Clinical characteristics of acute fatty liver of pregnancy in a tertiary Indonesian hospital

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ORIGINAL ARTICLE

Clinical characteristics of acute fatty liver of pregnancy in a tertiary Indonesian hospital

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ABSTRACT

Acute fatty liver of pregnancy (AFLP) is a rare, often autosomal recessive disorder with a major risk for maternal and perinatal mortality and morbidity. In order to achieve a more favorable outcome, awareness of its clinical signs and symptoms and early recognition are of pivotal importance. Over a 5-year period, 18 patients were diagnosed with AFLP (one twin, 19 babies). The most common sign and symptoms were jaundice, hypoglycemia, nausea and vomiting, encephalopathy, and hypertension. Abnormal laboratory test results included elevated total/conjugated (direct) bilirubin, AST, ALT, PT, APTT, creatinine, leukocyte count, and hypoalbuminemia. Maternal and fetal mortality rate was high: 66.7% resulted in a maternal death and 57.9% in an intrauterine fetal demise (IUFD). The number of complications was found to correlate with maternal death ($p = .042$). Surviving AFLP patients had ≤ 3 complications, while patients with >3 complications on presentation had a high risk of maternal death (OR = 5.0; 95% CI: 0.55–45.4). The presence of hypertension significantly increased the risk of maternal death (OR: 24.5; 95% CI: 1.1–542.8; $p = .01$). The risk of IUFD was primarily related to gestational age at delivery and birth weight. The high rate of jaundice as presenting symptom of AFLP suggests that Indonesian primary maternity care providers may often miss its important earlier signs and symptoms, in particular *de novo* onset of nausea and vomiting in late pregnancy.

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Introduction

Acute fatty liver of pregnancy (AFLP) is a rare, often autosomal recessive disorder with an incidence of 1/7000 – 1/16,000 pregnancies. AFLP is not related to maternal age, and has the potential to cause maternal and perinatal death in the third trimester [1]. The typical characteristics of AFLP include rapid liver failure and coagulopathy, which appears to be triggered by microvesicular fatty infiltration in the hepatocytes [2]. Multiple pregnancy, having a male fetus and first pregnancy are considered to be risk factors for AFLP [3].

The exact cause of AFLP is still unknown, but advanced biomolecular research indicates a defect in LCHAD (long chain 3-hydroxyacyl coenzyme a-dehydrogenase) activity in fetal liver mitochondria which will lead to fatty buildup in maternal hepatocytes secondary to fatty acid oxidation disorder followed by a microvesicular fatty steatosis. The LCHAD genetic defect is located on chromosome 2; 19% of LCHAD mutations involve the G1528C and E474Q single nucleotide polymorphisms [4].

The precise mechanism by which LCHAD-deficient fetuses cause AFLP in a heterozygote mother is still unclear. However, several factors appear to contribute in this fetal maternal interaction. First, the heterozygosity of the mother for a mitochondrial trifunctional protein (MTP) defect reduces her capacity to oxidize long chain fatty acids. Human defects in MTP complex are recessively inherited and cause LCHAD deficiency. Second, the stressful nature of pregnancy with its metabolic changes, the increased lipolysis, and decreased β-oxidation play a role. In the presence of the G1528C mutation, potentially hepatotoxic LCHAD metabolites, produced by the fetus or placenta, accumulate in maternal circulation [5].

The diagnosis of AFLP is mostly based on the Swansea criteria. A pregnant patient is diagnosed with AFLP if there are a minimum of six out of 14 criteria present of the following: (1) vomiting, (2) abdominal pain, (3) polydipsia/polyuria, (4) encephalopathy, (5) elevated bilirubin, (6) hypoglycemia, (7) elevated uric acid, (8) leucocytosis, (9) ascites, (10) elevated

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transaminases (AST/ALT), (11) elevated ammonia, (12) renal impairment, (13) coagulopathy, and (14) microvesicular steatosis on liver biopsy (Lata, 2013). Definitive diagnosis of AFLP is based on liver biopsy, in which swollen, vacuoled, and pale central zone hepatocytes with microvesicular fatty liver infiltration are typically found [6].

Maternal death in AFLP is associated with complications like DIC, encephalopathy, and acute renal failure. While fetal/perinatal death is associated with the state of maternal disease, premature birth and placental insufficiency. In developed countries, the maternal death rate caused by AFLP has declined over the past 50 years from 85% to <5%, while the in an intrauterine fetal demise (IUFD) rate stays high at 23–66% [3]. This is probably related to the earlier diagnosis of AFLP, recognition of the importance of immediate delivery, and access to intensive care [4]. To the best of our knowledge, this is the first publication in the international literature from Indonesia, the fourth most populous country in the world. The high maternal–fetal mortality rate of AFLP still poses a significant problem in Indonesia. The annual number of AFLP cases in our tertiary center appeared to increase over recent years, from three cases in 2011 to six cases in 2015. The aim of this report is, therefore, to present the clinical characteristics of AFLP in a tertiary center in Indonesia.

Materials and methods

Retrospective chart review of all ($n = 18$) cases of AFLP patients throughout January 2011–December 2015 at the Dr Soetomo Hospital, the main tertiary referral hospital in East Java, Indonesia.

Clinical data obtained from the medical records review included maternal age, parity and gravidity, fetal sex, multiple pregnancy, gestational age at onset of AFLP, presenting clinical manifestation, laboratory tests, and maternal–perinatal outcome. The data were further analyzed with standard descriptive statistical analysis using SPSS 19 (SPSS Inc, Chicago, IL).

Result

Over these 5 years, the number of AFLP patients in Soetomo Hospital increased from 2 to 3 patients per year at the start of this period to six patients in 2015.

General characteristics of AFLP patients

General maternal characteristics and fetal outcome of the 18 AFLP patients are presented in Table 1.

Table 1. General maternal characteristics of acute fatty liver of pregnancy (AFLP) patients.

Characteristic	*n*	Mean + SD
Age		29.67 ± 6.44
<20	0	(Range, 20–45)
20–24	4	
25–29	5	
30–34	4	
≥35	5	
Gravida		2.11 ± 1.18
Primigravida	6	
Multigravida	12	
Onset disease		33.93 ± 4.43
<12	0	
13–27	1	
28–36	11	
37–40	4	
Postpartum	2	

The mean age of AFLP patients was 29.67 ± 6.44 years (20−45 years old); six (33.33%) were primigravida, one patient was para 4, and the mean parity of AFLP patients was 2.11 ± 1.18 (CI 95%; 1.52–2.70). The mean gestational age at onset of AFLP was at 33.9 ± 4.4 weeks with one patient developing AFLP at 19-week pregnancy, in two patients, the disease was diagnosed 2 d postpartum following preterm delivery. One AFLP patient had a twin pregnancy. The number of male fetuses of the AFLP patients was 8 (42.11%).

Clinical manifestation of AFLP patients

The initial clinical manifestations of AFLP were unspecific, including nausea-vomiting, headache, and fatigue. All AFLP patients in this series had jaundice at time of admission, 14 (77.78%) patients had hypoglycemia, 11 (61.11%) patients complained about nausea and vomiting and showed signs of encephalopathy and eight (44.44%) patients had hypertension. Ultrasound demonstrated the presence of ascites in six (50%) out of 12 patients (six patients were not scanned because their critical condition did not allow transport to the imaging unit).

Laboratory results in AFLP patients

Laboratory results in AFLP patients on the first visit are all reflective of severe liver dysfunction. Compared with normal values, mean value of serum bilirubin direct (10.08 ± 5.59 versus <0.2 mg/dL), bilirubin indirect (14.38 ± 7.87 versus <1 mg/dL), AST (948.72 ± 2114.77 versus <35 IU), ALT (395.61 ± 726.43 versus <35 IU), leucocyte (21.99 ± 11.26 versus 3.6–11 × 10^9/L), PT (28.44 ± 26.68 versus 10–14 s), APTT (82.28 ± 157.53 versus 26–38 s), and creatinine (2.9 ± 1.64 versus 0.5–0.9 mg/dL) were higher. While the mean serum level of glucose (53.28 ± 23.98 versus 70–100 mg/dL)

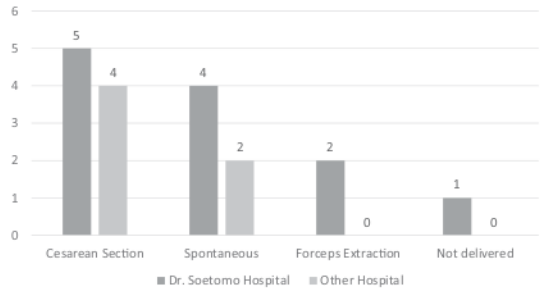

Figure 1. Methods and location of labor of AFLP patients. From 18 AFLP cases that we had, 11 was delivered in Dr Soetomo Hospital, six in the other hospital and one case not yet delivered because maternal–fetal death antepartum. Nine cases were delivered by cesarean section, six with spontaneous delivery, and two with forceps extraction.

and albumin (2.59 ± 0.60 versus 3.4–4.8 g/dL) were lower than normal levels. The platelet count (175.33 ± 127.72 × 10^3/μL) was not significantly altered.

Management of AFLP patients

All patients with an antepartum diagnosis of AFLP in or referred to Soetomo Hospital underwent immediate induction of labor as soon as possible following initial maternal stabilization. Nine (50%) AFLP patients had a caesarean section, six (33.33%) patients delivered a spontaneous vaginal delivery. Two patients needed to be delivered by forceps because they arrived in the very advanced stage of the disease process in a very poor condition (unconscious). Following induction of labor with misoprostol, the obstetrical team proceeded with forceps extraction in second stage to facilitate delivery (Figure 1). One AFLP patient did not give birth, she died during the initial attempt to stabilize her rapidly deteriorating condition because of septic shock. This patient was referred in with advanced disease, presenting with profound jaundice, severe vomiting, and hypertension.

Length of stay of AFLP patients in the intensive care unit ranged from <1 d to 13 d. The patient with <1 d ICU treatment was the aforementioned patient who progressively deteriorated and died after admission. The average length of hospital stay of these AFLP patients was 28 d.

Maternal and fetal outcome of AFLP patients

Over these 5 years, 12 (66.67%) out of the 18 AFLP patients died, survival rate appeared to improve (from 0% in 2011 to 66.6% in 2015). Several complications of AFLP patients were the direct consequences of liver failure. Complications of AFLP patients are shown in Table 2. Most of the AFLP patients, 15 (83.33%), developed acute renal failure. Septic shock was the main final cause of maternal death (58%).

Table 2. Maternal and fetal outcomes of AFLP patients.

Characteristic	*n*	Mean ± SD
Maternal complication		
Maternal death	12	
Sepsis	13	
Encephalopathy	11	
Lung edema	2	
Coagulopathy	13	
Acute renal failure	15	
Hypoglycemia	14	
Location of labor		
Dr Soetomo Hospital	12	
Other facility	6	
Antepartum maternal death	1	
Gestational age		34.53 ± 4.34
13–27	1	
28–36	11	
37–40	4	
Postpartum	2	
Method of labor		
Cesarean section	10	
Spontaneous	6	
Forceps	2	
Not delivered	1	
Fetal birth weight		2332.94 ± 615.64
<2000	4	
2000–2500	7	
2500–3000	3	
3000–3500	3	
>3500	0	
Unknown	2	
5-Minute Apgar Score		2.58 + 3.34
IUFD	11	
Severe asphyxia	1	
Moderate asphyxia	4	
Mild asphyxia	3	
Fetal sex		
Male	8	
Female	10	
Unreported	1	

Fetal and perinatal outcome of the 19 fetuses/babies (one twin) is presented in Table 2. Six (31.57%) babies were born and stayed in facilities other than Dr Soetomo Hospital with three live births (unfortunately no further clinical details available). Stillbirth occurred in 11 cases (57.9%), versus 8 (42.1%) live births. All babies from AFLP patients born at Dr Soetomo Hospital had Early Onset Sepsis, eventually all of them were released from hospital in good condition after a mean length of stay 9.4 ± 1.34 d. The mean birth weight of babies from AFLP patients was 2232 ± 615.94 g (Table 2).

Maternal death risk factors in AFLP patients

As is shown in Table 4, many patients had multiple complications. The mean number of complications on presentation was significantly different between surviving and deceased AFLP patients (3.00 ± 1.79 versus

Table 3. Comparison of laboratory test results of maternal death and surviving AFLP patients, and IUFD – life birth babies.

Mean value parameter	Maternal death	Surviving patient	p	IUFD	Life birth	p
Albumin (g/dL)	2.61 ± 0.68	2.54 ± 0.47	.824	2.72 ± 0.60	2.45 ± 0.59	.350
Bilirubin conj (mg/dL)	11.07 ± 5.72	8.11 ± 5.24	.305	9.25 ± 5.61	11.36 ± 5.32	.418
Bilirubin total (mg/dL)	15.49 ± 8.07	12.14 ± 7.78	.412	13.26 ± 8.35	16.33 ± 6.79	.407
AST (IU/L)	728.75 + 1818.78	1388.67 + 2753.14	.190	833.00 + 2058.72	1021.63 + 2201.66	.850
ALT (IU/L)	396.33 ± 843.63	394.17 ± 477.92	.160	295.64 ± 397.08	498.25 ± 1019.63	.554
Glucose (mg/dL)	54.75 ± 24.02	50.33 ± 25.89	.724	50.91 ± 8.35	56.87 ± 19.22	.596
PT (s)	31.54 ± 32.26	22.23 ± 7.91	.574	32.75 ± 33.57	21.38 ± 6.70	.297
APTT (s)	97.72 ± 193.59	51.40 ± 14.61	.373	102.59 ± 202.23	49.56 ± 13.56	.473
Creatinine (mg/dL)	3.15 ± 1.57	2.4 ± 1.79	.378	3.18 ± 1.72	2.41 ± 1.42	.311
Platelet ($\times 10^3/\mu L$)	197.00 ± 138.02	132.00 ± 100.84	.323	198.27 ± 144.83	136.86 ± 87.03	.303
Leukocyte ($\times 10^3/\mu L$)	24.39 ± 12.89	17.02 ± 4.89	.109	23.91 ± 12.21	18.77 ± 8.97	.327

4.58 ± 1.24; $p = .042$). Having more than three complications was correlated with higher maternal death risk (OR = 5.0; 95% CI: 0.55–45.4). However, the only parameter significantly correlated with maternal death in AFLP was the presence of hypertension. All AFLP patients presenting with hypertension did not survive. Hypertension significantly increases the risk of maternal death (OR: 24.5; 95% CI: 1.1–542.8; $p = .01$).

The laboratory results of AFLP patients were further analyzed to compare results between fatal and non-fatal AFLP cases, and also between IUFD and live birth cases (Table 3). There were no significant differences in overall laboratory parameters between surviving versus deceased patients, and IUFD versus live birth cases.

Risk factors of IUFD

The incidence of IUFD in AFLP patients was negatively correlated with gestational age at labor and birth weight ($p = .001$ and .004) (see Table 4). The analysis of mean laboratory results of AFLP patients with an IUFD versus life birth (as shown in Table 3) yields no statistically significant differences ($p > .05$). Further statistical analysis using categorical cut-off values for direct and indirect bilirubin (>0.2 and >1 mg/dL), decreased glucose (<70 mg/dL), prolonged PT/APTT (>14 and >38 s), elevated serum creatinine (>0.9 mg/dL), elevated AST/ALT (>35 IU), fetal sex, and the presence of encephalopathy also did not correlate with the risk of stillbirth.

Discussion

The maternal mortality rate associated with AFLP in Indonesia is still very high (66.67%) due to the often late referral by satellite hospitals/primary health care centers. Many patients seen in Indonesian tertiary care hospitals arrive in very advanced state of disease, suggesting that the primary health care providers do not recognize the importance of *de novo* onset of nausea and vomiting in the third trimester. Timely referral is essential since patients presenting with more than three complications have an increase risk maternal death (OR: 5.0). In particular, the presence of hypertension is a poor prognostic sign, its presence strongly increased the maternal death risk (OR: 24.5).

General characteristics of AFLP patients

The data on this series of AFLP patients in east Java are not in line with the typical textbook risk factors (first pregnancy, male fetus, and twin pregnancy); among these 18 patients, we did encounter six (33.33%) nulliparous, eight (42.11%) with a male fetus and one (0.06%) with a twin pregnancy. The mean gestational at onset of AFLP was at 33.93 ± 4.43 weeks. This was similar with other papers reporting that the majority of women with AFLP are in the3rd trimester of pregnancy; mean gestational age 35–36 weeks, with a range of 28–40 weeks [5,7,8].

Clinical manifestation of AFLP patients

The clinical presentation of AFLP is often non-specific with nausea-vomiting, epigastric pain, polydipsia, polyuria, and jaundice. Jaundice is often presumed to be a relatively late presentation, in contrast to nausea and vomiting, these may exist for several days and sometimes up to 1–2 weeks before the onset of jaundice. In the study performed in Parkland Hospital (1975–2012), with 51 AFLP patients, the most common complaints were persistent nausea and vomiting (57%), hypertension (57%), and abdominal pain (53%) [1]. However, in this Indonesian series, all patients had jaundice on presentation; higher compared with another report from Java (Bandung), which had 70% patients being admitted with jaundice [9]. Importantly, this might be because most pregnant women, their families, and even their primary maternity care providers do not recognize nausea and vomiting in third trimester of pregnancy as a potentially dangerous symptom.

Table 4. Maternal death versus survivor and IUFD versus life birth in 18 Indonesian AFLP patients.

Variable	Deceased patients (n)	Survived patients (n)	*p*	IUFD (n)	Life birth (n)	*p*
N	12	6		11	8	
Maternal age			.195			.365
20–24	1	3		3	1	
25–29	5	0		4	1	
30–34	2	2		2	2	
≥35	4	1		2	4	
Gestational age			.261			.001*
13–27	1	0		1	0	
28–36	9	3		10	2	
37–40	2	3		0	6	
Birth weight			.251			.004*
<2000	3	1		3	1	
2000–2500	5	1		4	3	
2500–3000	1	2		0	3	
3000–3500	1	2		0	3	
>3500	0	0		0	0	
Unknown	2	0		2	0	
Number of pregnancy			.344			.177
Primigravida	3	3		5	1	
Multigravida	9	3		6	7	
Vomiting and nausea			1.000			.147
Yes	7	4		5	7	
No	5	2		6	1	
Bilirubin			(—)			(—)
>0.81 mg/dL	12	6		11	8	
≤0.81 mg/dL	0	0		0	0	
Glucose			1.000			.603
<72.07 mg/dL	9	5		8	7	
≥72.07 mg/dL	3	1		3	1	
Leukocyte count			1.000			.546
>11 × 10^3/μL	10	5		10	6	
≤11 × 10^3/μL	2	1		1	2	
PT/APTT			.515			.228
PT >14 or APTT >34	9	6		8	8	
PT ≤14 or APTT ≥34	3	0		3	0	
Creatinine			.344			1.000
>1.69 mg/dL	9	3		8	5	
≤1.69 mg/dL	3	3		3	3	
AST and ALT			(—)			(—)
AST >42 IU/L or ALT >42 IU/L	12	6		11	8	
AST ≤42 IU/L or ALT ≤42 IU/L	0	0	0	0		
Mode of delivery			.406			.264
Cesarean section	5	4		4	6	
Spontaneous	4	2		4	2	
Forceps extraction	2	0		2	0	
Maternal death antepartum	1	0		1	0	
Fetal sex			.583			.182
Male	2	6		6	2	
Female	3	7		4	6	
Unknown	1	0		1	0	
Hypertension			.013*			.352
Yes	8	0		6	2	
No	4	6		5	6	
Encephalopathy			0.141			.181
Yes	9	1		8	3	
No	3	5		3	5	
Sepsis			1.000			.338
Yes	9	4		7	7	
No	3	2		4	1	

Education of midwifes and GPs should clearly emphasize that while hyperemesis gravidarum is typically restricted to a gestational age of up to 14–15 weeks, *de novo* onset of nausea and vomiting in the third trimester always needs immediate specialist attention because it may indicate the presence of several potentially lethal pregnancy complications including AFLP.

Laboratory results in AFLP patients

The laboratory findings were consistent with other reports and the typical presentation of AFLP cases: elevated liver biochemistry (serum AST and ALT), bilirubin direct and indirect, DIC (elevated level of PT and APTT), hypoglycemia, and hypoalbuminemia [7,10]. Typical additional laboratory features include raised

serum ammonia, lactic acidosis, very high uric acid levels, and hypoglycemia secondary to impaired hepatic glycogenolysis [11]. Marked leukocytosis was seen in 83% of our patients, making his very basic laboratory result an important warning sign.

Management of AFLP patients

In this series, pregnant patients presenting with AFLP either had an immediate induction of labor ($n = 8$) or cesarean section ($n = 9$), one patient died before induction of labor. Timely induction of labor is the most important part of the management of AFLP. By delivering the fetus and the placenta, the excess fetal fatty acid production will be stopped, and the maternal liver fatty acid oxidation "workload" will be reduced, and liver function will normalize [12]. Particularly, in case of coagulopathy, cesarean section should be avoided. Cesarean section is recommended in case of fetal distress, failed induction of labor and/or in the presence of other clear contraindications for vaginal birth and only after the coagulopathy has been corrected [4]. The obstetrical team should be prepared for the risk of PPH (Bakri or intrauterine condom catheter, prostaglandin F2α, tranexamic acid) [13].

Maternal and fetal outcome of AFLP patients

In this report, the maternal mortality rate in ALFP patients in East Java was still very high (66.67%), compared with current data from developed countries with often a much lower mortality rate (18%) [10]. The UK national data on AFLP cases showed an even much lower maternal mortality rates (case fatality rate 1.8, 95% CI 0–9.4%) compared with another developed countries [14].

The apparent decline in the maternal mortality rate in East Java over these 5 years may be explained by earlier diagnosis and referral, immediate induction of labor or cesarean section, and improvements in the peri-partum intensive care support. Treatment of AFLP patients requires multidisciplinary input from obstetricians, hepatologists, internists, anesthetists, ICU specialists, and neurologists.

Maternal sepsis was the most common direct cause of death in patients with major liver failure. In addition to sepsis, maternal death in AFLP cases is usually secondary to renal failure, circulatory collapse, pancreatitis, or gastrointestinal bleeding. The risk of maternal death in this series was associated with the number of complications on presentation, and, in particular, the presence of hypertension (OR maternal death 24.5; 95% CI: 1.1–542.8). Many patients were referred in an advanced disease state, often with scant clinical data from peripheral hospitals or care providers, although most patients had *de novo* hypertension we cannot exclude the possibility that some of these cases chronic hypertension.

Perinatal mortality rate in our center is still higher (57.89%) than the reported average rate worldwide (23%) [10]. All liveborn babies develop early onset sepsis, but all of them could be discharged in good condition after on an average of 9 d of care. The high perinatal mortality is related to the often too late diagnosis and also the suboptimal maternal-fetal surveillance following admission. The risk of perinatal death in this series was strongly correlated with gestational age at birth and birth weight.

This paper is based on a retrospective review of all cases in a tertiary referral hospital. Therefore, not all patients could be questioned on the presence of the typical "Swansea criteria". The presence of epigastric pain, polydipsia, polyuria symptoms could not be evaluated in this study because there were no complete data about these symptoms in the medical record. Although Soetomo hospital would typically be the hospital receiving the great majority of patients with full blown AFLP in East Java, we cannot calculate the prevalence of this condition in Indonesia since non-referral hospitals might be involved in the management of milder (and perhaps not even formally recognized) cases of AFLP.

Conclusion

Early recognition and diagnosis are the pivotal factors in the management of AFLP. Education of midwives and junior doctors should emphasize the importance of recognizing *de novo* onset of third trimester nausea and vomiting as a sign of possible AFLP. Immediate induction of labor (or cesarean section) followed by postpartum intensive care is essential to prevent later complications secondary to liver failure.

Disclosure statement

The authors report no conflicts of interest.

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