

Research Article

# Factors Determining the Intensive Care Need in Help Syndrome & AFLP in Pregnancy

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## Abstract

**Objective:** To compare factors affecting mortality and morbidity in HELLP (Hemolysis, Elevated Liver Enzyme Levels, and Low Platelets) syndrome & AFLP (Acute fatty liver of pregnancy).

**Methods:** 40 pregnancies with HELLP syndrome and 8 with AFLP were included in this retrospective study. Clinical characteristics and adverse maternal and perinatal outcomes were noted from medical records. The differences in maternal and perinatal outcomes and factors were compared among the study groups.

**Results:** There were no significant differences between HELLP syndrome and AFLP groups with respect to demographic characteristics. Comparison between clinic and laboratory findings of patients with HELLP syndrome and AFLP displayed significantly higher levels in AFLP especially in coagulation parameters, INR, fibrinogen, liver enzyme, LDH, total and direct bilirubin levels. Also a significant difference was observed the differences in treatment modalities applied to each group. The rate of ICU admission was 65%, 100 % for HELLP syndrome and AFLP respectively and mortality rate for women with HELLP syndrome and AFLP was 7.5%, 37,5 % respectively. Lastly no significant difference in perinatal morbidity and mortality was observed among the groups.

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**Conclusion:** Pregnancies complicated by AFLP syndrome had significantly higher maternal morbidity and mortality rates than HELLP. The factors changing these mortality rates were found to be bilirubin, fibrinogen levels significantly. Perinatal morbidity and mortality were similar in HELLP syndrome and AFLP mostly because of similar gestational ages in delivery.

**Keywords:** AFLP; HELLP syndrome; ICU; Morbidity; Mortality

## Introduction

The reported incidence of HELLP syndrome among all pregnancies is 0.17-0.85%, which increases up to 30% among all preeclampsia and eclampsia cases. Maternal mortality ranges between 1% and 24% in patients with HELLP syndrome. The characteristic features of the HELLP syndrome, which complicates 4% to 12% of gestations, are hemolysis, liver enzyme elevation and thrombocytopenia [1,2]. Acute Fatty Liver of Pregnancy (AFLP) is a rare disease with an incidence of 1 per 7000 to 16,000 pregnancies. It mostly occurs in the third trimester of pregnancy or during early postpartum period. Genetic mutation in long-chain 3-hydroxyl coenzyme A dehydrogenase probably leads to abnormal  $\beta$ -oxidation of fatty acids in fetal mitochondria and contributes to microvascular fatty infiltration of the liver of mothers. AFLP remains a serious disease with high mortality from 16.5-26.7% due to severe complications such as DIC, renal function impairment, hepatic encephalopathy, hypoglycemia and multiorgan failure [3].

Previous studies have revealed that both HELLP syndrome and AFLP are associated with an increase in maternal and neonatal morbidity and mortality, particularly when developed in the second trimester of pregnancy [1,3,4]. The aim of the present study was to compare the factors affecting mortality & morbidity rates in pregnancies complicated by HELLP syndrome and AFLP.

## Materials and Methods

All consecutive pregnant women presenting with HELLP syndrome or AFLP to the obstetrics unit of our institute -a tertiary center- between January 2016 and October 2018 were retrospectively recruited in the study. The study was conducted after the protocol was approved by the Institutional review board. All subjects provided a written informed consent. Demographic and clinical features of the study group were retrieved from institutional digital database. Gestational age was calculated based on the date of the last menstruation and first trimester or early second-trimester ultrasonography findings. Exclusion criteria were as follows: the presence of premature rupture of membranes, fetal anomalies and history of maternal chronic medical disease.

HELLP syndrome was diagnosed according to the following criteria: presence of hemolysis (total bilirubin > 1.2mg/dL or serum LDH > 600IU/L or decreased hemoglobin and hematocrit levels), elevated liver enzymes (AST > 70 IU/L and/or ALT > 70 IU/L) and thrombocytopenia (< 150000 cells/mm<sup>3</sup>) [5]. AFLP was diagnosed The

diagnosis of AFLP was based on both clinical features and laboratory findings, including: (a) symptoms of anorexia, nausea, vomiting, jaundice, fatigue, cold food preference and abnormal liver function during the third trimester of pregnancy or early postpartum period; (b) characteristic laboratory findings (e.g., elevated alanine transaminase, bilirubin and serum creatinine levels, prolonged prothrombin time and hypoglycemia); (c) ultrasonography showing fatty liver or liver biopsy sample with characteristic pathological changes; (d) All patients exhibited six or more of the Swansea criteria, which objectively confirmed the diagnosis of AFLP [4].

Presence of eclampsia, pulmonary edema, Disseminated Intravascular Coagulopathy (DIC) and placental abruption, the requirement for blood product transfusion, acute renal insufficiency, and death were the adverse maternal outcomes included in the statistical analysis. Adverse perinatal outcomes included the presence of fetal distress, preterm birth, low Apgar scores at 5 minutes low birth weight, and intrauterine death. All subjects underwent CTG monitoring at least twice daily to assess the fetal well-being.

Routine intravenous magnesium sulfate administration was performed to prevent and control seizures. Two doses of 12mg intramuscularly betamethasone were administered for those with <34 weeks' gestation aiming to accelerate the fetal lung maturity. Study population was divided into two groups according to the diagnosis. The difference in maternal and perinatal outcomes between the AFLP and the HELLP syndrome groups was the primary outcome measure of this study.

### Statistical analysis

SPSS version 20.0 (SPSS Inc., Armonk, NY, USA) was used for statistical analysis. Shapiro Wilk test was used to test the distribution pattern of the data. Normally distributed data were analyzed with parametric tests, whereas data of questionably normal distribution were analyzed with non-parametric tests. Continuous variables were compared with the independent samples t-test, while Pearson chi-square test was employed to analyze categorical variables.  $P < 0.05$  was accepted statistically significant.

### Results

40 (83,3%) subjects had HELLP syndrome and 8 (16,6%) were AFLP. The demographic and clinical features of study population are presented in table 1.

In table 2, a comparison between clinic and laboratory findings of patients with HELLP syndrome and AFLP is shown. When Hct, Hgb, platelet levels, coagulation parameters, INR, fibrinogen, liver enzyme, LDH, total and direct bilirubin levels were compared between patients with HELLP syndrome and patients with acute fatty liver of pregnancy, a significant difference was observed ( $p < 0.05$ ). AFLP group had significantly higher levels regarding... When these two groups were compared hemoglobin, hematocrit, platelet, fibrinogen levels were significantly lower whereas AST, ALT, LDH, INR levels were significantly higher in AFLP group compared with HELLP group. Mean AST level in the HELLP group was  $530 \pm 101$  IU/L and was  $1699 \pm 2031$  IU/L in the AFLP group. Mean ALT level in the HELLP group was  $361 \pm 826$  IU/L and was  $801.7 \pm 839$  IU/L in AFLP group. Fibrinogen and INR levels in the HELLP group were  $347.8 \pm 148$  mg/dl and  $1.09 \pm 0.6$ , respectively. Whereas these levels were  $152.3 \pm 116.3$  mg/dl for fibrinogen and  $2.0 \pm 0.8$  for INR in AFLP

Clinical and laboratory findings	HELLP (n=40)	Acute fatty liver of pregnancy (n=8)	p-value
Systolic blood pressure (mmHg ± SD)	157.2 ± 2.1	153.7 ± 28.2	0.2
Diastolic blood pressure (mmHg ± SD)	95.7 ± 9.3	90 ± 1.06	0.1
Hgb (g/dl ± SD)	9.3 ± 2.3	6.3 ± 0.9	<0.001
Hct (% ± SD)	27.9 ± 6.7	18.5 ± 2.7	<0.001
PLT (103/ ml ± SD)	66.2 ± 29	35.3 ± 20.1	0.005
Urea (mg/dl ± SD)	37.1 ± 20.1	41.1 ± 21.7	0.5
Creatinine (mg/dl ± SD)	1.1 ± 0.8	1.5 ± 1	0.1
AST (IU/L ± SD)	530 ± 101	1699 ± 2031	0.006
ALT (IU/L ± SD)	361 ± 826	801.7 ± 839	0.01
LDH (IU/L ± SD)	1101 ± 827	2423 ± 1933	0.01
Total bilirubin (mg/dl ± SD)	1.76 ± 3.2	12.6 ± 3.4	<0.001
Direct bilirubin (mg/dl ± SD)	0.97 ± 2.2	10.3 ± 2.7	<0.001
Indirect bilirubin (mg/dl ± SD)	0.78 ± 1.3	2.2 ± 0.9	<0.001
INR (mean ± SD)	1.09 ± 0.6	2.0 ± 0.8	<0.01
Fibrinogen (mg/dl ± SD)	347.8 ± 148	152.3 ± 116.3	<0.01
Proteinuria n (%)	36 (90%)	7 (87.5%)	0.6

**Table 1:** Comparison between clinical and laboratory findings of patients with HELLP syndrome and acute fatty liver of pregnancy.

HELLP: Hemolysis, Elevated Liver Enzymes, Low Platelet; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; LDH: Lactate Dehydrogenase; Hgb: Hemoglobin; Hct: Hematocrit; PLT: Platelet; INR: International normalized ratio

group. These findings were consistent with the literature and indicated a higher rate of DIC in patients with acute fatty liver of pregnancy.

Treatments	HELLP (n=40)	Acute fatty liver of pregnancy n=8	p-value
ES transfusion (mean ± SD)	3.2 ± 6.6	5.8 ± 3.2	0.003
FFP transfusion (mean ± SD)	1.9 ± 6.5	7.2 ± 5.4	< 0.001
PS transfusion (mean ± SD)	5.4 ± 10.4	14.1 ± 18	0.003
Hemodialysis, n (%)	4 (10%)	2 (25%)	0.25
Plasmapheresis, n (%)	3 (7.5%)	2 (25%)	0.18
ICU admission, n (%)	26 (65%)	8 (100%)	0.04

**Table 2:** Comparison of treatment modalities between patients with HELLP syndrome and patients with acute fatty liver of pregnancy.

HELLP: Hemolysis, Elevated Liver Enzymes, Low Platelet; ES: Erythrocyte Suspension; FFP: Fresh Frozen Plasma; PS: Platelet Suspension; ICU: Intensive Care Unit

In table 3 the differences in treatment modalities applied to each group can be seen. When treatment modalities of patients with AFLP were compared with patients with HELLP syndrome, the prior group received significantly more transfusions ( $p < 0.05$ ). Furthermore, the admission rate of these patients to ICU was also significantly higher ( $p = 0.04$ ). 3 patients died in both groups Calculation of morbidity and mortality rates can be seen in table 3. Maternal mortality and ICU admission was significantly higher in AFLP than HELLP syndrome ( $p < 0.05$ ).

When factors such as demographic properties, laboratory findings and treatment modalities were analyzed using a regression analysis, total bilirubin and fibrinogen levels were found to be significantly associated with mortality rates. An increase in total bilirubin caused

Maternal and neonatal outcomes	HELLP n = 40	Acute fatty liver of pregnancy n = 8	p-value
ICU admission (day ± SD)	3.6 ± 6.7	7.5 ± 7.3	0.02
Maternal mortality n (%)	3 (7.5%)	3 (37.5%)	0.04
Neonatal morbidity n (%)	24 (60%)	7 (87.5%)	0.23
Neonatal mortality n (%)	15 (37.5%)	1 (12.5%)	0.23

**Table 3:** Comparison of maternal and neonatal mortality and morbidity of patients with HELLP syndrome and acute fatty liver of pregnancy.

HELLP: Hemolysis, Elevated Liver Enzymes, Low Platelet

a 1.2 times increase in mortality rates, whereas an increase in fibrinogen levels decreased mortality rate with 2%. When Factors affecting maternal mortality analyzed OR for bilirubin was 1.28, 95% CI (1.03-1.58) p=0.02, OR for fibrinogen was 0.98, 95% CI (0.97-1) p=0.04.

## Discussion

AFLP is a rare condition seen 1 in 10,000-20,000 pregnancies. HELLP syndrome & AFLP are common causes of maternal and fetal morbidity and mortality. However, early detection and treatment of these diseases are critical to prevent severe complications resulting from these disorders. Management is prompt delivery. The increase in mortality and morbidity rates has been attributed to complications [5,6]. Complications associated with maternal morbidity include disseminated intravascular coagulopathy, acute renal failure, cerebrovascular hemorrhage, postpartum hemorrhage, placental abruption, pulmonary edema and acute respiratory distress syndrome. In the 1980s mortality rate AFLP was reported as 85% Due to early diagnosis and treatment, advances in ICU treatments, this rate has dropped to 10-15% [7]. AFLP and HELLP syndrome share common clinical, laboratory, histological and genetic features, and differential diagnosis between them are often difficult [4,8-10]. HELLP syndrome and AFLP manifest similar laboratory levels at first, diagnosis of AFLP is often delayed until manifestation of life-threatening complications. It is usually diagnosed in the second half of pregnancy and can potentially be fatal due to multiple organ failure. Experienced centers may differentiate both diseases according to billurubin components, coagulation factors or glucose levels. Therefore, a differentiation between these diseases can be difficult. In the present study, we identified factors affecting mortality rates. In HELLP group, one patient died due to eclampsia followed by respiratory and cardiac arrest, one died because of intracranial hemorrhage and in the other one the cause of death was the development of DIC. Three patients in AFLP group were followed in ICU and died because of multiple organ failure. In the latter group, the reason for the severe course of the disease with an increase in icterus leading to multiple organ failure. We found that outcomes and morbidity and mortality and ICU admission rates were much higher in AFLP group.

Severe preeclampsia, HELLP syndrome and AFLP manifest themselves with similar symptoms [7,11-14]. Symptoms such as nausea, vomiting, icterus, hypoglycemia and coagulopathy indicating hepatic failure are accompanied by high liver enzyme and bilirubin levels in laboratory findings of patients with acute fatty liver of pregnancy. On the other hand, hypertension and proteinuria are more common in patients with HELLP or severe preeclampsia [8,9,15]. The presence of multisystem failure including acute renal failure, encephalopathy, ARDS, pulmonary edema, pancreatitis or coagulopathy indicates acute fatty liver of pregnancy [12]. Pourrat et al., included preeclampsia, HELLP, AFLP, TTP and HUS as differential diagnosis for

conditions mimicking preeclampsia in their study where they evaluated pregnancy associated liver diseases [4]. Preeclampsia can be a comorbidity in patients with acute fatty liver of pregnancy, but in isolated preeclamptic patients icterus and hypoglycemia are not expected. In acute fatty liver of pregnancy hypoglycemia, hyperbilirubinemia and DIC along with elevated liver enzymes are in the foreground. Whereas TTP is associated with low platelet levels and central nervous system findings and HUS usually manifests itself with high levels of creatinine, renal and liver findings. Compared to these conditions preeclampsia has a milder course.

According to a general consensus perinatal and neonatal morbidity and mortality rates are higher among patients with severe preeclampsia and HELLP syndrome and AFLP. Perinatal mortality rate ranges from 7 to 60% in HELLP syndrome [5,16]. Need for mechanic ventilation, admission to Neonatal Intensive Care Unit (NICU), low APGAR scores and necrotizing enterocolitis rates are significantly higher. In our study, we did not see any significant difference between the groups in terms of admission to NICU, neonatal morbidity and mortality. This was most probably done to the similarity in gestational weeks at birth between groups. In studies conducted by, Haddad et al., and Abromovici et al., they showed an association between neonatal morbidity and mortality and gestational week at birth [14,16]. Advances in expectant/conservative management, application of steroid before birth expectant of patients with HELLP syndrome at weeks of gestation less than 28 in some tertiary care centers, in recent years let to an improvement in the neonatal outcomes [17,18].

In this study maternal morbidity rate is calculated 35% in the HELLP group and 62% in AFLP group. Patients with AFLP stayed longer in ICU compared to the HELLP group. These results were consistent with the literature [17,18]. In the HELLP group 6.25% had acute renal failure, and 4.16% had placental abruption. In AFLP group 25% had DIC, 12.5% had ARDS, 12.5% had intracranial hemorrhage and 12.5% had postpartum hemorrhage. With the advances in patient care mortality rates of AFLP dropped from 75% to less than 5% in world [3,4]. In our study, both transfusion rate and length of ICU stay were significantly higher in the AFLP group when compared to HELLP group. Maternal ICU admission was also different between groups which was 65% in HELLP and 100 % in AFLP. Maternal mortality rates were also significantly higher in the AFLP group than HELLP syndrome (37.5% vs. 7.5%). Fibrinogen and INR levels in the HELLP group were 347.8 ± 148 mg/dl and 1.09 ± 0.6, respectively. Whereas these levels were 152.3 ± 116.3 mg/dl for fibrinogen and 2.0 ± 0.8 for INR in AFLP group. These findings were consistent with the literature and indicated a higher rate of DIC in patients with AFLP. When demographic variables, laboratory findings and treatment modalities affecting maternal mortality were analyzed with logistic regression analysis, a significant effect of total bilirubin and fibrinogen levels on maternal mortality was observed. Total bilirubin levels increased maternal mortality rate 1.2-fold whereas an increase in fibrinogen levels decreased mortality rate by 2%. These findings indicate that an increase in total bilirubin is an indicator of liver failure and low levels of fibrinogen is a parameter of DIC. This is the first study identifying factors affecting mortality rates in pregnancy induced hypertensive diseases or liver diseases. On the other hand, Roberts et al. showed that the platelet levels is the best marker in detecting maternal and perinatal complications associated with hypertensive diseases of pregnancy [6]. Although number of AFLP patients is low in our study, the results are significant because the incidences of these diseases are very low and such a higher numbered studies will be too much time

consuming. This is one of the few studies analyzing these two diseases of pregnancy disorders together and analyzing detailly mortality & morbidity factors. Relatively small sample size, single-center setting, retrospective design, and study population consisting of a single ethnic group are the main limitations of the present study. Therefore, it remains unclear whether our results could be generalized to other ethnicities. In order to determine mortality and morbidity associated factors a larger patient cohort is required. But so far, these results will highlight the literature about the factors in mortality & morbidity rates.

## Conclusion

The management HELLP syndrome and AFLP aims to reduce maternal and perinatal morbidity and mortality. The differential diagnosis carries utmost importance to decrease mortality and morbidity. The factors affecting mortality & morbidity rates are identified in this study are important to decrease mortality.

## Disclosure Statement

The authors declare that they have no conflict of interest.

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## Ethics

This retrospective study organised according to ethical guidelines, informed consent was taken from subjects.

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