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ORIGINAL ARTICLE

Acute fatty liver of pregnancy

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Abstract
Objective Acute fatty liver of pregnancy (AFLP) is a rare and serious entity associated with significant maternal and neonatal mortality and morbidity. We describe our experience with the clinical diagnosis, management and course patients with AFLP.
Study design Medical records of patients with AFLP were reviewed over a 10-year period. Records were reviewed for symptoms, laboratory findings, clinical course, and maternal and perinatal outcomes.
Results The incidence of AFLP was 1 in 7,270 births. The mean gestational age at onset was 34.6 ± 4.9 weeks.Eight percent of the patients were multiparous with more than three pregnancies. The prodromic phase was variable; patients complained of nausea, abdominal pain, malaise, polyuria-polydipsia syndrome and headaches followed by jaundice. The laboratory results indicated coagulopathy, liver function abnormalities and hypoglycemia. Emergency cesarean section was performed in two cases. The diagnosis has been assessed by transcutaneous hepatic biopsies processed in all patients between the 4th and 15th day (8.4 ± 4.3 days). Maternal morbidity included hypoglycaemia (40%), coagulopathy (50%) encephalopathy (30%) and renal failure (40%). There were no maternal deaths but fetal mortality is high 66%.
Conclusion The early recognition of AFLP cases and prompt progressive management, including early termination of pregnancy and large dose infusion of fresh frozen plasma, the prognosis of AFLP is obviously improved.

Keywords Acute fatty liver · Pregnancy · Liver disease

Introduction

Acute fatty liver of pregnancy (AFLP) is a rare but life-threatening complication of pregnancy. Since it has been described by Sheehan in 1940, many cases have been described in the literature [1, 2]. The reported incidence of AFLP has been increasing, but maternal and fetal mortality rates, however, have been decreasing. AFLP has seen its prognosis totally modified these last years with full maternal recovery. This is mainly due to a better comprehension of this pathology allowing early diagnosis even if the treatment remains supportive. The causally therapy of this disorder is the termination of pregnancy. Recent advances in molecular diagnostic procedures provide evidence of a genetic basis for this condition and a potential role of an altered lipid metabolism in the physiopathology of AFLP [3–5].

The purpose of this study was to report our experience of AFLP and to discuss diagnosis and therapeutics problems, and evolutive features concerning ten cases observed during ten years in our intensive care unit (ICU).

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Materials and methods

During the period between January 1993 and December 2002, medical records of patients with the discharge diagnosis of AFLP were reviewed. Diagnosis of AFLP has been assessed by clinical symptoms, laboratory evidence of acute hepatic dysfunction in the third trimester of pregnancy with complete resolution of the liver dysfunction in the postpartum and histological data. Viral hepatitis diagnosis was eliminated by serology and that of HELLP syndrome (hemolysis, elevated liver enzymes, low platelet count) by laboratory findings. Abdomen ultrasonography eliminated other causes of jaundice such as gravidic cholestasis and biliary ducts anomalies. Liver biopsies were performed on all patients.

Records were reviewed for presenting symptoms, laboratory findings, maternal complications and neonatal outcome. Laboratory evaluation included measurement of liver function tests, complete blood cell count, coagulation profile and renal function tests. Abnormal liver function tests were defined as: bilirubin > 20 mg/dl, aspartate aminotransferase (ASAT > 60 UI/l), alanine aminotransferase (ALAT > 40 UI/l), prothrombine time < 50%. Disseminated intravascular coagulation (DIC) was defined as the presence of low platelets ($< 100 \times 10^3/mm^3$), low fibrinogen (< 300 mg/dl) and partial thromboplastin times and estimates of fibrinogen degradation products or D-dimer. Gestational age was determined by the last menstrual period.

Results

During this period, ten patients were admitted for gravidic jaundice. At the same time, 72,708 deliveries were performed in our hospital giving an incidence of 1 in 7,270 births.

The average maternal age and the gestational age of our patients was 33 ± 4 years and 34.6 ± 4.9 weeks, respectively (Table 1). Only one parturient was primipare while others were multiparous with more than three pregnancies (80%). None of the patients had experienced significant medical, surgical, or obstetric diseases in the past. None of pregnancies were medically followed. Cross-examination did not find ingestion of hepatotoxic medicines. The prodromal phase was variable, patients complained of nausea and vomiting ($n = 7$), abdominal pain ($n = 7$), malaise ($n = 4$), polyuria–polydipsia syndrome ($n = 5$), and headaches ($n = 3$). None had blood pressure hypertension or proteinuria. The diagnosis was suspected to be the existence of frank jaundice with deeply colored urines during the third trimester of pregnancy.

In all patients, we noted an increase of the aminotransferases rate (ASAT and ALAT) (Table 2). Nevertheless, this increase was moderate exceeding rarely three times the upper normal value. Hepatic cytolysis took some days to regress. Bilirubin remarkably increased. One major characteristic of AFLP is the diminution of the prothrombin time. In our series, it was below 50% in all patients and this depression

Table 1 Maternal characteristics and neonatal outcome

Patient	Maternal age (years)	Gestationnal age (weeks)	Parity	Maternal complications	Fetal outcome	Length of stay (days)
1	35	32	2	Sepsis mechanical ventilation DIC	Intrauterine fetal death	31
2	30	41	4	Sepsis postpartum haemorrhage DIC acute tubular necrosis	Live born	12
3	34	32	3	Postpartum haemorrhage DIC acute tubular necrosis	Intrauterine fetal death (twin)	8
4	36	39	5	Mechanicalventilation sepsis	Live born	13
5	35	37.2	3	None	Live born	4
6	35	37	4	Encephalopathy sepsis postpartum haemorrhage DIC acute tubular necrosis	Intrauterine fetal death	9
7	30	36	4	Encephalopathy sepsis postpartum haemorrhage DIC acute tubular necrosis mechanical ventilation	Live born	15
8	32	28	2	Acute tubular necrosis postpartum haemorrhage	Intrauterine fetal death (twin)	4
9	37	26	6	None	Prematurity death	4
10	24	36.5	3	Encephalopathy DIC acute tubular necrosis	Intrauterine fetal death	6

DIC Disseminated intravascular coagulation

Table 2 Laboratory values at admission

Laboratory test	Mean ± SD	Range
Aspartame transaminase (IU/l)	402 ± 371	49–1270
Alanine transaminase (IU/l)	321 ± 309	30–974
Alkaline phosphatase (IU/l)	651 ± 408	178–1249
Bilirubin total (mg/dl)	17 ± 11	7–44
White blood cells($\times 10^3$)	20 ± 10	10,6–42
Hemoglobin (mg/dl)	9.5 ± 2.4	4–12
Platelets ($\times 10^3/mm^3$)	141 ± 73	40–240
Protrombin time (%)	33 ± 17	10–55
Fibrinogen (mg/dl)	25 ± 4	20–32
Blood urea nitrogen (mg/dl)	70 ± 37	28–135
Creatinine (mg/dl)	1.7 ± 0.9	0.7–3.1
Glucose (mg/dl)	72 ± 26	40–122
Uric acid (mg/dl)	19 ± 20	7–49
Amylasemia UI/l	106 ± 124	19–285
Albuminemia g/l	25 ± 5	21–31

reached 20% in three cases (30%). It was associated to disseminated intravascular coagulation in five cases (50% of cases). Leucocytosis (leukocyte count > 13,000/mm^3) was noted in eight patients while thrombocytopenia was found in only three patients. Viral hepatitis serology: A, B and C were negative. Ultrasound was performed in all patients but showed specific alterations of AFLP in only two cases (20%).

Delivery was expedited in all patients after admission to the hospital. Any of them were admitted with the diagnosis of AFLP.

There were eight singleton pregnancies and two twins. Patients were delivered vaginally except two who underwent cesarean for foetal distress. Uterine revision was performed in all patients with natural way delivery. Eight patients (80%) received blood fractions to control whether coagulation disorders or anemia (packed red blood cells, 6.8 ± 6.6 units; fresh frozen plasma, 19 ± 10 units, platelets, 7±7.7 units).

The mean maternal ICU stay was 10.4 ± 8.4 days (range 4–31 days). Five patients presented postpartum haemorrhage constantly, which is associated to DIC in four patients. Three patients suffered hepatic encephalopathy (Table 1). Hypoglycemia (glucose < 60 mg/dl) was particularly marked in four patients requiring continuous infusion of dextrose solution. Six patients were admitted with acute renal failure treated successfully by fluid resuscitation. At their discharge, they had normal renal function. None patient required hemodialysis.

No maternal death occurred in association with AFLP during the 10-year study period, but there were eight foetal deaths (66%): seven intrauterine (two twins) and one because of prematurity.

If the diagnosis of AFLP was suspected between admission and 3 days post-partum (range 0–4 days), the confirmation has been assessed by transcutaneous liver biopsies processed in all patients but only after normalization of coagulation disorders between the 4th and the 15th day (8.4 ± 4.3 days).

Discussion

Our series has similarities to others reports in regards to incidence and its increasing with muliple gestations [2, 6, 7]. Incidence of AFLP remains weak between 1/7,000 and 1/15,000 pregnancies [2, 6].

The etiology is not known but a genetic component has been suggested. Recent research suggests that AFLP is associated with gene mutation in the long chain 3-hydroxyacyl-coenzyme A dehydrogenase, a fatty acid β oxidation enzyme [3–5]. Jaundice remains the first sign that attracts a physician, usually accompanied by nausea, vomiting, malaise and abdominal pain; it is the situation in most of our patients. Cross-examination found polyuria–polydipsia syndrome 3 weeks before hospitalisation (three patients). This syndrome should make evoke diagnosis [8]. It is linked to depression in antidiuretic hormone secretion. Viral hepatitis remains with HELLP syndrome, the main differential diagnosis, in our series. The challenging one was viral hepatitis. Differentiating fulminant viral hepatitis from AFLP may be difficult, as these disorders share similar clinical and laboratory features AFLP differs from severe acute viral hepatitis in that serum transaminase levels in AFLP rarely exceed 1,000 U/l, and viral serologic tests are negative. HELLP syndrome had symptoms, complications and biochemical findings clearly distinguished of AFLP [9].

Abdominal ultrasonography in all patients allowed us to eliminate biliary origin of jaundice. Its contribution to assess diagnosis is very weak nevertheless [10]. It allows to dismiss some diagnosis of jaundice.

Hypoglycemia is always found especially when infusion of dextrose solution is delayed. Associated to depressed prothrombin rate, it should make evoke liver failure. Thrombocytopenia may be seen during intravascular coagulation, a situation that will be confirmed by dosage of fibrin split products. Hyperleucocytosis is frequent but not constant as in two cases in our series. Renal failure in our patients was secondary to acute tubular necrosis explained mainly by vomiting, haemorrhage and polyuria–polydipsia syndrome.

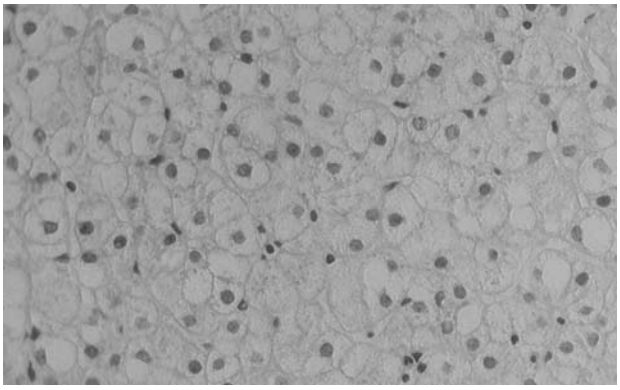

Fig. 1 Microvesicular steatosis in acute fatty liver of pregnancy: lipid is finely dispersed as small droplets in the hepatocytes with no displacement of the nucleus

In a recent review of 28 cases, Castro et al. [2] retained the diagnosis by clinical symptoms, laboratory findings and negative hepatitis serology. Nevertheless, editorials in the same journal contested that approach [11]. For Vigil-De Gracia et al. [12], cases in which liver biopsy may be justified are: clinically confusing cases, cases where liver function does not return to normal after delivery and in those cases where the definitive diagnosis in the early stages of AFLP is necessary as a primary indication for delivery. For Hamid et al. [13] hepatitis E is a usual cause of acute liver failure in pregnant women and the clinical and laboratory features do not permit accurate distinction between acute HEV infection and acute fatty liver of pregnancy.

According to some authors a careful history and physical examination in conjunction with compatible laboratory and imaging results are often sufficient to confirm diagnosis [14, 15]. If necessary, liver biopsy should be performed, in absence of coagulopathy, early in the post partum, in a period not exceeding 15 days and when jaundice is still present. AFLP is characterized histologically by microvesicular fatty cytoplasmic infiltration of hepatocytes with minimal hepatocellular necrosis (Fig. 1).

Assessing diagnosis of AFLP may be challenging but it never resolves before delivery: rapid termination of the pregnancy, and improvements in critical care medicine has all combined to improve the prognosis.

General anaesthesia constitutes the logical technique for cesarean section. In this case existence of haemostasis disorders make perimedullar anaesthesia dangerous. Two major precautions should be taken: avoid hepatotoxic drugs and preserve hepatic blood flow. Coagulopathy should be corrected with fresh frozen plasma, platelets, and vitamin K.

Another important management consideration in these patients is increased intracranial pressure, so careful neurologic monitoring is essential to AFLP management. Documentation of the mental status before and after a general anesthetic is crucial [16].

During post partum period, many complications may occur. Hypoglycemia should be prevented by continuous infusion of 10% dextrose solution. Hypoglycemia has been reported in 17–100% of the cases of AFLP and may persist for days or weeks [2–7]. DIC continue long time after delivery and may require daily a support of blood derivates. The antithrombin concentration was profoundly depressed in these patients [17]. Renal failure is successfully treated by aggressive fluid resuscitation and diuretics. Asepsia during procedures and an association of amoxicillin-clavulanic acid antibiotherapy started during labor and observed 5 days after delivery are recommended. Some other rare complications may be seen like pancreatitis [18].

Hepatic function improves some days after delivery. Improvement of the prothrombin rate and glycemia constitutes a reliable indicator of recovery [19], as it was the situation in our series. Maternal prognosis remains good if AFLP is rapidly suspected and delivery processed. Current maternal and fetal mortality rates are estimated to be 0–18 and 0–23%, respectively [2, 14, 20, 21]. The poor quality of antenatal care explains the high fetal mortality rate in our findings. Patients who recover usually have no long-term sequelae, and recurrence of AFLP in subsequent pregnancies is rare [22].

Patients with AFLP are at risk of organ failure and death. Admission in ICU is required for continuous supportive care. Maternal prognosis during AFLP has been remarkably improved, this is mainly due to better knowledge of its clinical presentation and its processing by immediate delivery and adequate supportive treatment.

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