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Case Series

Acute fatty liver of pregnancy: cases series and review of the literature

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ABSTRACT

Acute fatty liver of pregnancy (AFLP) is a condition that occurs during the third trimester of pregnancy, typically manifesting around 36 weeks of gestation. It represents a critical obstetric emergency with considerable neonatal mortality. To manage AFLP disease, a multidisciplinary approach is essential which helps meaningfully in the improvement of its prognosis during the post-partum period. Historically, it was considered a fatal disease for both mother and fetus. Nowadays, the prognosis is improved by rapid diagnosis, early delivery and administration of treatment. We reported three cases of Moroccan women diagnosed with AFLP in our hospital who received a multi-disciplinary care with good prognosis. The first and third parturient gave birth by vaginal delivery and the second one by caesarean section.

Keywords: Third trimester of pregnancy, Gravid hepatopathy, Hemostasis disorder, Kidney failure, Diffuse hepatic steatosis, Swansea criteria

INTRODUCTION

Acute fatty liver of pregnancy (AFLP) is a rare obstetrical complication that typically occurs in the last trimester of pregnancy, which can be fatal for both mother and fetus. Its current prevalence is estimated at 1 to 3 cases per 10,000 births.[1] First discovered by Sheehan in 1940**,** it is the only gravid hepatopathy that can cause acute liver failure. The main risk factors are: if the fetus is male, in twin pregnancies, and in primiparous women, but it can also occur in patients with previous normal pregnancies.[2,3]

The etiology of AFLP remains unclear. The main cause of AFLP is thought to be mitochondrial dysfunction in fatty acid oxidation of the parturient, leading to accumulation in hepatocytes. AFLP is characterized by micro-vesicular fatty infiltration of hepatocytes inducing acute liver failure, which is the cause of most of the symptoms of this pathology.[1] Primally diagnosis of AFLP is based on clinical symptoms which include anorexia, abdominal pain, nausea, vomiting, and jaundice, and laboratory findings are based on constant hypoglycemia, increased creatinine and urea levels, low prothrombin level, prolonged partial thromboplastin time, aspartate-amino-transferase, and alanine-amino-transferase levels often elevated. Imaging can provide supplementary support. However, differentiating AFLP from other liver diseases during pregnancy can be challenging.[3] The definitive confirmation of AFLP is typically achieved through a liver biopsy. That said, early delivery remains the gold standard of treatment for this disease.

If not diagnosed in the early phase, AFLP may progress to a potentially fatal hepatocellular failure, which can be fatal for both mother and fetus associated with hepatic encephalopathy and hemostasis disorders acute renal failure and hypoglycemia. Nevertheless, B-oxidation deficiency should be systematically investigated by screening for C1528G>C mutations in the HADHA gene encoding the alpha subunit of long-chain 3-hydroxyacyl-coenzyme A dehydrogenase (LCHAD). In the event of a deficiency, the child must be monitored at an early stage

by a pediatrician, using a suitable diet to avoid the appearance of complications and sudden death.

CASE SERIES

Case 1

A 30-year-old pregnant, primigest nulliparous woman with no significant past medical history was admitted to the emergency department at 36 weeks' gestation after reporting diarrhea and sub jaundice complicated by nausea, vomiting, and abdominal pain associated with fever at 39°F. She had no history of ingestion of medicinal herbs or medications. The pregnancy was not well monitored, the physical examination found a sub-icteric patient with a Glasgow score reduced to 13, fever at 39°, low blood pressure at 90 mmHg/60 mmHg, tachycardia at 104 bpm and polypnea at 18 cycles per minute. The obstetrical examination showed a patient in travail with 4 contractions per 10 min, negative fetal heart sounds, cervix dilated to 7 cm, with ruptured membranes, clear amniotic fluid, clinically normal pelvis. Biological tests revealed: B+ grouping, normal hemoglobin at 12.5 g/dl, hyperleukocytosis at 21600/µl with neutrophil predominance at 16.53.10³/mm³ and lymphocytosis at 3.24. 10³/mm³, normal platelet count 438000/µl, hypoglycemia at 0,53 g/l elevated serum lactate dehydrogenase 347 U/l, elevated aspartate aminotransferase 444.9 U/l, total bilirubin at 63 mg/dl, direct bilirubin 44 mmol, serum creatinine increased to 37 mg/dl, urea to 0.54 mg/dl, total protein to 60 g/dl, blood glucose decreased to 41 mg/dl, prothrombin level down to 27%, and activated partial thromboplastin time increased to 43 s. the C- reactive protein (CRP) was elevated at 52 mg/l, Hepatitis A, B and C serologies were negative. Obstetric ultrasound showed negative fetal heart activity in utero, placenta located anteroventral grading three, amniotic fluid decreased in quantity, estimated fetal weight 2700g. Abdominal ultrasound revealed discrete diffuse heterogeneity with a slight increase in echogenicity, probably reflecting diffuse steatosis (Figure 1).

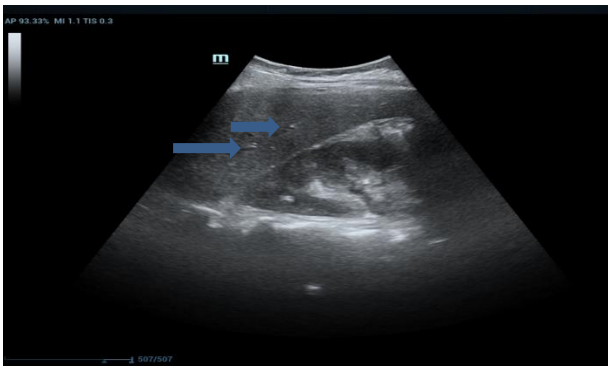

Figure 1: Sagittal section of abdominal ultrasound with diffuse hepatic steatosis.

Note: Abdominal ultrasound of the liver in sagittal section, showing a heterogeneous liver with hyperechoic zones associated with the appearance of a shiny liver (blue arrows).

The diagnosis of AFLP was based on 10 out of 15 positive Swansea criteria (Table 1), with chorioamnionitis suspected since premature rupture of membranes and infectious syndrome (fever, elevated CRP, hyperleukocytosis).

After an hour of admission, the patient gave birth to a female stillborn weighing 2800 g. She was stabilized and transferred to intensive care for monitoring and complementary multidisciplinary management, where she received a continuous infusion of 5% glucose serum for approximately 4 days to maintain normal blood sugar levels and was transfused with a total of 14 fresh frozen plasma (FFP). On day 5 of hospitalization, the patient's GCS improved, as did her clinical, biological, and liver parameters (Table 2). Then, she was transferred to obstetric department. On the 10th day the patient was discharged.

Table 1: Swansea criteria.

Swansea criteria	Patient		
	1	2	3
Abdominal pain	Yes	Yes	Yes
Polydipsia or polyuria	Yes	Yes	No
Vomiting	Yes	Yes	Yes
Encephalopathy	No	No	No
Hypoglycemia<72 mg/dl	Yes	Yes	Yes
Bilirubin>0.8 mg/dl	No	No	Yes
Elevated urea>950 mg/dl	No	Yes	Yes
Ascites	No	Yes	Yes
ALT>42 U/l	Yes	Yes	Yes
White blood cell count>11000/l	Yes	Yes	Yes
Ammoniac>66	No	No	No
AKI or creatinine>1.7 mg/dl	Yes	Yes	Yes
PT>14 s or coagulopathy present	Yes	Yes	Yes
Bright liver on ultrasound	Yes	No	No
Liver biopsy showing microvesicular steatosis	No	No	No

Table 2: Evolution of liver function and coagulation tests during hospitalization.

Variables	Day 1	Day 4 (postpartum day 3)
TP (sec) (%)	27	63
APTT (sec)	43	32
AST (u/l)	175	123
ALT (u/l)	115	91
Total bilirubin (µmol/l)	88	60

Note: TP- prothrombin time; APTT- activated partial thromboplastin time; AST- aspartate aminotransferase; ALT- alanine aminotransferase; ALP- alkaline phosphatase.

Case 2

A 25 year-old woman, gravida two para one, was pregnant at 36 weeks and two days of gestation. The first pregnancy gave birth to a healthy male newborn by vaginal delivery, currently three years old, with normal post-natal care. The present pregnancy was not monitored. She had no past medical history. The patient presented an abdominal pain, nausea, vomiting, polydipsia, and pruritus.

The physical examination on admission showed: an icteric patient, with a distended abdomen with positive Flot sign, normotensive to 120/82 mmhg, norm cardiac with 84 beats per min, eupneic with 16 cycles per min and apyretic to 37.4°C.

The obstetrical examination found abdominal palpation showed a cephalic pole below, podalic pole above, positive uterine contractions at the rate of one contraction every ten minutes, positive fetal heart sounds, the cervix dilated to 2 cm, water bag intact. Obstetrical ultrasound revealed: progressive mono-fetal pregnancy, positive cardiac activity, placenta located anteriorly, decreased amniotic fluid with a severe oligo-amnios: large cistern at 1.2 cm, estimated fetal weight was 2400g.

The cardio-fetal rhythm was micro-oscillatory are active with a basal rate of 120 bpm.

Laboratory evaluation showed: normal hemoglobin at 14.4 g/dl, white blood cell count at 11600/µl and lymphocytosis at (23.9%), platelet count of 524000/µl, serum lactate dehydrogenase (ALAT) increased to 803 U/l, aspartate aminotransferase (ASAT) elevated to 554, 9 U/l, total bilirubin increased to 52 mg/dl, direct bilirubin to 32 mol, serum creatinine elevated to 30.26 mg/dl, as well as urea at 1.36 mg/dl, total protein normal at 62 g/dl, but hypoglycemia at 53 mg/dl, prothrombin time was normal at 86 s, and activated partial thromboplastin time was prolonged to 30.6 s. Hepatitis A, B and C serologies were negative. Hypo-kalemia 2.8 meq/l, natremia 134 meq/l. Abdominal ultrasound revealed moderate ascites, liver normal.

Using the Swansea criteria, the patient met 10 of the 15 Swansea criteria, the diagnosis of AFLP was therefore retained (Table 1) and she underwent an emergency cesarean section for suspected severe chronic fetal distress. The new baby boy weights 2450 g. Apgar was 5/10 at the first minute, then 7/10 at the fifth minute, necessitating hospitalization in neonatology.

Post-operatively, the patient was transferred for two days to the intensive care unit for further management of acute hepatic and renal failure, and to treat hypokalemia.

On her fifth day of hospitalization, her clinical condition improved, and laboratory results progressed: the serum lactate dehydrogenase (ALAT) decreased to 103 U/l, aspartate aminotransferase (ASAT) reduced to 54, 9 U/l, total bilirubin decreased to 22 mg/dl, direct bilirubin to 12 mol, serum creatinine elevated to 11 mg/dl, as well as urea at 0.46 mg/dl, normal glycemia at 1.01 mg/dl, prothrombin time was normal at 86 s, and activated partial thromboplastin time was prolonged to 76 s, normo-kalemia at 3.8 meq/l, natremia 135 meq/l. The patient was discharged on the ninth postpartum day with a healthy baby. Although, a careful monitoring of the newborn by a pediatrician was recommended.

Case 3

18 years-old pregnant women, nulliparous, primigravida, without significant medical history, was admitted to emergency department at 32 weeks and six days of gestation after reporting vomiting, and abdominal pain, asthenia, fever at 38.6°F, generalized jaundice, and altered general state of health.

The patient was transferred to intensive care, the physical examination found an icteric patient with Glasgow score reduced to 14, febrile at 38.4°F, arterial tension at 110 mmHg/60 mmhg, tachycardic at 103 bpm, polypnea at 18 cycles per minute.

The obstetrical examination showed a patient in travail with 3 contractions per 15 min, negative fetal heart sounds, cervix dilated to 7 cm, with ruptured membranes, tinted amniotic fluid, clinically normal pelvis.

Biological tests revealed

A- grouping, hypoglycemia at 0,60 g/l, normal hemoglobin at 11.5 g/dl, hyperleukocytosis at 22700/µl with neutrophil predominance at 18.53.10³/mm³, thrombopenia at 438000/µl, elevated serum lactate dehydrogenase 519 U/l, elevated aspartate aminotransferase 116 U/l, total bilirubin at 153 mg/dl, direct bilirubin 81 mmol, serum creatinine increased to 23 mg/dl, urea to 1.41 mg/dl, total protein to 60 g/dl, blood glucose decreased to 41 mg/dl, prothrombin level down to 32%, and activated partial thromboplastin time increased to 43 s. the C-reactive protein (CRP) was elevated at 52 mg/l, Hepatitis A, B and C serologies were negative. Obstetrical ultrasound showed: negative fetal cardiac activity in utero, placenta located anteroventral grading two, amniotic fluid decreased in quantity, estimated fetal weight 1900 g. Abdominal ultrasound revealed diffuse steatosis and moderate ascites.

The diagnosis of AFLP was based on 10 out of 15 positive Swansea criteria (Table 1), with chorioamnionitis suspected because of infectious syndrome (fever, elevated CRP, hyperleukocytosis) and tinted amniotic fluid. Vaginal delivery was accepted in view of the maternal risk of hemorrhage for an emergency caesarean section. The patient was admitted to the delivery room with conditioning, monitoring, oxygen therapy and administration of antibiotics. She delivered a fresh male stillborn weighing 1800g and the placenta was sent for

anatomopathological examination. The parturient stayed in intensive care for monitoring and complementary multidisciplinary management, where she was transfused with a total of 11 fresh frozen plasma (FFP).

She was transferred to the obstetrics department on the 4th day of delivery, given the good evolution of her clinical and biological condition.

On the 10th day the patient left the hospital. Anatomopathological examination of the placenta showed a morphological aspect of chorioamnionitis with the presence of a cluster of germs, vascular ectasia and fibrinoid deposits (which is in favor of AFLP).

DISCUSSION

AFLP is a rare but potentially fatal hepatopathy for both mother and fetus. It is specific to pregnancy and usually occurs in the third trimester: the case of our two patients. Since its first description by Sheehan in 1940, its frequency has evolved from 1 case/10,00,000 pregnancies to approximately 1/7,000 to 1/16,000 today.[3,4] Nowadays, it is more frequent in primiparous women, but can also occur after several normal pregnancies, in twin pregnancies, when the fetus is male, in women with a body mass index of less than 20 kg/m^2 and in parturient with pre-eclampsia.[5]

The etiology of AFLP is poorly understood, but some hypotheses report that women diagnosed with AFLP syndrome are more likely to have heterozygous long-chain 3-hydroxyacyl-coenzyme a dehydrogenase deficiency (LCHAD). LCHAD is found on the mitochondrial membrane and is involved in the beta-oxidation of long-chain fatty acids. The mutation in this gene is recessive; therefore, outside of pregnancy and under normal physiological conditions, women exhibit normal fatty acid oxidation. But if the fetus is homozygous for this mutation, it will be unable to oxidize fatty acids.[1] These acids are then passed to the mother who, due to decreased enzyme function, is unable to metabolize the additional fatty acids. The result is liver overload leading to the development of AFLP and its symptoms, which can be remedied by delivery of the newborn.

AFLP is clinically characterized by two phases, a pre-icteric phase, and an icteric phase. The first phase lasts around ten days, with extremes of up to twenty-nine days, and is marked by a common, non-specific clinical presentation such as persistent nausea and vomiting, which occur in 80% of patients, lethargy, abdominal pain; AFLP may begin with a flu-like syndrome.[4,7] Pregnancy-induced hypertension may be associated with AFLP in 20-50% of cases.[3] Pre-eclampsia is present in 40% to 50% of cases.[5] The icteric phase begins with the appearance of mucocutaneous icterus, an alarming sign, with accentuation of the symptoms of the previous phase. This jaundice is of the retention type, generally preceding delivery by a few days (as in the case of our two patients) or occurring immediately post-partum. Neurological disorders of varying intensity, ranging from drowsiness, agitation and confusional syndrome to full-blown hepatic coma, may be observed.[8] Pruritus and ascites can also be described in the second phase. In rare cases, some patients may present with pancreatitis.[5]

The biological presentation of AFLP is manifested by aspartate-amino-transferase and alanine-amino-transferase levels often elevated by 5 to 25 times the upper limit of normal.[9] Hyperbilirubinemia, with a predominance of conjugated bilirubin's, was also observed as the disease progressed; early and constant hypoglycemia, characteristic of AFLP and indicative of the severity of liver damage, was also observed in our two patients; and the installation of disseminated intravascular coagulopathy, with the consumption of coagulation factors, as evidenced by a low prothrombin level and prolonged partial thromboplastin time. Acute renal failure, a critical prognostic component, is a frequent complication, occurring in 50-80% of patients with acute liver failure.[4] Hyperleukocytosis (>15,000 elements/mm^3), predominantly neutrophilic, is also characteristic of SHAG, but remains poorly explained.[2]

Abdominal ultrasound is the first-line examination of diagnostic interest, enabling differential diagnosis with other hepatic, biliary or extra-hepatic pathologies that have the same clinical and biological symptomatology. It may show a hyperechoic liver due to steatosis, or what is known as a glossy liver.[5] This ultrasound sign is inconstant and does not exclude the probable diagnosis of AFLP if it is not present.

A scan of the liver can be performed, showing a liver density equal to or less than that of the spleen. Normal liver has a density of 50 to 70 Hounsfield units, 6 to 12 HU higher than that of the spleen.[5]

The diagnosis of certainty is made by liver biopsy, which is the main feature of Centro-lobular micro vesicular steatosis.[8] Sometimes, however, the histological appearance is not typical, and some cases of AFLP may have been confused with viral hepatitis.

In AFLP, rare sites of hepatocyte necrosis may be observed, but there is never massive necrosis as in fulminant hepatitis.[9-11]

The presumptive diagnosis of acute fatty liver of pregnancy is usually made clinically based on the presence of characteristic, but nonspecific, symptoms observed also in viral, fulminant hepatitis; pancreatitis, and other diseases that are manifested by hepatic involvement.

Sixteen years ago, Ch'ing et al published a study setting out diagnostic criteria, known as the Swansea criteria, for the diagnosis of AFLP.[10] According to these criteria, the presence of at least 6 of these features in the absence of other etiologies suggests AFLP. The Swansea criteria have

a sensitivity of 100% and a specificity of 57%, with positive and negative predictive values of 85% and 100%, respectively, for the diagnosis of AFLP.[4] These Swansea criteria are intended for use when other diagnoses have been excluded or are less probable.

The aim of early diagnosis of AFLP is to deliver the fetus quickly and provide immediate care. The only curative treatment is early uterine evacuation.

AFLP is considered an obstetric therapeutic emergency, and management is multidisciplinary. There is no consensus on the route of delivery; the choice between Caesarean section and induction of work is made on a case-by-case basis. Nevertheless, vaginal delivery seems possible if work has already been induced, if there are no signs of maternal or fetal distress, or if the disease is not very severe.[10,11] In other cases, caesarean section seems preferable, at best under general anesthetic.

AFLP is a rare but serious condition with a reserved prognosis, linked to acute liver failure and medical complications such as renal failure, disseminated intravascular coagulation, septic complications, or acute respiratory distress syndrome.

The prognosis has improved considerably, thanks to early diagnosis of the disease and rapid management. Mortality is now less than 10%, but the risk of recurrence has been described one woman in five has reported suffering a recurrence of AFLP, most of them benign.[5,9]

In the case of our three patients, the evolution was characterized by an improvement in the clinical and biological symptoms, leading to recovery and discharge from hospital, due to their early, rapid, and multidisciplinary management.

CONCLUSION

In conclusion, AFLP is a rare disease that can lead to hepatocellular failure and death in both mother and fetus if not diagnosed in time. The diagnosis of certainty is made by post-partum liver biopsy, and the main treatment remains uterine evacuation. The medical team must consider this diagnosis, particularly when clinical signs such as nausea or vomiting, abdominal pain, jaundice, high blood pressure, surprising elevations in liver biology parameters, renal failure or thrombocytopenia are present during the third trimester of pregnancy. That said, further scientific research is needed to understand this rare and fatal disease and improve its management.

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