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

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BACKGROUND AND AIMS: Acute liver failure (ALF), characterized by sudden onset of coagulopathy (international normalized ratio [INR] ≥ 1.5) and encephalopathy, may occur during pregnancy either as a pregnancy-associated etiology or an unrelated and coincidental 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.

APPROACH AND RESULTS: 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 (pregnancy-associated liver disease; PAALD) and how many were attributed to other etiologies. Thirty-five of the 70 were considered PAALD, of whom nearly half were attributed to hemolysis, elevated liver enzymes, and 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 before 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.

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 etiology of liver failure. (Hepatology 2020;72:1366-1377).

Acute liver failure (ALF) is a rare condition, affecting approximately 2,000-3,000 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 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 acute liver diseases (PAALDs).[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

Abbreviations: AFLP, acute fatty liver of pregnancy; AIH, autoimmune hepatitis; ALF, acute liver failure; ALI, acute liver injury; ALFSG, Acute Liver Failure Study Group; ALT, alanine aminotransferase; APAP, acetaminophen (N-acetyl-p-aminophenol); AST, aspartate aminotransferase; HELLP, hemolysis, elevated liver enzymes, low platelets syndrome; HSV, herpes simplex virus; INR, international normalized ratio; LT, liver transplantation; NAC, N-acetylcysteine; PAALD, pregnancy-associated acute liver disease; TFS, transplant-free (spontaneous) survival; VH, viral hepatitis.

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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 >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 international normalized ratio [INR] ≥ 1.5) and those with acute liver injury (ALI; severe injury with INR of ≥2.0, but without encephalopathy).[12] To better understand and manage future pregnant women with ALF/ALI, 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 intrauterine 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, whereas those with ALF, by definition, are not capable of consent, requiring the signature of next of kin or other legally authorized representative. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki. Prior approval was obtained from institutional review committees at each of the participating sites. 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 (Charleston, SC). Data included demographics, etiology, detailed laboratory profiles, imaging, and liver biopsy information, where available, outcomes at 21 days: death, liver transplantation (LT) or "spontaneous" or transplant-free survival (TFS), and fetal outcomes as well, where available. Etiological diagnosis was initially established by the site principal investigator 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 were not available at the time of initial etiological 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

Nonparametric Kruskal-Wallis analysis or Mann-Whitney U analysis was used for laboratory data and Fisher's exact test for demographic data across the various etiological subgroups, using SPSS software (v25; IBM Corp., Armonk, NY).

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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 postpartum period, defined as within a week of delivery; 6 were initially classified as ALI, including 2 with PAALD (AFLP), 2 with APAP, and 2 with other etiologies. Median age of enrollees was 29; 67.1% were white, 22.9% black, 4.3% Asian, and 4.3% Hispanic (Table 1). The specific PAALDs (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, APAP, and the remaining "other" groups (Tables 1 and 2). All PAALD patients were enrolled in the study postpartum, given that emergent delivery of the infant invariably had occurred once the obstetrical team became aware of a liver-related issue. Median gestational age of the PAALD group was 36 weeks (range, 28-39). PAALD patients were further adjudicated as AFLP (n = 14), HELLP (n = 16), and those where delineation was uncertain (n = 5; Tables 3 and 4). APAP toxicity was present in 21 (30% of the overall group, 60% of the remainder). Of these, 4 were considered intentional (attempted suicidal ingestion), 15 unintentional (without suicidal intent, typically for pain relief), and 2 were unknown; 11 of the 21 APAP cases had received *N*-acetylcysteine (NAC), route unspecified, but virtually all intravenously, and the remaining 10 were unknown with regard to NAC. Ten non-APAP subjects received NAC, including 3 AFLP, 2 HELLP and 5 "others." The remaining 14 "other" group was comprised of many etiologies: autoimmune hepatitis (AIH; 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

TABLE 1. Comparison of Demographics, Pregnancy Features, and Outcomes Between the PAALD, APAP, and Other Groups

	All	AFLP/HELLP	APAP	Other	*P* Value
N	70	35	21	14	
Age, years*	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%)	
Black	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	34 (6-39)	36 (28-39)	30 (6-38)	30 (10-35)	<0.001‡
Preeclampsia	13 (41.9%)	11 (68.8%)	2 (28.6%)	0 (0%)	0.002
Eclampsia	3 (12.5%)	2 (15.4%)	1 (16.7%)	0 (0%)	0.796
C-section	34 (75.6%)	25 (89.3%)	4 (44.4%)	5 (35.7%)	0.130
Maternal outcome (21 days)					
TFS	48 (68.6%)	23 (65.7%)	17 (81.0%)	8 (57.1%)	0.217
Transplant	11 (15.7%)	6 (17.1%)	1 (4.8%)	4 (28.6%)	0.159
Death	8 (11.4%)	4 (11.4%)	2 (9.5%)	2 (14.3%)	0.777
Unknown	4 (5.7%)	2 (5.7%)	2 (9.5%)	—	
ALF 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 (625.%)	

*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* $\times 10^3$/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* $\times 10^3$/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(45-13,288)	117 (45-7,194)	2,368 (73-13,288)	846 (191-8,925)	<0.001†
ALT* [IU/L]	340 (3-5,458)	60 (3-1,805)	2,333 (109-5,458)	582 (131-2,572)	<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.
Abbreviations: T Bili, total bilirubin; WBC, white blood cells.

TABLE 3. Comparison of Pregnancy Features and Outcomes of the AFLP and HELLP Groups

	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)					
TFS, 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	0.890
Unknown, n (%)	2 (5.7)	1 (7.1)	—	1 (20.0)	
ALF 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)	—	

Limited data were available in some categories, such as fetal outcomes. Percentages reflect, in some instances, incomplete data.

testing for hepatitis E was performed on 5 patients, 3 with PAALD, 1 with autoimmune hepatitis, and 1 with APAP-induced hepatotoxicity. All were negative for antibody to hepatitis E virus (anti-HEV) immunoglobulin M; 1 (AIH) was positive for anti-HEV immunoglobulin G.

Subsequent testing for APAP adducts was performed on 23 subjects, including 17 presumed to have APAP toxicity as well as 3 PAALD and 3 "others." All APAP adduct levels were confirmed positive in those adjudicated as APAP overdose on clinical grounds; of the 6 remaining patients tested, 5 had undetectable adducts; however, 1 subject did test positive for APAP adducts (see below).

COMPARISON OF CLINICAL FEATURES AND OUTCOMES FOR THE THREE GROUPS

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 two-thirds 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

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, years	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)	0.480
WBC* $\times 10^3$/cu mm	20.4 (5.8-58.0)	21.0 (6.0-58.0)	21.9 (5.87-44.40)	17.4 (8.4-25.4)	0.670
Platelet* $\times 10^3$/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 (45-7,194)	85.5 (45-165)	642 (48-7,194)	119 (71-177)	0.009‡
ALT* [IU/L]	60 (2-1,805)	49 (23-154)	336 (3-1,805)	57 (33-258)	0.045‡
T Bili* [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)	0.060‡
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.
Abbreviations: T Bili, total bilirubin; WBC, white blood cells.

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 PAALD patients when compared to the other two groups. Hemoglobin, INR, ammonia, and lactate values were similar across the groups, whereas median aminotransferase, phosphate, and bilirubin levels varied by etiological group as well. For example, 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 of 70 (82.8%), broken down as follows: spontaneous survival or TFS, 48 of 70 (68.6 %); 11 of 70 (15.7%) LT, 1 of whom died post-LT; and 7 of 70 (12.9%) died without LT. Outcome at 21 days was unknown in 4; 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 TFS using the ALFSG Prognostic Index (Table 1).[17] The three main groups differed significantly, with PAALD having a predicted 72% TFS versus 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 microvesicular fat or periportal necrosis on biopsy (Fig. 1), or evidence of hepatic rupture, zonal infarction, or intraperitoneal hemorrhage in HELLP. Less

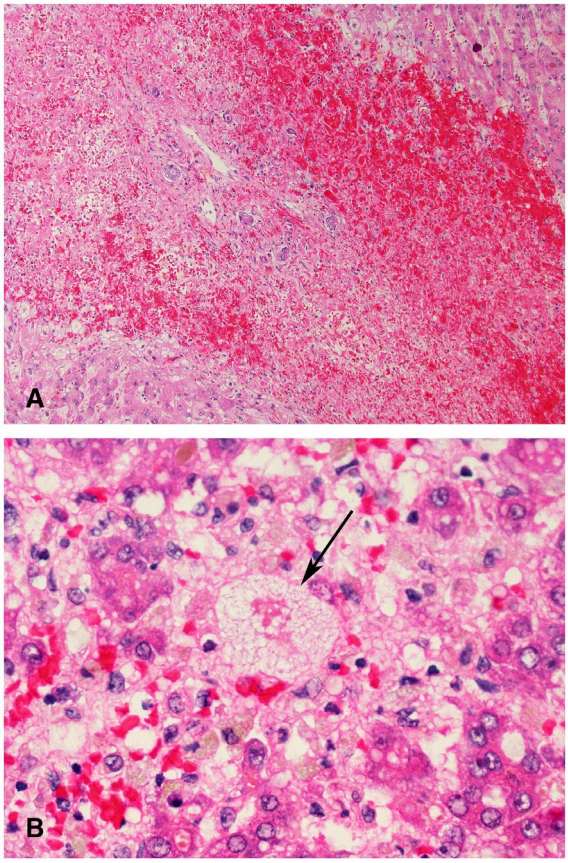

FIG. 1. Pregnancy-associated liver injury. (A) Periportal necrosis and hemorrhage in a patient with HELLP syndrome. Centrilobular area, upper right, is well preserved (H&E, ×100). (B) Injury suggestive of fatty liver disease of pregnancy with evidence of microvesicular steatosis (arrow; H&E, ×600). Abbreviation: H&E, hematoxylin and eosin.

certainty was associated with presence of hypoglycemia or pancreatitis (both presumably supporting AFLP), or pre-eclampsia or eclampsia, hemolysis, and 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 microvesicular 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. Groups differed in aminotransferase levels, the median AST level in the HELLP group being 642 (48-7,194) versus 85 IU/L (45-165) 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 of 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; 1 PAALD patient initially diagnosed as ALI only met criteria when she became encephalopathic, whereas the remaining patients all met criteria at study entry. Even within the "other" group, 11 of 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 etiological diagnoses, with one exception. Our adjudication found 1 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.

TABLE 5. Fourteen "Swansea" Diagnostic Criteria for AFLP and Three for HELLP

	APAP (21)	Other (14)	PAALD (35)	AFLP (14)	Mixed (5)	HELLP (16)
AFLP						
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 × 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 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 >14 sec; aPTT >34 sec)	21	14	35	14	5	16
14. Microvesicular steatosis on liver biopsy	7	2	10	10	0	0
Met six 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 × 10^9/L)	5	5	24	7	4	13
17. Hemolysis	13	10	22	9	5	8
Met two or more criteria	16 (76.2%)	10 (71.4%)	29 (82.9%)	10 (71.4%)	5 (100%)	14 (87.5%)

Six or more of the above features qualify for AFLP without explanation of another condition and two of three for HELLP.
Adapted from Ch'ng et al.[7]
*ALI-HELLP subject met five initially, then converted to ALF and met six.
†Information not collected as part of the ALF study.
Abbreviations: US, ultrasound; PT, prothrombin time; aPTT, activated partial thromboplastin time.

DEATH AND TRANSPLANTATION IN PAALD

Features and outcomes for the 10 patients who 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 posttransplant death, and there were four other deaths without transplantation among the PAALD group; only 1 of the 4 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 extrahepatic 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 LT 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, given that 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 peripartum. 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.

TABLE 6. Diagnoses, Outcomes and Other Features of the 10 PAALD Patients Who Died or Required LT

Patient 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	Previous gastric bypass	C/S	1.7	1,023	6.8	Seizures, pulmonary embolus, cerebral edema
2	AFLP	OLT	3	6	Previous 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 weeks, seizures, cerebral edema
4	Both	OLT ×3, late death	5	1 first OLT	UTI, nitrofurantoin toxicity	C/S	>10.0	748	70.0	Primary nonfunction ×2, Aspergillus pneumonia, subdural hematoma
5	HELLP	Death	7	7	Placental abruption	C/S	2.3	9,810	11.8	Pulmonary embolus, cerebral edema
6	HELLP	OLT	2	10	Pre-eclampsia	C/S	2.1	4,929	—	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	>8,000	—	Intra-abdominal infection, cerebral edema
9	HELLP	OLT	3	10	Labor @ 28 weeks	C/S	2.5	1,891	—	Continued worsening post-C/S
10	HELLP	OLT	3	6	Pre-eclampsia, multiparity	C/S	4.6	1,392	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.
Abbreviations: C/S, cesarean section; D&C, dilation and curettage; OLT, orthotopic liver transplantation; IDU, injection drug use; UTI, urinary tract infection.

PAALD was associated with fetal survival of 88.9% and 88.6% overall maternal survival; however, overall maternal TFS 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] Although we did not collect lactate levels uniformly, several of those who 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 who survived and those who died or were transplanted (2.9 mmol/L [1.7-6.2] vs. 8.8 [1.4-76.7]), but this was not significant ($P \leq 0.72$). 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% (range, 17-92) likelihood of survival, ($P \leq 0.049$). 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 postpartum; however, this was not always promptly carried out. 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 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 <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 four deaths and six transplants among the 35 PAALD patients. The deaths were equally distributed between AFLP and HELLP diagnoses. Causes of death appeared largely to be extrahepatic in origin, whereas those receiving transplants had demonstrated ongoing liver injury postpartum 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, given that imaging is not definitive and clinical symptoms and serological data often nonspecific.[20] Only a biopsy showing periportal necrosis (HELLP) or microvesicular fat (AFLP) (Fig. 1) 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, nonalcoholic fatty liver might also be present, in addition to possible microvesicular fat.[21] The main value of hepatic imaging is to exclude intra- or extrahepatic hemorrhage. More recently, magnetic resonance-based proton-density fat fraction 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] Given that 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), 4 of whom

converted to ALF thereafter; we did not analyze this group separately because of its small size. Preeclampsia, eclampsia, platelet counts, and 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 postpartum 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 1, indicating that the Swansea criteria truly represent features common to ALF patients, but not specifically to AFLP patients.[3] Whereas most APAP cases are readily recognized and would be excluded from Swansea consideration given that 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 nonspecific 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 the Scientific Registry of Transplant Recipients, can be trusted given that 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.

APAP toxicity, the second-largest group after PAALD, represents the most frequent cause of ALF in the United States and 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 APAP-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, given that earlier studies featured viral hepatitis (VH) as the most common cause of jaundice in pregnancy.[29,30] The low incidence of VH in our cohort may be attributable to previous hepatitis A and B vaccinations among younger American patients.[31,32] Hepatitis E, long recognized as particularly prevalent in the developing world, was also not noted in the present study, likely because of 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, given that 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 were 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 peripartum blood pressures, was 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 long-chain 3-hydroxyacyl-CoA dehydrogenase (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 over-represented in pregnant women with HELLP and pre-eclampsia.[37,38] Testing was not feasible because of 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 VH. 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, given that 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 postpartum. Early referral and transplant consideration are mandated as it is for anyone with signs and symptoms of ALF.

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