CASE REPORT

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Acute fatty liver of pregnancy, a diagnostic challenge

Hígado graso agudo del embarazo, un desafío diagnóstico

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ABSTRACT

Acute fatty liver disease of pregnancy is a rare disease that usually presents in the third trimester of gestation, the pathogenesis of which is still unknown. The diagnosis is clinical and is made using the Swansea criteria. This condition causes liver and renal dysfunction, with a maternal mortality rate of 10% and perinatal mortality up to 20%. Initial management consists of termination of pregnancy and maternal hemodynamic support. We present the case of a 32-year-old woman at 38 weeks of gestation who presented with jaundice, abdominal pain and vomiting on the first postpartum day. Laboratory tests revealed alterations in the hepatic and renal profile, coagulopathy and hypoglycemia. Treatment consisted of correction of the metabolic alterations, which improved the laboratory parameters and led to complete recovery of the patient.

Key words: Fatty liver, Pregnancy complications, Liver failure, acute

RESUMEN

El hígado graso agudo del embarazo es una enfermedad rara que suele presentarse en el tercer trimestre de gestación, cuya patogenia aún se desconoce. El diagnóstico es clínico y se realiza mediante los criterios de Swansea. Esta condición provoca disfunción hepática y renal, con una tasa de mortalidad materna del 10% y perinatal hasta 20%. El manejo inicial consiste en la finalización del embarazo y soporte hemodinámico materno. Presentamos el caso de una mujer de 32 años con 38 semanas de gestación que sufrió de ictericia, dolor abdominal y vómitos el primer día del posparto. Los análisis de laboratorio revelaron alteraciones en el perfil hepático y renal, coagulopatía e hipoglucemia. El tratamiento consistió en la corrección de las alteraciones metabólicas, que mejoró los parámetros de laboratorio y a la recuperación completa de la paciente.

Palabras clave. Hígado graso, Complicaciones del embarazo, Falla hepática aguda

Introduction

Acute fatty liver of pregnancy (AFLP) is an uncommon complication. It is considered an obstetric emergency for both the fetus and the mother and usually manifests mostly during the last trimester of pregnancy, although it is not exclusive to this period[1].

The incidence ranges from 1/7,000-20,000 pregnancies[2]. Mortality rates of over 70% have been reported. However, recognition of mild presentation and early intervention have reduced the maternal mortality rate to 10% and perinatal mortality by 10%-20%[3-5].

The pathophysiology is still not clear. It is postulated to be caused by a genetic defect in fatty acid oxidation, due to deficiency of the long-chain 3-hydroxyacyl-CoA dehydrogenase enzyme. During normal pregnancy, the fetoplacental unit metabolizes free fatty acids for fetal growth and development. Placental dehydrogenases break down triglycerides into free fatty acids, which then enter the fetal compartment. However, when there are defects in the fatty acid oxidation pathway, this leads to the accumulation of metabolites that enter the maternal circulation. These fatty acids and their metabolites are absorbed by the maternal liver and cause microvesicular fatty infiltration, activating inflammatory processes and hepatic cell necrosis. This dysfunction can lead to coagulopathy, electrolyte imbalance and multiple organ failure. In addition,

increased fatty acids within the placenta can result in a deficient oxygen supply to the fetus. Although most cases of AFLP are not conclusively associated with disorders of fatty acid oxidation in the infant, it is recommended that newborns be screened and monitored for complications of hypoglycemia and metabolic disturbances[2,4,6].

Risk factors associated with this pathology include nulliparity, multiple pregnancy, male fetus, history of a previous episode of fatty liver, fatty acid oxidation disorders, as well as other conditions, such as obesity, body mass index <20, diabetes mellitus and preeclampsia[7,8].

Clinical manifestations are variable, such as nausea and vomiting (50%-82%), abdominal pain (32%-70%), hypertension (70%), jaundice (30%-60%). Some authors report polyuria, polydipsia, intestinal bleeding and pruritus. For clinical diagnosis, application of the Swansea criteria is recommended; although they are not designed for early diagnosis, they have a high negative predictive value[2,6].

The importance of this pathology lies in its low frequency but high severity. Early diagnosis is vital, and some affected patients may require liver transplantation. We present a case with early diagnosis and favorable maternal-fetal evolution.

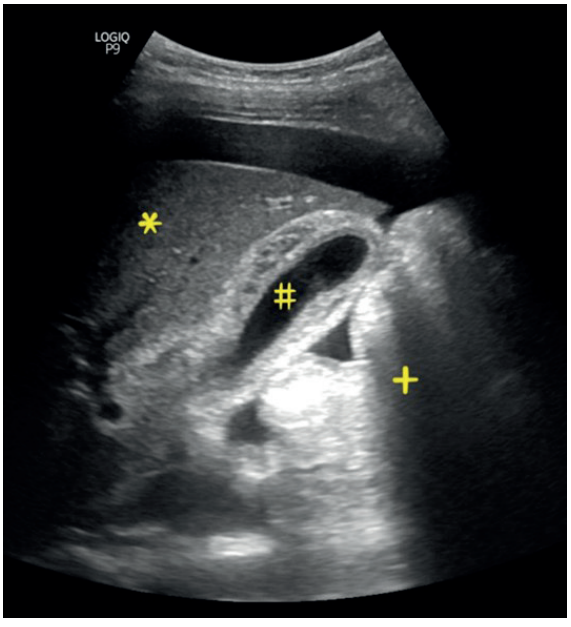
Case report

A 32-year-old woman from Lima, Peru, presented with a 38-week pregnancy by first trimester ultrasound, with a previous cesarean section and no pathological or surgical history of interest. She had 8 prenatal controls in another hospital center, with no clinical or biochemical alterations in her previous exams. She came to the emergency room for uterine contractions. On physical examination she presented stable vital signs, without cardiac or pulmonary alterations, abdomen with a pregnant uterus, single fetus in cephalic position with 130 beats per minute, regular uterine activity. On vaginal examination, the cervix appeared softened, with 80% effacement, no bleeding and intact membranes. She was hospitalized for labor surveillance, conduction and care. During the evaluation, fetal bradycardia was evidenced, so an emergency cesarean section was performed. During the intervention, thick meconium fluid was observed. A live male newborn was obtained weighing 3,100 grams, Apgar 5 at one minute and 8 at 5 minutes.

On postoperative day one, the patient was jaundiced and presented edema in the lower limbs (+/+++). Laboratory tests showed leukocytosis, elevated levels of transaminases, alkaline phosphatase, creatinine, urea and total bilirubins with direct predominance. During the following two days, abdominal pain and vomiting were added. Suspecting acute cholecystitis versus choledocholithiasis, an abdominal ultrasound was performed (Figure 1), which showed a liver of normal shape and size with homogeneous parenchyma, gallbladder with thickened walls, gallbladder polyp, perihepatic free fluid and puerperal uterus. A cholangioresonance ruled out biliary and pancreatic pathology. Tests results for viral hepatitis, autoimmune hepatitis, lipase, amylase, serology for syphilis, cytomegalovirus, urinalysis and proteinuria were within normal range.

On day four the jaundice persisted, she presented bradypsychia and lethargy, oliguria, increased ascitic fluid volume, prolongation of coagulation times, elevated lactate dehydrogenase, hypofibrinogenemia, acid-base disorder and worsening of blood tests. She was transferred to the intensive care unit (ICU) with the diagnoses of acute liver failure, acute renal injury type 2, obstructive icteric syndrome and metabolic acidosis.

Figure 1. Abdominal ultrasound: liver (*) of normal location, size and shape without focal lesions or dilatation of portal vessels, gallbladder (#) of normal shape and size with thickened walls, and intestinal loops (+) with presence of free fluid in the abdominal cavity.



On day six she presented repeated hypoglycemia, increased ammonium dosage, thrombocytopenia and increased abdominal perimeter. More than one liter of ascitic fluid was quantified by ultrasound, so percutaneous drainage was performed. The diagnosis of HELLP syndrome was proposed initially. Due to the clinical picture, the analytical results of hypoglycemia, renal dysfunction, coagulopathy and liver function abnormalities, the Swansea Criteria were applied and a diagnosis of acute fatty liver of pregnancy was made.

In the following days, the patient presented a favorable evolution. On the eleventh day she was discharged from the hospital and 5 days later, at the gastroenterology outpatient control, she showed good general condition with improvement of the laboratory parameters. The laboratory findings are summarized in Table 1.

Discussion

AFLP is a rare and potentially fatal complication frequently occurring in the third trimester of pregnancy. Cases have also been reported prior to 20 weeks and from 5%-16% up to 4 days postpartum, of which 80% were diagnosed within 48 hours[9-11]. In the present case, the clinical manifestations occurred from the first postpartum day.

The clinical presentation is variable and there may be nonspecific symptoms. For diagnosis, the application of the Swansea Criteria (Table 2) is recommended, which includes clinical, biochemical, imaging and histological data, of which 6 or more criteria are required in the absence of other causes of acute liver failure[12]. These criteria have been validated by a prospective study by Knight[9] and have a sensitivity of 100%, specificity of 57%, positive predictive value of 85% and negative predictive value of 100%, as reported by Goel[13]. Vigil-de Gracia[14], in a series of cases of AFLP finds a typical triad consisting of symptoms such as nausea or vomiting, jaundice, epigastralgia; laboratory results show hypoglycemia, thrombocytopenia, hypofibrinogenemia and elevated levels of creatinine, transaminases, bilirubin, leukocyte count, lactate dehydrogenase and ammonium; as well as renal failure, coagulopathy, ascites and encephalopathy. In our case, the presence of this triad oriented the diagnosis and use the Swansea Criteria, of which 11 of the 14 criteria were present. In addition, imaging tests were performed which, although they have a limited role in the diagnosis, are useful to exclude other hepatic pathologies, as pointed out by Chen[5] and Chang [11].

Table 1. Laboratory data during postpartum hospitalization

	Day 1	Day 4	Day 6	Day 9	Day 11	Day 16
Leukocytes (x10^3cel/µL)	19.92	12.89	10.57	13.76	13.65	6.16
Segmented neutrophils (%)	77.3	76.5	60	69.2	75.7	43.7
Band neutrophils (%)	2.8	1.8	2	0	0	0
Platelets (x10Λ3cel/µL)	143	112	80	103	155	450
Hemoglobin (g/dL)	12.8	12.8	10.7	10.4	8.8	9.2
Glucose (mg/dL)	115	65	45	85	88	86
Creatinine (mg/dL)	2.27	2.17	1.47	0.87	0.66	0.6
Urea (mg/dL)	44	94	90	37	26	28
Ammonium (µmol/L)	-	-	115.09	-	-	-
LDH (U/L)	-	875.6	714.2	-	-	-
AST (U/L)	104	118	146	130	92	67
ALT (U/L)	83	48	69.6	83	77	62.4
Alkaline phosphatase (U/L)	465.8	345.7	395.4	424.7	346.2	211
GGT (U/L)	106.5	98.6	550.6	654	485.3	145
Bilirubin total (mg/dL)	6.5	8.64	6.69	6.78	4.78	1.74
Bilirubin indirect (mg/dL)	0.07	0.31	0.11	0.29	0.5	0.23
Bilirubin direct (mg/dL)	6.43	8.33	6.58	6.49	4.28	1.51
PT (seconds)	-	29.7	12.7	12.1	-	-
INR	-	3.24	1.28	1.21	-	-
aPTT (seconds)	-	71.3	34.1	28.4	-	-
Fibrinogen (mg/dL)	-	150	318	365	-	-

LDH: lactate dehydrogenase, AST: aspartate aminotransferase, ALT: alanin aminotransferase, GGT: gamma glutamyl transferase, PT: prothrombin time, INR: international normalized ratio, aPTT: activated partial thromboplastin time

Table 2. Swansea criteria[12].

Vomiting
Abdominal pain
Polydipsia or polyuria
Encephalopathy
Elevated bilirubin (>0.82 mg/dL)
Hypoglycemia (<72 mg/dL)
Leukocytosis (>11,000 cells/µL)
Elevated transaminases (AST or ALT >42 U/L)
Elevated ammonium (>47 µmol/L)
Hyperuricemia (>340 µmol/L)
Acute renal failure or elevated creatinine (>1.7 mg/dL)
Coagulopathy (PT > 14 seconds or aPTT > 34 seconds)
Ultrasound: ascites or hepatic hyperechogenicity
Microvesicular steatosis in liver biopsy.

Liver biopsy has been considered necessary to confirm the diagnosis. However, due to its invasive nature and complications due to coagulopathy, it is now accepted that only clinical and laboratory findings be present for the diagnosis. In cases where the diagnosis is uncertain, biopsy may still be beneficial[2,5]. In our case it was not necessary to perform liver biopsy, as indicated in the case of Zagaceta[15] and the 57 cases reported by Knight[9].

It is important to make the differential diagnosis with pathologies that are associated with acute liver involvement, such as hyperemesis gravidarum, preeclampsia, HELLP syndrome, hepatitis, intrahepatic cholestasis, toxicity related to paracetamol or other drugs, thrombotic microangiopathy and exacerbation of systemic lupus erythematosus[2,10]. It should be noted that, due to the similarity in the clinical presentation of AFLP, it is frequently confused with HELLP syndrome. Although both pathologies have variable incidences and degrees of association with hypertension, thrombocytopenia and elements of hepatocellular necrosis characterized by elevated serum transaminase levels, the fundamental difference is the magnitude of the hepatic and renal damage observed in AFLP[12,16,17]. In the case presented the patient had hypoglycemia, coagulation disturbances, leukocytosis, high levels of bilirubin, ammonium and creatinine, which are distinctive features of AFLP compared to HELLP syndrome.

Management should include rapid assessment of the mother and fetus and recognition of the disease, planning supportive care such as reversal of coagulopathy, preparation for delivery, and multidisciplinary care[2]. AFLP treatment priority is delivery. Although there is no consensus on the mode, cesarean section has been performed more frequently[3,5]. Subsequently, medical treatment is applied to the mother, consisting of hemodynamic support. Due to the potential risk of the development of acute liver failure, hemorrhagic complications, acute respiratory distress syndrome and renal failure, which increase maternal morbidity and mortality in AFLP, patients need to be admitted to the ICU for ongoing management and monitoring. Worsening of the condition is an indication for liver transplantation[6,7].

It should be noted that recovery time depends on the severity of the disease and the presence of complications. It is observed that most women experience clinical recovery within 3-4 days after delivery, although normalization of blood work is often delayed[5].

Nelson[2] and Naoum[4] suggest that both mothers and offspring undergo molecular testing for genetic defects in fatty acid oxidation. Although recurrence of AFLP in a subsequent pregnancy is uncommon, an increased risk is found in women heterozygous for one of the fatty acid oxidation enzymes, such as long-chain 3-hydroxyacylCoA dehydrogenase.

In conclusion, acute fatty liver disease of pregnancy is a rare obstetric emergency that can occur during the third trimester of pregnancy and postpartum. It presents a typical triad consisting of symptoms, alterations in laboratory tests and complications. Diagnosis is based on the Swansea Criteria and liver biopsy is reserved for atypical cases. The differential diagnosis should be made with acute liver disease, especially HELLP syndrome, and treatment consists of termination of pregnancy and maternal supportive therapy.

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