

# Acute fatty liver of pregnancy. Brief review and case-presentation

*Ficatul gras acut de sarcină (AFLP). Scurt review și prezentare de caz*

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## Abstract

Acute fatty liver of pregnancy (AFLP) is a rare obstetrical pathology that occurs usually in the last trimester of pregnancy and postpartum, but it can rarely be encountered in the second trimester, but never in the first one. We are about to present the case of a 27-year-old patient with a 28-week gestation with an accurate surveillance and a critical and severe evolution following the diagnosis because of the multiple organs and systems failure: hepatic, renal and pancreatic, followed by fetal death and hysterectomy. AFLP is a rare gastro-intestinal disease peculiar to gestation, with an unfortunate outcome for both the mother and foetus, especially if the diagnosis is delayed together with the onset of complications. The peculiarity of this case-presentation is the atypical occurrence (28 weeks of gestation, it usually starts around 35 to 36 weeks of pregnancy), the infectious trigger being represented by a urinary infection, and with a severe outcome and multiple consequences once the presumption of AFLP has been done.

**Keywords:** acute fatty liver, pregnancy, hypoglycemia, hepatic cytolysis

## Rezumat

Ficatul gras acut de sarcină (acute fatty liver of pregnancy - AFLP) este o complicație obstetricală rară, care apare de obicei în trimestrul al III-lea de sarcină sau în lăuzie, dar poate apărea și în trimestrul al II-lea, niciodată în trimestrul I. Expunem în această lucrare cazul unei paciente în vârstă de 27 de ani, cu sarcină de 28 de săptămâni, corect dispensarizată, la care evoluția după momentul diagnosticului a fost foarte gravă din cauza insuficiențelor funcționale multiple: hepatică, renală și pancreatică, soldate cu exitus fetal și histerectomie interanexială de necesitate la mamă. AFLP este o afecțiune digestivă specifică perioadei de gestație, rară, cu prognostic nefavorabil matern și fetal, mai ales atunci când diagnosticul este pus tardiv, în momentul apariției complicațiilor. Particularitatea cazului expus este debutul atipic al acestei afecțiuni (28 de săptămâni de gestație, de obicei apărând în săptămâna 35-36 de gestație), trigger-ul infecțios fiind reprezentat de infecția urinară și evoluția fulminantă, cu tot cortegiul complicațiilor din momentul suspectării diagnosticului de AFLP.

**Cuvinte-cheie:** ficat acut gras, sarcină, hipoglicemie, hepatocitoliză

## Introduction

Acute fatty liver of pregnancy is a rare disease that usually occurs in the 3<sup>rd</sup> trimester of pregnancy or childbed, rarely in the 2<sup>nd</sup> trimester, and never in 1<sup>st</sup> trimester. It has a poor maternal and foetal outcome especially in delayed diagnose when complications are present. We present the case of a young woman with a 28-week live pregnancy, whose onset AFLP symptoms mimicked other disorders and misled the clinicians before the actual diagnosis was established, with poor outcome for the mother and poorer for her baby.

## Case Report

We present the case of a 27-year-old primiparous woman with a 28-week live pregnancy. She has unremarkable history, having regular monthly check-ups, normal tension values during pregnancy, no other pathology until during current gestation except for an *E. Coli* urinary infection treated with success. An ultrasound performed at seven days before highlighted a 3-week intrauterine growth restriction (9.36 percentile), foetal umbilical and middle cerebral artery blood flow velocity equalized, high PI blood flow velocity on both uterine arteries, the patient being undergoing investigations for thrombophilia (D Dimers 7973.47 ng/ml). At the

last consult, she was already experiencing for 7 days long symptoms that consisted of fatigue, asthenia, insomnia, and nausea, that emerged gradually and aggravated in the last 24 hours. Blood samples showed multiple changes: increased liver enzymes (AST =147U/L, ALT=312 U/L), leukocytosis (WBC= 15500/mm<sup>3</sup>), hypoglycemia (46 mg/dl), slightly increased serum creatinine (1.46 mg/dl), decreased level of serum fibrinogen values compared to the previous tests (331 mg/dl) and a decreased prothrombin activity (aPTT= 56%).

The patient presented herself with the blood test results, out of her good will, at the emergency room of an infectious diseases department, being immediately admitted to the hospital with a suspicion of acute viral hepatitis, in the sight of the recent onset of jaundice. During her time in hospital, her health state progressively altered: extreme leucocytosis (26000/mm<sup>3</sup>), serum direct bilirubin level increased (5.18 mg/dl), hypofibrinogenemia (108 mg/dl), thrombocytopenia (100000/mc), increased serum creatinine level (2 mg/dl), urinary test positive for *Bacteroides Fragilis* infection (PCR method), and decreased foetal activity. The acute viral hepatitis diagnosis was invalidated, the patient being transferred into a tertiary centre for accurate diagnosis and treatment.

The clinical examination of the patient at the admission in the third level care unit revealed an impaired general health state, severe jaundice, oliguria, reduced foetal active movements, cerebral-umbilical blood flows velocity reversed. She was transferred in the intensive care unit for rebalancing therapy before C-section in both mothers and child's interest. The following day, a 1120 g live male newborn was delivered by caesarean, receiving 2 points on Apgar scale and whose demise occurred two days later despite the intensive treatment in NICU department.

Subsequent to the C-section and after resuming food intake, the general health state of the patient continues to worsen. When severe hypoxemia is detected, the CT scan reveals multiple opacities inside the lung parenchyma associated with bilateral pleural effusion. Fibrinolysis persists, needing large amount of transfusion fluids (25 U cryoprecipitate, 5 U PPC, 2g Hemocompletan). Large spectrum antibiotics therapy (Meronem, Targocyd, Metronidazole) was already used. Despite all these efforts, no health state improvement is seen. After a new evaluation, the local medical committee decided to perform an emergency hysterectomy with adnexal preservation, considering the uterus as a possible starting place for systemic inflammatory response syndrome (SIRS). The surgical maneuvers worsened the disseminated intravascular coagulation (DIC), requiring blood volume replacement and coagulation restoration using 7 U cryoprecipitate, 2 U PPC, 2U MER, and also respiratory support (PEEP) during and few hours after surgery.

The patient's evolution was dominated by multiple systems and organs complications after the hysterectomy. The anaemia worsened in the first day after surgery, rising the suspicion of stress-induced ulcer, later confirmed by gastric endoscopy, located near the cardiac sphincter and showing signs of recent bleeding. Its treatment scheme included pump proton inhibitors and blood transfusions. In the third day, the patient presented paralytic ileus with pseudo-occlusive syndrome, confirmed by CT-scan, and acute pancreatitis (on MRI) with reappearance of jaundice and increased levels of total bilirubin up to 6.18 mg%, with the predominance of direct bilirubin, needing prolonged antisecretory therapy and fasting. The further evolution showed slow improvement of the health state, allowing first the transfer of the patient to the Obstetrical-Gynecology Unit and 14 day later the release from the hospital. Analyzing retrospectively, the event is considered to be part of the group of the specific gastrointestinal disease of pregnancy, respectively acute fatty liver of pregnancy.

## Discussions

Together with intrahepatic cholestasis and HELLP syndrome, AFLP is one of the hepatic dysfunctions typical for the gestation period, having a potential fatal outcome.

AFLP represents a potential complication in the evolution of pregnancies with preeclampsia, HELLP syndrome or urinary or respiratory tract infections (39%). It occurs more often in nulliparous than multiparous pregnancies, and is more frequently associated with male foetuses. The infectious trigger was present in our case as well, but it was difficult to identify due to the technical limitations of laboratories conducting routine tests. *Bacteroides fra-*

*gilis*, an anaerobic bacterium, requires for identification special sampling on growth environment, and further processing expensive equipment, inaccessible to many medical establishments, leading to above-average costs of analyses, both for the population and medical services providers, which hinders the possibility of diagnosis outside the centres of excellence<sup>(1,2)</sup>.

For a long time, the pathogenesis of AFLP was a mystery.

Fatty acid oxidation disorder forms a heterogeneous group of inherited metabolic diseases (more than 20) with a wide range of clinic and metabolic manifestations. LCHAD deficiency was described for the first time in 1989, but the physiopathological mechanism was understood later, in 1992<sup>(3)</sup>.

Studies within the field of molecular biology have shown that AFLP develops when the foetus has LCHAD dysfunction (long-chain 3 hydroxyacyl coenzyme A dehydrogenase). The mitochondrial enzyme is part of a triple enzymatic complex - MTP (mitochondrial trifunctional protein) attached to the inner side of the mitochondrial membrane. MTP is a hetero-octamer of four alpha and four beta subunits. The carboxyl-terminal domain of the alpha subunit has LCHAD enzymatic activity. Beta-oxidation of fatty acids represents the source of energy for the muscular tissue and the heart, while the liver uses fatty acids during periods of starvation and intense physical activity, thus generating metabolic products further used by the other organs as alternative source of energy in case of hypoglycaemia. LCHAD dysfunction determines the intra-cytoplasmic accumulation of medium- and long-chain fatty acids<sup>(3)</sup>.

The genes for alpha and beta subunits of the MPT are located on chromosome 2 (2p23). Molecular genetic techniques have allowed to identify the G1528C mutation in exon 15 for the alpha subunit, which replaces the position 474 of glutamic acid with glutamine (E474Q), changing the polarity and structure of the enzymatic chain and inactivating LCHAD<sup>(3)</sup>.

**Table 1** Swansea criteria for the diagnosis of AFLP<sup>(4)</sup>

6 or more signs/symptoms in the absence of other causes:
Vomiting
Abdominal pain
Polydipsia/polyuria
Encephalopathy
Hyperbilirubinemia
Elevated transaminases
Hypoglycaemia
Azotate retention
Renal impairment
Leukocytosis
Coagulopathy/CID
Ascites/bright liver on ultrasound scan
Microvesicular centrilobular liver steatosis on HP examination
Source: Chang et al., 2009

Multi-centre research conducted independently since the '90s have confirmed the existence of a strong relation between the mutation of the LCHAD gene in the foetus and AFLP in the mother. Even though the incidence of the enzymatic deficit in the general population is 1:150-1:200, with autosomal recessive transmission, the disease occurs with a frequency of 1:9000-13 000 pregnancies, and women at first pregnancy carrying male babies represent the prototypical case. Rarely, AFLP may reoccur during the next pregnancy<sup>(3)</sup>.

The mechanism by which foetal LCHAD deficiency determines AFLP in the heterozygous mother is still unclear. Apparently, the mother's heterozygosity, alongside third trimester metabolic stress, toxic hepatic metabolites of placental or foetal origin, and external causes force the liver, which already has a reduced capacity of long-chain fatty acid oxidation, to over-work, thus causing a major hepatic dysfunction<sup>(3)</sup>.

The classical landscape of AFLP includes third trimester pregnancies (35-36 weeks), with non-specific digestive symptoms (nausea, vomiting, anorexia, abdominal pain located in the epigastrium, right hypochondrium), polydipsia with or without polyuria, fever, jaundice and ascites (Table 1). Often, jaundice is a symptom that occurs too late, delaying the diagnosis and increasing the maternal and perinatal mortality and morbidity.

In our case, as in most cases, the diagnosis was made at the time of complications: hepatic encephalopathy (13%), hypoglycaemia (55%), DIC (56%), renal impairment (50%), preeclampsia (50%) or sepsis<sup>(8,9)</sup>. The development of secondary jaundice, not simultaneous with the moderate modifications of hepatic enzymes, misguided towards an acute viral infectious pathology and delayed the correct diagnosis, and implicitly the appropriate treatment, until the clinical and biological picture had been fully outlined

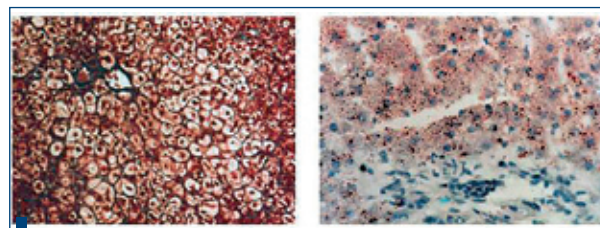


Figure 1. A. Sudan III (400X); B. Red oil O (520X)

(Table 2). The onset of sepsis further increased maternal morbidity, as well as the perinatal mortality, alongside prematurity and intrauterine growth restriction.

The histopathological diagnosis, gold-standard in the past, is reserved for cases in which the suspicion is not supported by clear evidence provided by other tests. In terms of microscopic analysis, the Sudan III staining indicates the centrilobular fat accumulation in the hepatocytes, with minimal inflammation and necrosis. A characteristic feature is the absence of impairment in zone 1 of the hepatic acinus, which is closest to the common hepatic artery - Picture A. The intra-cytoplasmic fat granules can be identified with other staining methods - Picture B<sup>(5)</sup>.

The differential diagnosis includes: acute fulminant liver failure (A, E, and herpetic hepatitis), autoimmune and drug induced hepatitis (e.g. Paracetamol), preeclampsia, HELLP syndrome, intrahepatic cholestasis of pregnancy (Table 3)<sup>(4-6)</sup>.

Unfortunately, AFLP treatment often begins after the onset of severe complications. Pregnant women suspected of AFLP must be admitted to hospital!<sup>(6)</sup>

In case of severe forms of the disease, it is recommended to admit the patient into intensive care unit, monitored by a multi-disciplinary team, receiving full parenteral nutrition, hydroelectric re-balancing, correction of coagulation

Table 2 Paraclinical tests in AFLP<sup>(4)</sup>

	Test	Disorder
<b>Essential tests</b>		
Tests for diagnosis purposes	HLG, urea, creatinine, electrolytes, coagulation tests, glycaemia, transaminases, bilirubin	Leukocytosis, renal impairment, coagulopathy, hypoglycaemia
Tests required to exclude other pathologies	PCR, viral serology, septic condition screening, urine analyses	Viral hepatitis B, C, E infection, CMV infection, proteinuria
Abdominal ultrasound	Ascites, bright liver on ultrasound scan	Present in 1/3 of AFLP patients, useful for the exclusion of obstructive jaundice
<b>Additional tests</b>		
CT	Limited antenatal role	Fatty infiltration of the liver, which is not apparent on abdominal ultrasound scan
MRI	Does not provide additional information	
Liver biopsy	Microvesicular hepatic infiltration (steatosis)	Gold-standard diagnosis in the past, increased risk due to coagulopathy

**Table 3** Differential diagnosis in AFLP<sup>(4-6)</sup>

Specific to pregnancy	HELLP Severe preeclampsia Cholestasis of pregnancy Hyperemesis gravidarum
Infectious	A, B, C, E viral hepatitis Malaria Sepsis Other viral infections (HIV, CMV, HSV)
Haematological	Haemolytic uremic syndrome
Autoimmune	Autoimmune hepatitis Primary biliary cirrhosis Sclerosing cholangitis
Metabolic	Haemochromatosis Wilson's disease
Toxic	Acetaminophen intoxication
Organic	Biliary lithiasis

disorders, antiseptics, analgesic and liver protection medication, external foetal monitoring with Doppler velocimetry on middle cerebral and umbilical arteries and non-stress tests, with the patient well-balanced in order to perform emergency C-section, delivering the baby and suppressing the vicious cycle. The sooner the treatment begins, the better the maternal prognosis becomes, while the foetal prognosis is conditioned by prematurity.

Maternal mortality because of AFLP has decreased significantly to 12-18%, and in some centres even below 10% (from 85% in the '80s), due to better understanding and management of the disease, and is associated in particular to complications such as DIC or infections<sup>(7)</sup>.

After birth, the evolution is positive, due to the fact that the stimulus for lipid overburdening has been eliminated. It is recommended that the patient diagnosed after the onset of complications remains in intensive care unit, under careful monitoring, until stabilisation, regardless of the improvement of biological samples that occurs as early as the first 48 hours after birth<sup>(7)</sup>.

The remission, both in terms of clinical manifestation and laboratory parameters, is complete after 4 weeks.

There is a 25% theoretical genetic risk of recurrence of the disease during future pregnancies.

Foetal mortality remains high (20-25%), and is partially correlated with the necessity of premature birth.

## Conclusions

AFLP is a diagnosis challenge for the clinician. There are no specific laboratory tests for the diagnosis of this disease. Signs and symptoms are diverse and occur during the third trimester on the background of other pre-existent medical conditions.

The alarm signal must be triggered by hypoglycaemia, which, alongside modifications of the hepatic enzymes, leukocytosis and changes in coagulation, complete the clinical picture of AFLP before the onset of organ or system failure (acute pancreatitis, renal impairment, cerebral edema, postpartum haemorrhages, CID, sepsis, foetal death, maternal death).

Emergency delivery improves the maternal prognosis, but increases foetal mortality and morbidity, in particular in case of prematurity.

The particularity of the case presented here is the atypical date of onset of the disease (28 weeks of gestation, while the typical age of onset is 35-36 weeks), with an infectious trigger represented by the urinary infection caused by an anaerobic germ that eluded identification during routine tests due to the specific features required for the identification of the pathogen germ, and the violent evolution accompanied by a whole suite of complications since the moment of suspicion of an AFLP diagnosis. ■

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