The Diagnosis and Management of Acute Fatty Liver of Pregnancy

Ahmad Fariz MZ Zein, Irma Wahyuni Anwar**, Andri Sanityoso Sulaiman****

*Department of Internal Medicine, Faculty of Medicine, Universitas Swadaya Gunung Jati
Waled General Hospital, Cirebon, West Java
**Department of Internal Medicine, Awal Bros Hospital Pekanbaru, Riau
***Division of Hepatobiliary, Department of Internal Medicine
Faculty of Medicine, Universitas Indonesia/Dr. Cipto
Mangunkusumo General National Hospital, Jakarta

Corresponding author:
Andri Sanityoso. Division of Hepatobiliary, Department of Internal Medicine, Dr. Cipto Mangunkusumo National General Hospital. Jl. Diponegoro No. 71 Jakarta Indonesia. Phone: +62-21-31900924; facsimile: +62-21-3918842. E-mail: andri_sani@yahoo.com

ABSTRACT

Acute fatty liver of pregnancy (AFLP) is a rare catastrophic illness constituting an obstetric emergency in third trimester of pregnancy and may have complications for both mother and fetus, including death. Yet it is still unclear, the pathogenesis of AFLP has been identified related to defects in fatty acid metabolism during pregnancy, especially in the setting of fetal genetic defects in fatty oxidation. Establishing the diagnosis of AFLP is challenging, further it may overlap with other liver diseases of pregnancy, such as preeclampsia and hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome. The management of AFLP is a multidisciplinary progress providing the prompt intervention more than the termination of the pregnancy. The awareness of AFLP is highly needed to provide early diagnosis and management so that it can reduce the morbidity and mortality.

Keywords: *acute fatty liver of pregnancy, diagnosis, management*

ABSTRAK

Acute fatty liver of pregnancy (AFLP) merupakan penyakit yang jarang ditemukan namun memiliki gambaran klinis yang berat dan merupakan salah satu kegawatdaduratan dalam bidang obstretik ginekologi yang terjadi di trimester ketiga dan dapat menyebabkan komplikasi baik bagi ibu maupun janin yang bisa mengakibatkan kematian. Patogenesis terjadinya AFLP masih belum jelas, namun dikatakan hal ini terjadi terkait dengan defek yang berhubungan dengan metabolisme asam lemak pada saat kehamilan, terutama defek terjadi secara genetik yang melibatkan proses oksidasi lemak. Menegakkan diagnosis AFLP merupakan tantangan karena dapat terjadi tumpang tindih dengan penyakit hati pada kehamilan lainnya, seperti preeklamsia dan hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome. Penanganan dan tata laksana AFLP melibatkan berbagai macam disiplin ilmu karena terkait pula dengan masalah terminasi kehamilan dan intervensi lanjutan yang dapat diberikan kepada pasien. Kewaspadaan terhadap AFLP sejak dini dibutuhkan agar menurunkan angka morbiditas dan mortalitas.

Kata kunci: *acute fatty liver of pregnancy, diagnosis, tata laksana*

INTRODUCTION

A 28 years old pregnant women brought to the emergency unit with altered mental status since 4 hours before admission. She seemed having difficulty in breathing. She was 34 months of her second pregnancy. No fever was reported. On her last antenatal care, the condition of pregnancy was normal for both mother and baby. The vital signs were Glasgow coma scale (GCS) 11, high blood pressure (190/130 mmHg), tachycardia, and tachypnea. Laboratory findings revealed elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST), slightly increased bilirubin, slight prolongation of both prothrombin time (PT) and activated partial thromboplastin time (aPTT). She was diagnosed as acute fatty liver of pregnancy (AFLP). She was then intubated and underwent emergency cesarean delivery. She survived after 6 days ICU hospitalization and then she was discharged on the 9th day of hospitalization. Unfortunately, the baby did not survive.

There are alterations of physiological and hormonal profiles during normal pregnancy, including liver biochemical profiles. Abnormality of the liver test during pregnancy occurs in 3-5% of pregnancies, which can caused by several condition.[5] Liver disease in pregnancies is rarely happen, but it can still occur and can relates to high morbidity and mortality for both mother and the fetus.[1,2,3] Liver disease in pregnancy can divided into 2 categories, one depending on their association with or without preeclampsia. The preeclampsia-related liver disorders include preeclampsia, HELLP syndrome, and AFLP. Hyperemesis gravidarum (HG) and intrahepatic cholestasis of pregnancy (ICP) were not preeclampsia-related liver disorders.[3-5]

AFLP is a rare, but potentially fatal, complication of the third trimester of pregnancy (median gestation age is 36 weeks).[1-4] It remains an obstetric emergency for both mother (20-30% mortality) and fetus (20-50% mortality).[3] However, the need for early diagnosis and treatment is still the unmet crucial aspect.

EPIDEMIOLOGY

The AFLP is a relatively rare disease of pregnancy. The incidence of AFLP ranges between 1:7,000-15,000.[1,3] One study reported that the incidence of AFLP in Southeastern Wales was as high as 1:1,000.[5] Qiang G et al reported that the proportion of AFLP at four tertiary hospitals in China was 9.8%.[6] Muhammad IAA et al showed that the incidence of AFLP at tertiary hospital in Indonesia was 2-3 patients per year.[7] It affects woman in all ages during pregnancy and there is no evidence of distinctive epidemiologic feature related.[2,8]

Some risk factors for AFLP have been identified (Table 1). Multiple gestation are believed to be at greater risk because of increased fetal production of fatty acid metabolites by more than one fetus.[9] It is unclear if other liver disease of pregnancy might predispose women to AFLP or are merely associated, but some studies showed the comorbidities. Studies showed that up to 20% women with AFLP may also be diagnosed with hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, which itself is associated with preeclampsia.[10-11] Other study showed that there is association between AFLP and intrahepatic cholestasis of pregnancy (ICP).[12]

Table 1. Risk factors for AFLP

Nulliparity[1, 3, 13-14]
Co-existing of other liver disease of pregnancy (HELLP, preeclampsia)[2, 13]
Pregnancies with a male fetus[2-3, 13]
Previous episode of AFLP[2]
Multiple gestation[3, 13-14]
Low body mass index[13, 15]

HELLP: hemolysis, elevated liver enzymes, low platelets; AFLP: acute fatty liver of pregnancy

PHYSIOLOGICAL CHANGES DURING PREGNANCY

In normal pregnancy, physiological and hormonal changes occur within the human body, some of which can mimic those seen in women with liver disease. There is an increasing maternal heart rate, cardiac output rises by 40%, the circulating plasma volume increases by 30%, and peripheral vascular resistance is reduced. However, blood flow to the liver remains essentially unchanged (approximately 25-33% of cardiac output) during pregnancy. Due to the enlarging uterus, the liver may be slightly elevated within the abdomen with increasing gestation.[16-18] Gall bladder decreases its motility results in higher risk of developing gallstones.[17-18]

Physiological changes in liver function tests during pregnancy must not be mistaken for liver dysfunction (Table 2). Liver enzymes including alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), and bilirubin remain normal. Alkaline phosphatase (ALP) increases with advancing gestation as a result of placental production and fetal bone development, and high level should not be considered abnormal. The alpha fetoprotein (AFP) level increases as AFP

is produced by the fetal liver. Total protein decreases during pregnancy, primarily because of a decreased in albumin. Increased estrogen causes an increase in fibrinogen and other clotting factors (factor VII, VIII, IX, and X), so called pro-coagulant state.[3, 16-18]

Table 2. Physiological changes in liver function tests during normal pregnancy[3, 19]

Test	Normal range
Bilirubin	Not change or slightly decrease
ALT	Not change
AST	Not change
Prothrombin time	Not change
Alkaline phosphatase	Increase 2 to 4-fold
Fibrinogen	Increase 50%
Globulin	Increase in alpha & beta globulins, decrease in gamma globulin
Alpha-fetoprotein	Moderate increase, especially with twins

ALT: alanine aminotransferase; AST: aspartate aminotransferase

PATHOGENESIS

The pathogenesis of AFLP still has not been fully elucidated. Though, studies showed association between defect in fetal mitochondrial fatty acid beta-oxidation and development of maternal AFLP, especially fetal defects in long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD). Further, it is described in Figure 1.[2, 20]

Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency is categorized within a group of disorders so-called as fetal fatty acid oxidation defects (FAOD). FAODs affect the mother because of physiologic metabolic changes during pregnancy that result in increased demand for free fatty acids (FFA). These FFA are also metabolized by the fetus and placenta for utilization in growth and development. The placenta contains lipoprotein lipase, fatty acid-binding proteins, carnitine transporters, and enzymes involved in fatty acid oxidation (FAO), such as LCHAD. These enzymes may contribute to overall metabolic stress on the mother. Due to fetus and placenta share a uniform genotype, the placenta is similarly unable to proceed with normal metabolic pathways if FAO fails in the fetus and the intermediate products of metabolism may accumulate in the placenta and the maternal blood, creating toxic effects in the mother.[2-3, 20]

Toxic metabolic intermediates build up in maternal hepatocytes. Lipotoxicity, due to the accumulation of fatty acids and their metabolites in the maternal blood, causes increased reactive oxygen species (ROS). It has deleterious effects on hepatocytes, including activation of inflammatory pathways and cellular necrosis, leading to acute maternal hepatic failure, which may manifest as AFLP. Several factors appear to contribute to the fetal-maternal interaction. First, the heterozygosity of the mother for an mitochondrial trifunctional protein (MTP) defect reduces her capacity to oxidize long chain fatty acids. Second, third trimester is accompanied by changes in metabolism, an increased lipolysis, and a reduction in mitochondrial FAO, all increase the susceptibility of the mother carrying a fetus with LCHAD deficiency.[2-3, 20]

DIAGNOSIS

Acute fatty liver of pregnancy resembles symptoms that are unique to pregnancy. The onset is usually between 30th and 38th week of gestation, though few were reported starting in the second trimester.[20] It is more frequent in primiparous women and can return in subsequent pregnancies.[20] The patients may reveal non-specific symptoms. The initial manifestations include headache, fatigue, nausea, and vomiting.[13]

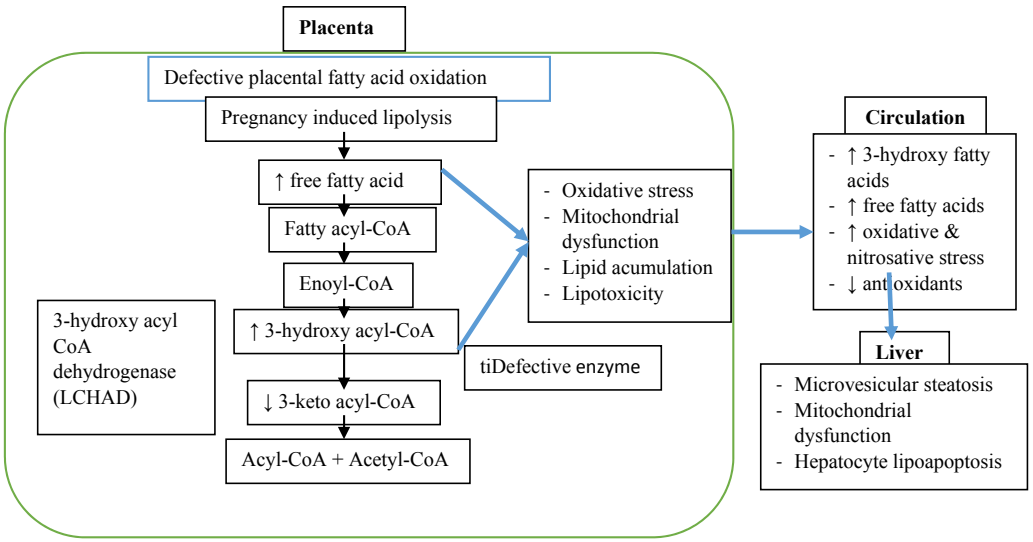

Figure 1. The sequence of events during acute fatty liver of pregnancy[21]

Clinical manifestation may vary from abdominal pain, jaundice, hypoglycemia, hepatic encephalopathy, coagulopathy.[13] Jaundice appears 1-2 weeks after the onset of symptoms.[3] Polyuria and polydipsia are found in about 5% of cases, though the mechanism is not clear.[22] Some patients may have a low-grade fever.[14] Concomitant preeclampsia is present in approximately one half of the patients.

Laboratory findings revealed anemia, leukocytosis, thrombocytopenia, elevated aminotransferases levels (from mild to 1000 IU/L, usually 300-500 IU/L), elevated bilirubin (frequently > 5 mg/dL), increased alkaline phosphatase, increased uric acid, renal impairment, proteinuria, metabolic acidosis, hyperammonemia, and biochemical pancreatitis. Hypoglycemia may also be noted, which is uncommon in other pregnancy-related liver disorders. Hypoglycemia is a poor prognostic sign. Hemostatic changes include thrombocytopenia, prolonged prothrombin time, and reduced fibrinogen levels. Procoagulant deficiency and DIC is due to hepatic dysfunction which is found in AFLP. Profound hemostatic dysfunction commonly exacerbates obstetric hemorrhage. David BN et al reported that hemostatic dysfunction with AFLP persists 4-5 days postpartum.[22-27]

Imaging studies, include ultrasound, abdominal computed tomography (CT), or MRI, may be helpful in supporting the diagnosis of AFLP. Fatty liver may be detected in ultrasound showing increased echogenicity (bright liver) and a CT indicating decreased liver density. Qiang Wei et al reported that rate of positive AFLP diagnosis was 79.7% by ultrasound, and 85.3% by CT, with no significant difference between the two methods.[23]

Liver biopsy is the gold standard for AFLP, though it is rarely necessary. It should be avoided in cases with bleeding tendencies. The hallmark histopathologic finding of AFLP is microvesicular fatty infiltration of hepatocytes involving the pericentral zone and sparing the periportal hepatocyte (Figure 2). Microvesicular steatosis is confirmed on a special stain called Oil-red-O which must be done on fresh-frozen sections. Beside the fatty change, the histopathologic findings may also encompass giant mitochondria, lymphocytic infiltration, and lack of sinusoidal fibrin deposition. It is reported that intrahepatic cholestasis, including bile canalicular plugs and acute cholangitis was found in two-thirds of cases. Upper gastrointestinal hemorrhage due to coagulation abnormalities may be seen in some cases. In severe untreated cases, it may complicate progressively into hepatic failure with coma, hypoglycemia, hyperammonemia, renal failure, and severe coagulopathy, with hemorrhage leading to death of the mother and fetus.[1-2, 18]

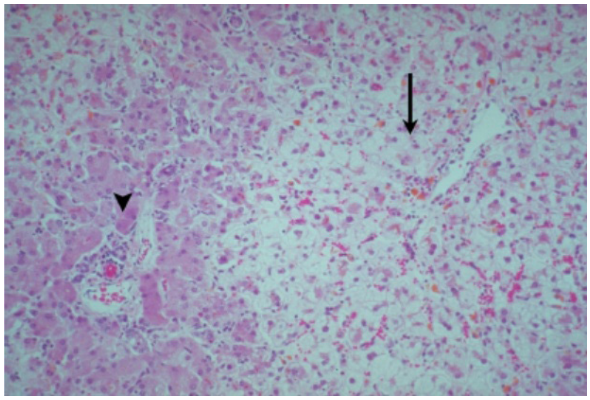

Figure 2. Liver biopsy of acute fatty liver of pregnancy[1]

The diagnosis of AFLP is made clinically based on compatible manifestation, laboratory, and imaging results. The Swansea criteria have been proposed as a clinically diagnostic tool for AFLP, with 100% sensitivity, 57% specificity, 85% positive predictive value, and 100% negative predictive value (Table 3). Based on this criteria, the AFLP is considered if at least 6 out of the 15 criteria are met. Shan Wang et al reported that the criteria without liver biopsy are good screening tools for AFLP diagnosis, and further it may be useful for assessing disease severity. This criteria is used in the absence of other diagnosis of liver dysfunction (HELLP syndrome, preeclampsia), which further makes application challenging if multiple conditions co-exist.[2,28]

Table 3. Diagnostic criteria of acute fatty liver of pregnancy based on Swansea criteria[2, 4]

The criteria
Vomiting
Abdominal pain
Polydipsia/polyuria
Encephalopathy
Hyperbilirubinemia (bilirubin > 0.8 mg/dL)
Hypoglycemia (blood glucose < 72 mg/dL)
Elevated urea (> 960 mg/dL)
Leukocytosis (WBC > 11,000/
Ascites
Bright liver on ultrasound scan
Elevated transaminases (ALT >42 U/L)
Elevated ammonia (> 66)
AKI or creatinine > 1.7 mg/dL
Coagulopathy or PT >14 s
Microvesicular steatosis on liver biopsy

WBC: white blood count; AKI: acute kidney injury; PT: prothrombin time

The differential diagnosis of AFLP encompass hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome, preeclampsia, and intrahepatic cholestasis of pregnancy. The clinical characteristics and findings of several liver disorders of pregnancy are shown in Table 4.

Table 4. The comparison of clinical characteristics and findings of AFLP and its differential diagnosis

Characteristics & findings	AFLP	HELLP	Preeclampsia	ICP
Prevalence	0.005-0.010%	0.2-0.6%	5-7%	0.1-0.3%
Maternal age	>20 years	>25 years	<20 years and >45 years	Advanced maternal age
Parity	Nulli-/multiparity, multifetal pregnancy, pregnancies carrying a male fetus	Multiparity	Nulli-/multiparity, multifetal pregnancy	Multiparity, multifetal pregnancy
Family history	Occasionally	No	Often	Often
Onset	3rd trimester or postpartum	Late 2nd/3rd trimester or postpartum	Late 2nd/3rd trimester	3rd trimester
Symptoms	Abdominal pain, vomiting, polydipsia/polyuria, encephalopathy	Abdominal pain, vomiting, proteinuria, headache, peripheral edema	Abdominal pain, hypertension, proteinuria, headache, blurred vision, peripheral edema	Pruritis, jaundice
Sign	Ascites ±	No ascites	No ascites	Icteric, no ascites
Laboratory				
Thrombocytopenia	± ↓	± ↓	± ↓	± ↓
Bilirubin	<10 mg/dL	<5 mg/dL	<5 mg/dL	<5 mg/dL
Hypoglycemia	±	-	-	-
Aminotransferases	5-10x	1-100x	1-100x	1-5x
Uric acid	↑ (80%)	↑	↑	-
Hemolysis	-	↑	±↑	-
Creatinine	↑	-	↑	-
Proteinuria	±↑	±↑	↑	-
Histopathology	Microvesicular steatosis	Fibrin deposition, hemorrhage, hepatocellular necrosis	Fibrin deposition, hemorrhage, hepatocellular necrosis	Hepatocellular bile and canalicular bile plugs, cholestasis

AFLP: acute fatty liver of pregnancy; HELLP: hemolysis, elevated liver enzymes, low platelets; ICP: intrahepatic cholestasis of pregnancy

MANAGEMENT

AFLP has been considered an obstetric emergency that can lead to multiple organ failure in a short time unless it is diagnosed promptly. As a disease of the last trimester of pregnancy, AFLP appears with intriguing features, including non-specific gastrointestinal symptoms that are easily overlooked or misdiagnosed.

The management of AFLP encompasses three aspects, those are: (1) Early recognition and diagnosis. Defining appropriate screening guidelines for outpatient pregnant women could be life-saving. The 34th week of gestation has been recommended for this screening context. Firstly, liver and coagulation function tests could be performed for any pregnant woman who complains of new-onset gastrointestinal symptoms (e.g. abdominal pain, nausea, and vomiting). Once abnormal results are found, further tests should be performed, including renal function tests, blood glucose, and abdominal ultrasound.[13,29]; (2) Aggressive maternal stabilization. Intensive care admission should be needed to perform it through adequate supportive therapy. The supportive therapy consists of: (a) Diet low in fat and protein, high in carbohydrates; (b) Correction of dehydration, electrolyte and acid-base imbalance; (c) The correction of concurrent coagulopathy with adequate blood products should be considered first. The transfusion of fresh frozen plasma, cryoprecipitate, or platelet concentrates in the presence of abnormal tests, such as PT, activated partial thromboplastin time (aPTT), or fibrinogen could prevent further bleeding complications. Prothrombin time improvement is the first sign of hepatic recovery.[1,4,13,19,26]; (3) Expeditious termination of the pregnancy is the cornerstone of AFLP management, with cesarean section being the preferred mode of delivery. When vaginal delivery cannot be obtained quickly, caesarian section should be performed. A meta-analysis and systematic review by Hong-Yan Wang et al. revealed that caesarian section is associated with better pregnancy outcomes. Further they emphasized that caesarian section is the safest method of delivery and should be recommended to reduce the risk of adverse pregnancy outcome in patients with AFLP. The selection in anesthesia modalities in patients with AFLP requiring cesarean section should be invidualized. GuoXia, Z et al. reported that general anesthesia with rapid-sequence induction may be the best choice for patients with severe coagulopathy. [1,4,13,30,31]

Liver transplantation is considered as a last measure, though it remains controversial. The fulminant liver failure due to AFLP is usually reversible, and patients may be expected to recover normal function in weeks. If liver function worsens, it may be a sign of concurrent sepsis or hypoxic-ischemic liver injury. Use of liver transplantation in AFLP has been reported for cases of worsening clinical status, such as encephalopathy and lactic acidosis, and persistent liver failure despite optimal medical treatment. Yet, there is no official

guidelines for determining when transplantation should be considered.[2]

PROGNOSIS

Most patients with AFLP improve in 1 to 4 weeks postpartum though cholestatic phase with hyperbilirubinemia and elevated alkaline phosphatase still persist. They can get recovery in days or months with no signs of chronic liver disease. Studies reported that there is no recovery before delivery. The prognosis in these patients were determined by the severity of liver dysfunction (serum bilirubin and prothrombin time), serum creatinine, and delay in delivery.[10,19,32]

There are some complications related to AFLP, including acute liver failure (ALF), acute renal failure, DIC, infections, acute respiratory distress syndrome, and acute pancreatitis. Yan-Ping Z et al reported that PT (OR = 1.558; 95% CI: 1.248-1.946, p = 0.016) and INR (OR = 40.034; 95% CI: 2.517-636.693; p = 0.009) are risk factors for fatal complications in patients with AFLP. Further, they also reported that fibrin degradation products is associated with perinatal mortality.[33]

ALF is a common complication of AFLP. Recent studies reported that 20-52% subjects develop ALF. The pathologic changes in patients with ALF due to AFLP are reported as 'of a reversible kind', with the clinical course and histopathologic findings clearly lead to a functional failure –not a destructive form of hepatic insufficiency. Further, Hao-Feng X et al reported that patients with ALF due to AFLP do not need specific long-term follow-up after recovery from AFLP if their liver function tests have normalized and they remain well.[33,34]

The morbidity of renal impairment in AFLP is 39-72.0%, and incidence of AKI requiring renal replacement therapy is 32.0%. Hao-Feng et al reported that renal function completely recovered at discharge and 6-months follow-up, suggesting that the renal damage in AFLP patients is reversible.[33,34]

Compared to other liver diseases in pregnancy, AFLP revealed poorer outcome on maternal mortality. The maternal mortality of AFLP in 2000s was 7-18% (vs. 0% for ICP vs. 1-25% for HELLP syndrome). Compared to AFLP in the 1980s, this number were decreasing due to greater recognition of AFLP, improving time-to-diagnosis and time-to-subsequent delivery scheme, and improvement of obstetric intensive care. In Indonesia, 12 of 18 patients with AFLP were died with the maternal sepsis as the common direct cause. The risk or maternal mortality was associated with multiple complications and the presence of hypertension. Further, several complications were direct consequences of liver failure.[2, 7, 19]

Perinatal mortality is still challenging. Perinatal mortality is 9-23% (vs. 0.4-1.4% for ICP vs. 11% for HELLP syndrome) and remains high. It is due in part to maternal acidosis that has immediate detrimental effects on fetus. In Indonesia, the perinatal morbidity as the outcome of AFLP was 57.89% with all neonates were developing early onset sepsis. This high burden is related to late diagnosis and suboptimal maternal-fetal surveillance following admission.[2, 7, 19]

Many patients with AFLP do not become pregnant again due to the devastating effect of the illness and/or hysterectomy. There is small but definite risk of recurrence during subsequent pregnancies. Further studies and long-term postpartum evaluation are highly needed to evaluate the need of screening and the recurrence of AFLP.

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