

# Acute Fatty Liver on Pregnancy

## Risk Factors, Management, and Pregnancy Outcome

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**Abstract--**This study aimed to get the symptoms, complications, clinical summaries, mortality and morbidity in the mother and fetus (neonates) with AFLP in Hasan Sadikin hospital Indonesia. The study design in the form of a descriptive study on 7 AFLP cases are diagnosed and treated period 2010-2013. There were a total of 10 patients who carried the diagnose of AFLP, but only 7 patients who continued treatment and management further. Based on the medical record of patients with AFLP obtained clinical features, laboratories results, inspection, as well as maternal and fetal prognosis. Laboratories examination showed hyperbilirubinemia, increased liver enzymes, and all patients were negative for hepatitis examination. The main symptoms are gastrointestinal disorders include nausea, vomiting, and jaundice. While the majority of complications that arise include acute kidney injury, Disseminated intravascular coagulation and metabolic acidosis. Maternal mortality is very high (85.7%), only one case both of mother and baby can survive and be able to hospital discharge with permission.

**Index term--** AFLP, jaundice, complications, maternal mortality.

### I. INTRODUCTION

Acute fatty liver of pregnancy was first described in 1934 by Sheehan was referred to as Acute Yellow Atrophy of the Liver.<sup>1</sup> In 1940 AFLP obstetric emergency was classified in the high risk of maternal and child mortality.<sup>2</sup> Since 1980, the incidence of AFLP reported 1 per million pregnancies. In

1999 the incidence increased to 1 per 7000 pregnancies.<sup>3</sup> Prior 1970s, maternal and infant mortality rates as a result of AFLP reached 75% and 80%.<sup>4</sup> Recent research shows maternal and infant mortality as a result of AFLP ranges from 8-25%.<sup>5</sup>

The cause of AFLP was not certain. Based on the development of molecular research, concluded that AFLP was due to disturbed of the process of  $\beta$  oxidation of fatty acids into the mitochondria in hepatic cells with the clinically important markers of this disease was jaundice, coagulopathy, metabolic acidosis and ensefalopati.<sup>6</sup> Disorders in the liver as a vital organ resulting in high maternal and fetal mortality.

### II. METHOD

This research was conducted at the General Hospital dr.Hasan Sadikin (RSHS) descriptively. Data taken from medical record year period 2010-2013. In that period obtained 10 pregnancies were diagnosed AFLP from 10.766 deliveries. 7 patients (1: 1538 or 0.065%) were continued with specific treatment and ended with delivery complicated by AFLP, while 3 patients did not conduct further investigation and refused further treatment at RSHS.

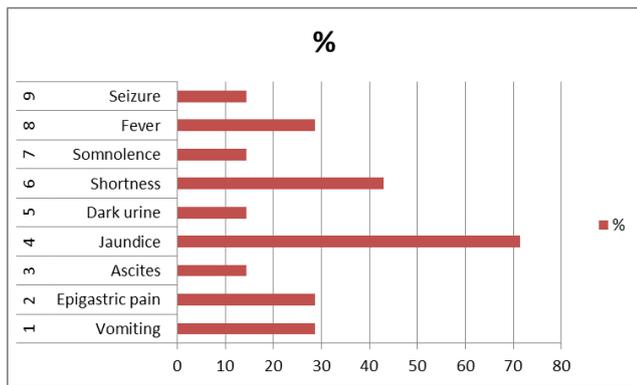
All patients AFLP not recorded at obstetrics clinic RSHS, all of them came on from district general hospitals and satellite maternity clinics. AFLP diagnose was made based on clinical complaints and laboratory results. The data covers symptoms, tests carried out, complications, and mode of delivery, further presented in the table.

III. RESULT

The average age of the AFLP patients was 32 years (22-41 years), gestational age at diagnosed was 33 weeks (27-38 weeks) and average time length of treatment was 5 days (2-10 days). Four patients were primigravida while the rest multigravida. One patients died prior to the termination of pregnancy .

Seven patients were diagnosed with AFLP came with varied complaints such as nausea / vomiting , epigastric pain and upper right abdominal, skin color changes to yellow, urination such as tea, ascites and loss of consciousness. All patients had a combination of the symptoms mentioned above ,although the type of combination of different symptoms for each patient.Treatment involves internal medicine and intensive care specialist.

Table 1. Clinical manifestations



Among the seven patients, three patients with fetal death in utero undergo vaginal delivery, while one patient with intrauterine fetal dead (IUFD) died prior to termination of pregnancy. Two patients underwent surgery cesarean section for fetal distress ,but then the baby died within the first 24 hours after birth. Only one patient after delivery survive both of the mother and baby further then can discharge from hospital with permission (table 2 no 1).

Abnormal results of laboratory (table3) are as follows:Increased liver aminotransferase, total bilirubine, direct bilirubine, creatinine ,leucocytosis, decreased platelet count,and prothrombin time elongated. Three patients with hypoglycemia and one patient with glucose intolerance. Coagulopathy characterized by thrombocytopenia, prolonged prothrombin time and partial thromboplastin elongated. Examination of serum amylase and lipase was not done .

Only one person who done liver ultrasound examination with normal results. None of the patients who underwent CT scan and MRI . Liver biopsy is not performed for all patients.

Table 2. Age , gravid , symptom onset , and the outcome of seven pregnancies with AFLP

No	Age (year)	GPA	Onset (weeks)	Length of treatment (days)	Delivery route	APGAR Score 1'/5'	After Treatment	
							Mother	Baby
1.	30	G3P2A0	32	10	Vaginal	6 / 8	L	L
2.	41	G1P0A0	27	-	-	IUFD	†	-
3.	40	G4P3A0	34	4	Vaginal	Stillbirth	†	†
4.	28	G1P0A0	33	7	Vaginal	3 / 5	†	L*
5.	31	G1P0A0	35	2	CS	2 / 2	†	†
6.	22	G2P0 A1	38	4	Vaginal	Stillbirth	†	†
7.	38	G1P0A0	37	5	CS	Stillbirth	†	†

Note: \*The baby in good condition when the family refused further treatment for the baby and take to went home.

CS: Cesarean Section †: Death L: life

Table 3. Results of laboratory examination

No	Examination	Mean	Interval
1	SGOT	2270.6 u/l	202 – 7663
2	SGPT	730.5 u/l	125 – 1790
3	LDH	5497.4 u/l	659 - 10947
4	Bilirubine total	14.91 mg/dl	2.11 - 22.79
5	Bilirubine direct	13.7 mg/dl	6.29 - 19.10
6	PT	2.5 sec	1.69 - 3.94
7	TT	30.4 sec	22.1 - 44.5
8	aPTT	69.5 sec	50.5 - 90.8
9	Fibrinogen	104.6 mg/dl	10.1 - 228
10	D dimer	17.2 ug/ml	2.5 - 56.8
11	Ureum	42.8 mg/dl	17 - 52
12	Creatinine	2.2 mg/dl	0.9 - 3.77
13	Glukose	84 mg/dl	30 - 160
14	Leucocyte	21.8x10 <sup>3</sup> /mm <sup>3</sup>	9.4 - 42.3
15	Trombosite	118.428x10 <sup>3</sup> /mm <sup>3</sup>	17.0- 241.0
16	Hemoglobin	12.8 mg/dl	9.9 – 16.4

Complications in patients with AFLP form of acute renal insufficiency, metabolic acidosis, pulmonary edema, hemorrhage shock, acute respiratory distress syndrome ,multiple organ failure, sepsis, uterine atony, ascites, and mortality. Six patients had acute renal insufficiency, five patients suffered a coagulation disorders such as DIC, four patients had metabolic acidosis and six patients died. Maternal deaths are caused by combination complications (as listed in table 4), although each patient has a different combination of complications. A survive mother has a major complication of acute renal failure without metabolic acidosis or multiple organ damage. Good response with hemodialysis and general symptoms improved after childbirth .

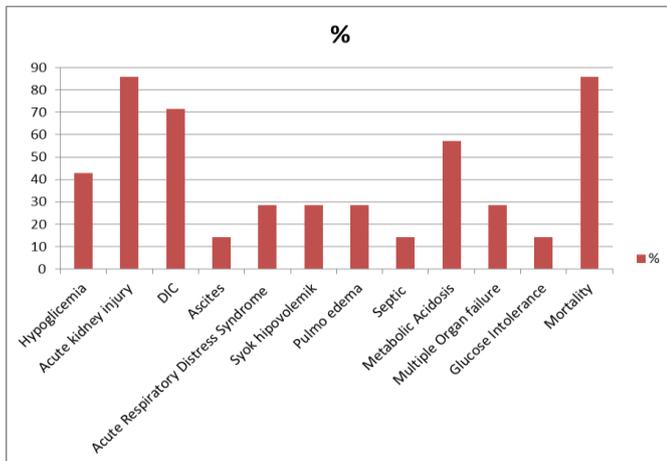
IV. DISCUSSION

AFLP can occur in pregnant women with no differences in geographical epidemiology, age, or race. Although very rare incidence in RSHS (1: 1538), but if compared to the literature review still has relatively higher incidence with a very high mortality rate (85.7%). Onset AFLP start at late second trimester, between weeks 27 to 38 of pregnancy as has been previously reported. AFLP more events befall primigravida than multigravida.<sup>6</sup> Unlike fatty liver disease which usually affects patients who are obese, AFLP was more common in women weighing less than normal.

The exact cause of AFLP still can not be explained with certainty. Last molecular research developments stated that occur as a result of disruption beta oxidation of fatty acids in the mitochondria of liver cells due to lack of long-chain

enzyme 3 Hydroxyacyl - CoA Dehydrogenase (Long Chain 3 Hydroxyacyl - CoA Dehydrogenase = LCHAD). LCHAD circuit is part of an enzyme complex mitochondrial trifunctional protein (Mitochondria trifunctional Protein/ MTP). LCHAD deficiency caused by mutations in the gene G1528C and E474Q of MTP enzyme complex. Fatty acid oxidation in mitochondria produce the main energy source for skeletal muscle and heart.<sup>7,8</sup>

Table 4. Complication related



Oxidation of fatty acids also plays a role in the formation of ketone bodies, 3-hydroxybutyrate and acetoacetate used as a backup energy source by vital organs other than the liver, such as the brain when blood sugar levels are low. Long chain fatty acids carried by specific proteins which bind fatty acids and is actively moved past the plasma membrane and taken into mitochondria. Fatty acids are further broken down in the mitochondria, into two shorter carbon through 4 beta spiral reaction oksidation.<sup>7,8</sup>

Women who experience AFLP have metabolic enzyme LCHAD deficiency. This enzyme deficiency inherited recessive and women suffering carrying heterozygous gene. If pregnant women who have a homozygous gene for this enzyme deficiency, then the fetus will not be able to oxidize fatty acids. These fatty acids are subsequently entered into the mother's blood circulation with a deficiency of the enzyme LCHAD anyway, so it is unable to process the fatty acid addition. Long chain fatty acids excess can not be broken down and along with triglycerides accumulate in the liver cells. These changes result in swelling, necrosis and inflammation of liver cells that function is impaired and causes AFLP.<sup>9</sup> Extent of liver cell damage level is reflected on the symptoms and complications that arise primarily because of liver cell metabolism was disturbed, such as jaundice, elevated liver enzymes, bilirubin, coagulation disorders, until the metabolic acidosis.<sup>7,8</sup>

In Table 4 shows that the metabolic acidosis becomes high enough complications (57.1%), due to a damaged liver cells are not able to clear lactic acid in serum. While the correction of metabolic acidosis with sodium bicarbonate in this state is still controversy as a result of changes to the form of carbon dioxide can aggravate intracellular acidosis. Depending on the extent of fatty liver, coagulation disorders can occur in the form of lengthening the time until occurrence of clotting and bleeding disorders thorough intravascular coagulopathy or DIC.<sup>10</sup>

AFLP state classified into obstetric emergency. The introduction and rapid and precise handling can prevent maternal and infant mortality. The relationship between clinical symptoms, laboratory test results and medical personnel experience in making diagnose and taking quick decisions was important in the treatment without confirmation with liver biopsy.<sup>11</sup> Gold standard examination to rule out the diagnose of AFLP was a liver biopsy, but was not routinely done because the importance of immediate treatment, in addition to the risk of liver biopsy be greater in the presence of coagulopathy. For that reason, in most cases the diagnose was made only based on clinical symptoms and results laboratory without histopathological evidence of AFLP histopatologi.<sup>12</sup> Hepatic steatosis microvesikular was characteristic appearance of histopathological abnormality.<sup>13</sup>

Average 5-day length treatment (table2) may still be less aggressive to reduce maternal mortality in this cases. Supportive treatment done to improve the patient's general condition and do some supporting diagnose prior to termination of pregnancy. Termination of pregnancy was the best option, because post deliveries showed significant improvement of the general state. Corticosteroids for lung maturation should still be done for 2 days on the state of preterm pregnancy. Nevertheless choice of accelerated pregnancy termination without lung maturation may be considered based on the mother's condition.

Diagnose can be made if there are 6 or more clinical signs and symptoms according to the criteria of Swansea without other causes.<sup>14</sup>

Swansea criteria for establish diagnose AFLP

1. Vomiting
2. Abdominal Pain
3. Polidipsy / polyuria
4. Encephalopathy
5. Increased bilirubine > 14 mol / l
6. Hypoglycemia < 4 mmol / l
7. Increased urea > 340 mol / l
8. Leucocytosis > 11 x 10<sup>3</sup> /ml
9. Ascites or "bright liver" appearance in ultrasound
10. Increased transaminases ( AST or SGPT ) >42 IU / l
11. Increased ammonia > 47 mol / l
12. Renal impairment , creatinine > 150 mol / l
13. Coagulopathy ; Prothrombin time> 14 seconds or aPTT >34 seconds
14. Microvesicular steatosis on liver biopsy.

AFLP has nonspecific early manifestations such as headache, nausea, vomiting and weakness. Bleeding can occur early stage due to coagulation disorders, acute renal failure, infection, pancreatitis, and hepatic encephalopathy hypoglycemy.<sup>11,15</sup> Acute renal failure accompanied by a mild increase in blood pressure, resembling a sign of preeclampsia if accompanied by proteinuria.

AFLP was difficult to distinguish from the symptoms of fulminant viral hepatitis or liver function damage HELLP.<sup>15</sup> Syndrome severe hypoglycaemia and significant prolongation of the prothrombin time thus can help differentiate AFLP with HELLP syndrome. Another important indicator was the increasing urea in the serum, as well as increased amylase and lipase which show symptoms pancreatitis.<sup>13,16</sup>

Histologically, the liver biopsy examination of patients with HELLP syndrome showed periportal hemorrhage and fibrin deposits while there on AFLP was found that fat infiltration mikrovessikular.<sup>17</sup>

The key in the treatment of AFLP were correcting coagulopathy, monitor and resolve hypoglycemia, regulate fluid balance (hemodialysis if there is kidney failure), and pregnancy termination. Although it must terminate the pregnancy, management of peripartum and postpartum complicated by severe coagulation disorders that need adequate supportive therapy.<sup>10</sup> Improvement of clinical and laboratory conditions usually occur quickly after delivery. Morbidity that occurs usually associated with severe coagulopathy.<sup>3,9,10</sup>

Patients usually have a good response to induction of labor so that intervention by cesarean section was rarely done (because of the coagulopathy disorder) and performed only on obstetric indications. Nevertheless whatever the chosen route of delivery, the risk of bleeding after delivery is greater risk than improvement physiological conditions. Internal compression by tamponade balloon was quite effective in controlling post partum hemorrhage. After the termination usually the patient's condition improved within 24-48 hours but in severe circumstances can take several days until the liver function return to normal.<sup>10</sup>

AFLP can be repeated occurrences by 25% in the next pregnancy, but only a few cases reported. Newborns from pregnancies with AFLP should be examined to detect the presence of mutations G1528C so as to save the baby with LCHAD enzyme deficiency. Early intervention by way of setting a diet high in carbohydrates, low in fat, and replace the long chain fatty acid with a fatty acid chain medium.<sup>19,20</sup> Women who experience AFLP require genetic counseling before planning future pregnancies. Prenatal diagnose can be performed through chorionic villous sampling (CVS) to identify the risk of AFLP.<sup>21</sup> Although the concept can be used as an early detection, CVS examination for detection of abnormalities in the fetus LCHAD enzyme has not done routinely.

AFLP is a pathological condition although very rare but very threatening life. Better outcomes for mothers depends on early diagnose, and gave birth soon. This applies especially when there is suspicious symptoms at late of second trimester or early third trimester, there is jaundice, nausea, vomiting, and accompanied by signs of liver damage.<sup>22</sup>

## V. CONCLUSION

AFLP was a rare case but a very threatening maternal and fetal life. Symptoms are nausea, vomiting and jaundice in the third trimester with liver disorders contemplated suspect of AFLP. Early diagnose, supportive care, and immediate termination is the key for a better pregnancy outcome.

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