groups, while median aminotransferase, phosphate and bilirubin levels varied by etiologic group as well. For example, the median aspartate and alanine aminotransferase (AST/ALT) levels were higher and phosphate levels lower in the APAP group compared to the PAALD or Other groups and bilirubin levels likewise were lower in APAP patients consistent with the 'hyperacute' clinical course of APAP patients.

Overall survival at 21 days was 58/70 (82.8%), broken down as follows: spontaneous or transplant-free survival (TFS), 48/70 (68.6 %); 11/70 (15.7%) liver transplantation (LT), one of whom died post-LT, and 7/70 (12.9%) died without LT. Outcome at 21 days was unknown in four; subsequent calculations were based on the total group number of 70, rather than 66. When outcomes per etiology were considered separately (Table 1), APAP toxicity cases were associated with better overall survival (85%), with fewer requiring LT and fewer deaths. Fetal outcomes were available on 42 subjects and differed greatly between groups, with survival rates as follows: PAALD 96%, APAP 43%, and Other 55%, again reflecting the presentation of the latter two groups at almost any time during parturition including the first trimester. We also compared the three groups for prediction of transplant-free survival using the ALFSG prognostic index (17; Table 1). The three main groups differed

significantly, with PAALD having a predicted 72% TFS, vs. APAP 86% and Other 34%, each group reflecting differing pathogenesis and likelihood of survival.

Comparison of patients with AFLP and HELLP

Criteria available for discerning AFLP from HELLP with certainty included the presence of micro-vesicular fat or peri-portal necrosis on biopsy (Figure), or evidence of hepatic rupture, zonal infarction or intraperitoneal hemorrhage in HELLP. Less certainty was associated with presence of hypoglycemia or pancreatitis (both presumably supporting AFLP), or pre-eclampsia or eclampsia, hemolysis, higher aminotransferase elevations (favoring HELLP). Despite these limitations, we attempted adjudication to one or the other diagnosis, AFLP or HELLP (Tables 3 and 4). Six of 14 cases designated as AFLP had undergone biopsies, all demonstrating micro-vesicular fat. There were no biopsies obtained in the HELLP group; 43.8% of the HELLP group had evidence of intra-abdominal hemorrhage or hepatic hematoma or rupture. After best efforts at adjudication, there were no differences observed between the groups in terms of hemoglobin, platelet count, glucose level, ammonia, lactate or phosphate levels, evidence or incidence of pancreatitis, or presence of eclampsia/pre-eclampsia. The groups differed in aminotransferase levels, the median AST level in the HELLP group being 642 IU/L (48-7194 IU/L) versus 85 IU/L (45-165 IU/L, for AFLP ($p < 0.009$). Serum ALT values were also significantly higher in the HELLP group. Lactate dehydrogenase and haptoglobin levels as measures of hemolysis were not uniformly collected. Comparing the three PAALD groups for likelihood of TFS using the ALFSG Prognostic Index, there were no apparent differences between AFLP, HELLP and the Mixed group, varying between 74 and 67% (Table 3).

Swansea criteria to diagnose AFLP

The Swansea criteria to diagnose AFLP or HELLP developed in 2002 (7), including both clinical symptoms and laboratory and imaging findings were applied to this cohort. Table 5 delineates the features of the Swansea criteria and how they were met within each of the study groups. Six of 14 criteria are required to confirm a diagnosis of AFLP *in the absence of another diagnosis* and two of three HELLP criteria must be met for HELLP. We could adequately determine the criteria for 66/70 patients but were limited by not having available uric acid for most patients. Several other criteria (e.g., ultrasound liver imaging) were missing in additional cases. Despite these limitations, the median number of diagnostic criteria that were met, as evidence for AFLP for the PAALD, APAP and Other groups were 10, 11 and 12 respectively. Thus, we found that 100% of PAALD and 100% of APAP patients met Swansea AFLP criteria; one PAALD patient initially diagnosed as ALI only met criteria when she became encephalopathic, while the remaining patients all met criteria at study entry. Even within the Other group, 11/14 met Swansea criteria. There were no differences in numbers of AFLP or HELLP criteria met between those adjudicated to AFLP versus those adjudicated as HELLP; however, those not meeting HELLP criteria typically lacked data concerning hemolysis (Table 5). There were no evident overlaps of etiologic diagnoses with one exception. Our adjudication found one subject that might have had both APAP and HELLP combined, presenting with elevated liver enzymes at term, leading to Caesarean section and a subsequent elevated APAP adduct level; for purposes of the study, the patient was considered to have HELLP with secondary APAP overdose.

Death and transplantation in PAALD

Features and outcomes for the 10 patients that died or underwent transplant among the PAALD cases were carefully reviewed (Table 6). Nine of 10 had undergone Caesarean section; 6 transplants were performed with one post-transplant death and there were four other deaths without transplantation among the PAALD group; only one of the four was listed for transplantation then subsequently removed from listing because of cerebral edema: the others had multiple factors, including cerebral edema, that precluded listing, and appeared to develop extra-hepatic complications including pulmonary emboli, pancreatitis, intra-abdominal infection and seizures. Of note, lactate levels available for 6 of the 10 were markedly elevated in 4. Individual times from delivery to study admission as well as time from study admission to outcome are also shown in Table 6. The 6 transplanted PAALD patients had a median time from admission and urgent Caesarean section (same day) to transfer to the transplant center of 5.0 days, with an overall time from delivery to liver transplant of 10.5 days. Median time from hospitalization to study admission was 3.0 days for those who survived without transplantation.

Discussion

Hepatologists are often consulted by the obstetrical service when liver disease occurs in pregnancy, since liver diseases unique to pregnancy, though rare, carry a poor prognosis (5,6). Our study encompassed not only those with PAALD but any patient presenting with ALF/ALI while pregnant. Our main finding was that only 50% of ALFSG registry subjects were accounted for by pregnancy-related conditions, all occurring peri-partum. The remaining cases were largely APAP overdoses plus a miscellaneous 'Other' etiologies group. For analysis purposes, we separated the patients into these three groups: PAALD, APAP and Other.

PAALD was associated with fetal survival of 88.9% and 88.6% overall maternal survival; however, overall maternal transplant-free survival was only 68.6% and 11 received a liver graft, 6 with PAALD and 5 in the APAP (1) or Other (4) categories. More transplants occurred in those with HELLP (4) than AFLP (1), Mixed (1), although the difference was not statistically significant. PAALD is easily recognized in most obstetrical settings and is often heralded by pre-eclampsia in the third trimester, both in HELLP and AFLP. There is currently no specific prognostic score to determine outcome or need for transplantation in this patient population. A possible prognostic score was proposed recently that includes lactate level and presence or absence of hepatic encephalopathy (16). While we did not collect lactate levels uniformly, several of those that died or required transplants among the 10 PAALD patients had remarkably high lactate levels. If larger numbers of patients were available to study, this might prove to be a valuable prognostic tool. Median lactate levels differed between those that survived and those that died or were transplanted (2.9 mmol/L (1.7-6.2) vs. 8.8 1.4-76.7) but this was not significant ($p = 0.72$). We also examined the performance of the ALFSG prognostic index in this population (17). Overall, those with TFS had a median likelihood of survival of 75% (range 20-92%) whereas those who died or required transplantation had a 40% (17-92%) likelihood of survival, ($p = 0.049$). Future

prospective studies might combine lactate levels with the ALFSG prognostic index specifically for determination of pregnancy-related outcomes.

For all PAALD patients, the initial hepatology consultation and/or transfer to a transplant center occurred post-partum; however, this was not always promptly carried out. The median time to transfer to the transplant center for those who died or required transplant was 5.0 days and time to transplant or death was 10.5 days. Recognition of the severity of disease and early transfer may be crucial in preventing maternal deaths. It should be recognized that these data are biased toward the most severe cases: we only observed 35 instances of PAALD over a 22-year period in this North American tertiary care study. The total number of PAALD cases is difficult to discern but has been estimated at between 1 in 7,000 to 1 in 16,000 pregnancies (4,13).

Outcomes among the three groups were poorest among the PAALD and Other groups, the latter being a heterogeneous mixture of etiologies including cancer, DILI, AIH and HSV infection, that all have less than 50% TFS once ALF is present (12). Virtually all the deaths and transplants occurred within these two groups. Table 6 details some of the features of the 4 deaths and 6 transplants among the 35 PAALD patients. The deaths were equally distributed between AFLP and HELLP diagnoses. Causes of death appeared largely to be extra-hepatic in origin, while those receiving transplants had demonstrated ongoing liver injury post-partum but survived long enough to receive a graft. Delayed recognition of ALF and its consequences may lead to late referral that may contribute to these unfortunate and possibly avoidable deaths.

A committee of senior hepatologists reviewed all cases in the series, some of which lacked complete information and most of which did not include liver biopsies, to help categorize the PAALD cases as AFLP and HELLP. Although these are thought to be two distinct clinical syndromes with unique clinical and histological features (18), there is a clear overlap of presenting features which has long been recognized (19). Diagnosis on clinical grounds is challenging, since imaging is not definitive and clinical symptoms and serological data often nonspecific (20). Only a biopsy showing peri-portal necrosis (HELLP) or micro-vesicular fat (AFLP) (Figure) or evidence of hepatic hematoma or rupture with intra-abdominal hemorrhage provided any certainty in differentiating HELLP and AFLP. Little has been written about use of imaging to distinguish the two; however, non-alcoholic fatty liver might also be present, in addition to possible micro-vesicular fat (21). The main value of hepatic imaging is to exclude intra- or extra-hepatic hemorrhage. More recently, magnetic resonance-based proton density fat fraction (PDFF) testing has shown to be a very sensitive and specific means of detecting steatosis in the liver in a quantitative manner but this technique has not been applied to ALF patients with suspected AFLP to our knowledge (22). Since biopsy is rarely performed, certainty of diagnosis in many cases will continue to be limited, given the number of features shared by both conditions.

Likewise, we could not identify any additional specific clinical features that assisted in clarifying either diagnosis. Only 10 of the 70 fulfilled criteria for ALI (INR >2.0 and no encephalopathy, four of whom converted to ALF thereafter; we did not analyze this group separately because of its small size. Pre-eclampsia, eclampsia, platelet counts, presence of

pancreatitis or hypoglycemia, have all been alleged to be somewhat specific but were not more common in one condition or the other in the present study. We did find that aminotransferases were significantly higher in HELLP than in those adjudicated cases with AFLP.

We were also intrigued to test whether the Swansea criteria applied to this patient population of severely ill post-partum patients could validate their use for clinicians. We found that most Swansea features were also present in those with ALF of any cause. All patients met criteria save one, indicating that the Swansea criteria truly represent features common to ALF patients, but not specifically to AFLP patients (3). While most APAP cases are readily recognized and would be excluded from Swansea consideration since the criteria also mention *absence* of another cause, some APAP cases and many ALF etiologies are not so easily discerned (23). In our hands, the Swansea criteria, including so many non-specific items, failed to provide any clear delineation between AFLP and HELLP, with a low specificity and positive predictive value among pregnant ALI and ALF patients. It remains unclear whether these very severe examples of AFLP and HELLP can be reasonably separated using clinical or biochemical criteria (13,24). Given these uncertainties, we wonder whether diagnoses in recent studies based on pooled data such as SRTR can be trusted since histological diagnosis is so rarely available (25).

Thus, from clinical information alone and without a biopsy, an accurate diagnosis is hard to achieve. Should a liver biopsy be performed in all cases? This is doubtful--we question the risk of liver biopsy in these patients most of whom have diminished platelet counts. Whether there are, in fact, any clinical differences in management that follow from determining whether AFLP or HELLP is found remains to be seen, at least for full term pregnancies (3). Evidence of hepatic hemorrhage or rupture, of course, mandates steps to control the bleeding.

Acetaminophen toxicity, the second largest group after PAALD, represents the most frequent cause of ALF in the USA and in Europe (26,27). An overdose may occur during any trimester, some representing suicide attempts and others inadvertent excessive use for relief of symptoms (28); in the present series most were thought to be unintentional overdoses. Overall, outcomes remain quite good, although fetal demise and occasional maternal deaths do occur, in similar numbers to those women not pregnant at the time of the incident. In the current series, at least 11 of the 21 APAP cases received NAC with information lacking on the remaining subjects. Fetal outcomes did not appear to be related to the route or duration of NAC administration (data not shown). Confirmatory testing for serum acetaminophen-protein adducts (14,15) was undertaken in 17 of the 21 cases and a level exceeding 1 nmol/mL was present in all subjects tested. One additional positive adduct subject represented a patient at term who likely had taken an unintentional overdose but underwent emergent delivery given her elevated liver tests and term status at 38 weeks. That most cases appeared to be unintentional suggests that they should be avoidable with better consumer/prenatal education (13).

The Other group was of interest in that no single diagnosis predominated; 3 HSV-hepatitis cases were found, as well as several other causes generally associated with poor outcomes

(9-11). We were surprised to find no cases of viral hepatitis A through E in pregnancy during the 22 years of this study, since earlier studies featured viral hepatitis as the most common cause of jaundice in pregnancy (29,30). The low incidence of viral hepatitis in our cohort may be due to prior hepatitis A and B vaccinations amongst younger American patients (31,32). Hepatitis E, long recognized as particularly prevalent in the developing world, was also not seen in the present study, likely due to the different genotypes and disease patterns observed in North America that do not seem prone to severe liver injury (33,34). We also did not identify any patients with intrahepatic cholestasis of pregnancy leading to ALF or ALI, since this group does not typically lead to severe liver cell injury, though it may occur in the third trimester (35).

This study is limited by its retrospective nature although the data was collected in a prospective fashion. We identified and enrolled those cases of ALF and ALI of all etiologies that came to the attention of liver specialists in tertiary care centers. In some instances, information such as peri-partum blood pressures were not captured. In other instances, details of fetal outcome were unknown. An additional limitation of our study was the lack of genetic testing of the mothers and infants with PAALD for LCHAD mutations that have been identified in up to 20% of women with AFLP (36). However, more recent studies have identified that some LCHAD mutations may be overrepresented in pregnant women with HELLP and preeclampsia (37,38). Testing was not feasible due to the lack of available DNA samples in many of the subjects.

In conclusion, half of the women who develop ALF or ALI during pregnancy are not suffering from a disease directly related to the pregnancy itself but rather from other diseases that are relatively common in this age group, but not currently including the common varieties of viral hepatitis. Maternal outcomes are generally favorable for both PAALD and APAP, but less so for those with other etiologies. In contrast, fetal outcomes are not as satisfactory, particularly for the Other and APAP causes, since their occurrence across all trimesters limits fetal maturity. Recognition of PAALD in the third trimester is the first step to diagnosis and initial treatment. Hepatologists are typically consulted when the associated liver disease does not resolve immediately post-partum. Early referral and transplant consideration are mandated as it is for anyone with signs and symptoms of ALF.

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Abbreviations

ALF	acute liver failure
ALI	acute liver injury

ALFSG	Acute Liver Failure Study Group
AFLP	Acute fatty liver of pregnancy
APAP	acetaminophen (N-acetyl-p-aminophenol)
HELLP	Hemolysis, Elevated liver enzymes, low platelets syndrome
LT	liver transplantation
NAC	N-acetylcysteine
PAALD	Pregnancy-associated liver disease
PI	Principal investigator at the study site
TFS	Transplant free (spontaneous) survival

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Figure.
Pregnancy-associated liver injury. A. Periportal necrosis and hemorrhage in a patient with HELLP syndrome. Centrilobular area, upper right, is well preserved (H&E, 100x). B. Injury suggestive of fatty liver disease of pregnancy with evidence of microvesicular steatosis (arrow) (H&E, 600x)

Table 1.

Comparison of demographics, pregnancy features and outcomes between the PAALD, APAP and Other groups.

N	All 70	AFLP/HELLP 35	APAP 21	Other 14	P-value
Age *	29 (19-43)	31 (19-40)	27 (19-43)	29 (22-38)	0.334
Race **					0.098
White	47 (67.1%)	22 (62.9%)	18 (87.5%)	7 (50.0%)	
AA	16 (22.9%)	8 (22.9%)	3 (14.3%)	5 (35.7%)	
Other	7 (10.0%)	5 (14.3%)	-	2 (14.3%)	
Ethnicity					0.584
Hispanic	3 (4.3%)	2 (5.7%)	-	1 (7.1%)	
Pregnancy / Delivery					
Gestational Age Preeclampsia	34 (6-39)	36 (28-39)	30 (6-38)	30 (10-35)	<0.001 ***
	13 (41.9%)	11 (68.8%)	2 (28.6%)	0 (0%)	0.002
Eclampsia C-Section	3 (12.5%)	2 (15.4%)	1 (16.7%)	0 (0%)	0.796
	34 (75.6%)	25 (89.3%)	4 (44.4%)	5 (35.7%)	0.13
Maternal Outcome (21 days)					
TFS Transplant	48 (68.6%)	23 (65.7%)	17 (81.0%)	8 (57.1%)	0.217
	11 (15.7%)	6 (17.1%)	1 (4.8%)	4 (28.6%)	0.159
Death Unknown	8 (11.4%)	4 (11.4%)	2 (9.5%)	2 (14.3%)	0.777
	4 (5.7%)	2 (5.7%)	2 (9.5%)	-	
Acute Liver Failure Prognostic Index					
% TFS	74(6-97)	72 (17-92)	86 (22-97)	34 (6-77)	<0.001 ***
Fetal Outcome (21 days)					
Alive	32 (76.2%)	24 (88.9%)	3 (57.1%)	5 (37.5%)	
Dead	10 (23.8%)	3 (11.1%)	4 (42.9%)	3 (62.5%)	

* Median (range)

** n (%)

*** p-value significant at <0.05

Table 2.

Comparison of laboratory features on admission for the three groups: PAALD, APAP and Other.

	All	PAALD	APAP	Other	P-value
N	70	35	21	14	
Hemoglobin * [g/dL]	9.4 (6.0-14.8)	9.2 (6.7-14.4)	9.8 (7.7-13.9)	9.6 (6.0-14.8)	0.679
WBC * x10 ³ /cu mm	16.5 (2.9-58.0)	20.4 (5.8-58.0)	13.3 (6.5-34.9)	9.6 (2.9-29.1)	0.001 **
Platelet * x10 ³ /cu mm	108 (26-452)	84 (26-258)	138 (37-452)	178 (26-343)	0.009 **
INR *	1.9 (1.2-12.2)	1.8 (1.2-4.6)	2.1 (1.3-6.0)	2 (1.6-12.2)	0.012 **
AST * [IU/L]	524 (45-13288)	117 (45-7194)	2368 (73-13288)	846 (191-8925)	<0.001 **
ALT * [IU/L]	340 (3-5458)	60 (3-1805)	2333 (109-5458)	582 (131-2572)	<0.001 **
T Bili * [mg/dL]	7.4 (0.7-42.4)	10.5 (2.5-42.4)	3.3 (0.7-8.6)	11 (1.6-28.5)	<0.001 **
Creatinine * [mg/dL]	1.7 (0.3-5.8)	2.4 (0.4-5.8)	1.4 (0.3-5.4)	0.7 (0.3-2.7)	0.003 **
Ammonia * [μmol/L]	99.5 (21-200)	89 (21-193)	104 (39-200)	166 (120-175)	0.110
Phosphate * [mg/dL]	3.3 (1.0-10.8)	4.0 (1.7-10.8)	2.9 (1.6-8.70)	3.4 (1.0-8.7)	0.032 **
Lactate * [mmol/L]	3.6 (0.7-76.6)	3.7 (1.4-76.6)	3.4 (0.9-16.5)	3.5 (0.7-12.1)	0.909

* Median (range)

** p-value significant at <0.05; all lab values obtained at study admission

Table 3.

Comparison of pregnancy features and outcomes of the AFLP and HELLP groups. Limited data were available in some categories, such as fetal outcomes. Percentages reflect, in some instances, incomplete data.

	All (n=35)	AFLP (n=14)	HELLP (n=16)	Mixed (n=5)	p-value
G1/P1 n (%)	16 (57.1%)	6 (60.0%)	8 (53.3%)	2 (66.7%)	
Maternal Outcome (21 days)					
Transplant-free survival n (%)	23 (65.7%)	10 (71.4%)	10 (62.5%)	3 (60.0%)	0.764
Transplant n (%)	6 (17.1%)	1 (7.1%)	4 (25.0%)	1 (20.0%)	0.469
Death n (%)	4 (11.4%)	2 (14.3%)	2 (12.5%)	0	0.89
Unknown n (%)	2 (5.7%)	1 (7.1%)	-	1 (20.0%)	
Acute Liver Failure Prognostic Index					
% TFS	72 (17-92)	70 (35-85)	74 (19-92)	67 (17-92)	0.669
Fetal Outcome (21 days)					
Alive n (%)	24 (88.9%)	8 (80.0%)	13 (92.9%)	3 (100%)	0.689
Dead n (%)	3 (11.1%)	2 (20.0%)	1 (7.0%)	--	

Table 4.

Comparison of clinical and laboratory features at study admission between the AFLP and HELLP groups.

	All	AFLP	HELLP	Mixed	p-value
N	35	14	16	5	
Age	31 (19 - 40)	32 (22 - 40)	30 (23 - 37)	28 (19 - 37)	0.272
Hypoglycemic **	14 (66.8%)	7 (50.0%)	6 (60.0%)	1 (100%)	1.000
Pancreatitis **	13 (50.0%)	7 (58.0%)	5 (45.5%)	1 (50.0%)	0.836
Pre-Eclampsia **	12 (66.7%)	2 (40.0%)	9 (90.0%)	1 (100%)	0.074
Eclampsia **	2 (13.3%)	1 (25.0%)	0 / 8	1 (33.3%)	0.200
AFLP on biopsy **	6 (50.0%)	6 (85.7%)	0/4	0/1	0.015
Hemorrhage **	13 (37.1%)	4 (28.5%)	7 (43.8%)	2 (40.0%)	0.721
Hemoglobin * [g/dL]	9.2 (6.7 - 14.4)	9.2 (6.7 - 11.5)	9.9 (7.4 - 14.4)	9 (6.7 - 9.9)	0.48
WBC * x10 ³ /cu mm	20.4 (5.8-58.0)	21.0 (6.0-58.0)	21.9 (5.87-44.4)	17.4 (8.4-25.4)	0.670
Platelet * x10 ³ /cu mm	84 (26 - 258)	95.5 (31 - 203)	82 (26 - 258)	76 (45 - 170)	0.644
INR *	1.8 (1.2 - 4.6)	1.8 (1.2 - 2.1)	1.7 (1.3 - 4.6)	1.6 (1.4 - 2.7)	0.988
AST * [IU/L]	117 (45 - 7194)	85.5 (45 - 165)	642 (48 - 7194)	119 (71 - 177)	0.009 **
ALT * [IU/L]	60 (2 - 1805)	49 (23 - 154)	336 (3 - 1805)	57 (33 - 258)	0.045 **
T Bilirubin * [mg/dL]	10.5 (2.5 - 42.4)	8.0 (2.5 - 25.8)	12.9 (3.6-42.4)	12.4 (3.1 - 30.5)	0.171
Creatinine * [mg/dL]	2.38 (0.4 - 5.8)	1.65 (0.5 - 2.9)	2.85 (0.4 - 5.8)	2.7 (0.8 - 3.5)	0.06 ***
Ammonia * [μmol/L]	89 (21-193)	107 (72-145)	69 (46-104)	107 (21-193)	0.328
Phosphate * [mg/dL]	4.0 (1.7-10.8)	3.5 (2.1-6.0)	4.7 (1.7-10.8)	6.0 (2.2-7.7)	0.354
Lactate * [mmol/L]	3.7 (1.4-76.6)	5.5 (1.4-76.6)	2.4 (1.7-11.8)	7.8 (3.7-20.1)	0.223

* Median (range)

** n (%)

*** p-value significant at <0.05; all lab values obtained at study admission

Fourteen, 'Swansea' diagnostic criteria for AFLP and 3 for HELLP (6 or more of the above features qualify for AFLP without explanation of another condition and two of 3 for HELLP). Adapted from reference 7.

Table 5.

AFLP	APAP (21)	Other (14)	PAALD (35)	AFLP (14)	Mixed (5)	HELLP (16)
1. Vomiting	15	6	20	9	4	7
2. Abdominal pain	9	9	23	7	5	11
3. Polydipsia/polyuria **						
4. Elevated transaminases (AST 42 IU/L)	21	14	35	14	5	15
5. Elevated bilirubin (>14 umol/L or 0.8 mg/dL)	21	14	35	14	5	16
6. Hypoglycemia (<4 mmol/L or 72 mg/dL)	3	4	10	4	2	4
7. Elevated urate (>340 umol/L or 5.7 mg/dL) **						
8. Leukocytosis (>11 x 10 ⁹ /L)	13	7	24	13	4	15
9. Elevated ammonia (>47 umol/L)	13	5	25	10	2	13
10. Ascites or bright liver on ultrasound (US)	2	7	24	10	4	10
11. Encephalopathy	19	12	32	12	5	15
12. Renal failure (Creatinine > 1.7 mg/dL or 150 umol/L)	9	4	26	14	5	16
13. Coagulopathy (PT > 14s; aPTT > 34s)	21	14	35	14	5	16
14. Microvesicular steatosis on liver biopsy	7	2	10	10	0	0
Met 6 or more Criteria	21 (100%)	11 (78.6%)	34* (97.1%)	14 (100%)	5 (100%)	15* (93.8%)
HELLP						
15. Increased AST (>70 iu/mL)	21	14	31	11	5	15
16. Decreased Platelets (<100 x 10 ⁹ /L)	5	5	24	7	4	13
17. Hemolysis	13	10	22	9	5	8
Met 2 or more criteria	16 (76.2%)	10 (71.4%)	29 (82.9%)	10 (71.4%)	5 (100%)	14 (87.5%)

* ALI - HELLP subject met 5 initially then converted to ALF and met 6

** Information not collected as part of the ALF study

Table 6.

Diagnoses, outcomes and other features of the 10 PAAALD patients who died or required liver transplantation.

Pt. no.	AFLP/HELLP	OLT/Death	Days Hosp – Study Admit*	OLT/Death Date**	Other history	Delivery mode	Peak INR	Peak AST [IU/L]	Lactate [mmol/L]	Complications
1	AFLP	Death	11	6	Prior gastric bypass	C/S	1.7	1023	6.8	Seizures, pulmonary embolus, cerebral edema
2	AFLP	OLT	3	6	Prior AFLP	C/S	1.7	50	1.4	Acute pancreatitis/sepsis
3	AFLP	Death	3	6	IDU, amphetamine cocaine	D&C	2.8	210	76.6	Fetal demise at 31 wks, seizures, cerebral edema
4	Both	OLT X3, late death	5	1 1 st OLT	UTI, ? nitrofurantoin toxicity	C/S	>10.0	748	70.0	Primary non-function x2, Aspergillus pneumonia, subdural hematoma
5	HELLP	Death	7	7	Placental abruption	C/S	2.3	9810	11.8	Pulmonary embolus, cerebral edema
6	HELLP	OLT	2	10	Pre-eclampsia	C/S	2.1	4929	-	Continued worsening post C/S
7	HELLP	OLT	11	1	Pre-eclampsia	C/S	1.5	88	-	Continued worsening post C/S
8	HELLP	Death	2	2	Pre-eclampsia, bleeding	C/S	3.6	>8000	-	Intra-abdominal infection, cerebral edema
9	HELLP	OLT	3	10	Labor @ 28 wks	C/S	2.5	1891	-	Continued worsening post C/S
10	HELLP	OLT	3	6	Pre-eclampsia, multiparity	C/S	4.6	1392	1.7	Fluid overload, continued worsening post C/S

Days from Hospital admission to study admission

** Days from study admission to outcome: total time from delivery to outcome is determined by summing the two numbers for each patient. C/S: Cesarean section; D&C: dilation and curettage; OLT: orthotopic liver transplantation.