Liver disease late in pregnancy without pre-eclampsia

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Abstract

We describe the case of a first twin pregnancy in a 27 year old patient, who experienced acute onset epigastric and right upper quadrant pain at a gestational age of 32 weeks and 2 days. She was diagnosed with acute liver and renal failure and possible disseminated intravascular coagulopathy (DIC) syndrome without pre-eclampsia. Early labor induction was mandatory to save both mother and foetuses. In this overview we describe the differential diagnosis of severe pregnancy related liver injury in the third trimester of pregnancy without pre-eclampsia. (Acta gastroenterol. belg., **2017**, 80, **53-57**).

Case report

A 27 year-old patient (gravida 1 para 0) presented during a twin pregnancy with acute onset of epigastric and right upper quadrant pain at a gestational age of 32 weeks and 2 days. This was the second episode in 2 weeks time. Until 20 weeks of pregnancy, she had been followed in another hospital. So far, her pregnancy was uncomplicated. At 28 weeks betamethason and atosiban, an inhibitor of the hormones oxytocin and vasopressin, used to halt premature labour, were given because of early cervix insufficiency.

The patient didn't complain of nausea, vomiting or colic pain. There was no oedema or headache. Blood pressure was 123/81 mmHg and temperature was normal. Clinical examination was unremarkable. Urine analysis at admission revealed no proteinuria. Laboratory testing showed elevated liver enzymes with aspartate transaminase (AST) of 554 U/L (normal 9-37 U/L), alanine transaminase (ALT) of 871 U/L (normal 12-78 U/L), no cholestasis and normal prothrombin time (PT) (83%, normal 82-126%). The glycaemia was 112 mg/dL. Platelet count was normal (212 x 10^9/L, normal 173-390 x 10^9/L) and lactate dehydrogenase (LDH) was slightly elevated (569 U/L, normal 84 – 246 U/L). There were no other signs of haemolysis (normal bilirubin and reticulocyte count or decreased haptoglobin). Serum creatinine was elevated (1,06 mg/dL in comparison to 0,30 mg/dL earlier in pregnancy) with uric acid of 6.8 mg/dL. No inflammation was present. Viral serology was negative for hepatitis A, C, E, and Human Immunodeficiency Virus (HIV). The patient had been vaccinated for hepatitis B and antibodies against Cytomegalovirus and Epstein-Barr virus infection were indicative of resolved infection. Ultrasound and doppler examination showed normal liver parenchyma with a normal gallbladder, no dilated bile duct and patent hepatic and portal veins. Family history was negative for liver disease or pregnancy-related complications.

The patient was admitted to the hospital for close monitoring. Serial blood testing showed prolongation of prothrombin time (PT 61%) during the next thirty-six hours (Figure 1). Hypoglycaemia was noted despite early glucose 5% infusion. There was no encephalopathy. Platelets remained normal, serum creatinine was unchanged. Despite normal urine analysis at admission, twenty-four hour urine collection one day later showed proteinuria of 266 mg/1900 ml. Blood pressure stayed normal. At that point in time the decision was made to induce labour by administration of dinoproston. No additional corticosteroids were given. Induction was followed by dilation and progression according to a normal partogram. Delivery was atraumatic without need for labour analgesia. Postpartum bleeding was quickly resolved by administration of carbetocin. Foetal monitoring during labour was reassuring. Birth weights were 1590 and 1390 grams and Apgar score of both girls was 9 after 1 and 5 minutes.

Postpartal observation showed even further deterioration of liver function with a drop in PT to 40%, elevation of creatinine (1,38 mg/dL) and a decrease in platelets (100 x 10^9/L) and fibrinogen (65 mg/dL, normal 180-385 mg/dL). Antitrombine III was decreased to 14% (normal > 70%). Close clinical monitoring including evaluation of mental status, IV fluid resuscitation and vitamin K administration was given. Twenty-four hours after delivery biochemical tests stabilized and a slight clinical improvement was noticed. On the second day postpartum she was transferred to a conventional nursing unit. At consultation four weeks after delivery, blood results were all normal. Genetic testing for the most common LCHAD-mutation showed no homozygosity for the G1528C mutation.

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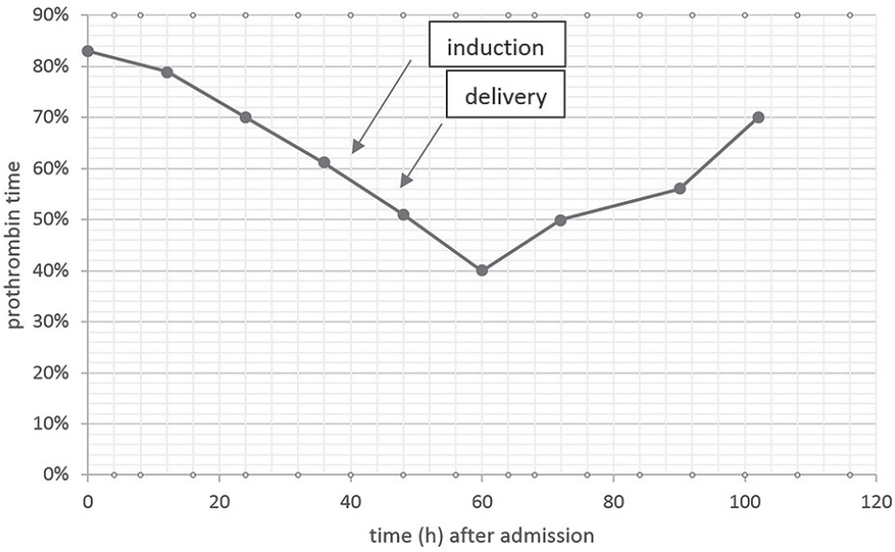

Fig. 1. — **Evolution of prothrombin time from admission until day 3 postpartum**

Discussion

Introduction

When liver test abnormalities occur during pregnancy, diagnosis has to take into account the expected normal physiological changes and the gestational timing. Diagnostic and therapeutic decisions have to consider the implications for both mother and foetus.

Up to five percent of pregnancies are associated with abnormal liver tests (1). These abnormal liver tests can be due to 1/ co-incidental hepatobiliary disease (for example cholelithiasis, viral hepatitis, drugs, sepsis and thrombotic diseases such as Budd-Chiari syndrome or antiphospholipid syndrome associated with systemic lupus) 2/ exacerbation of an underlying chronic liver disease or 3/ the pregnancy itself. This last group may or may not be associated with pre-eclampsia (respectively eclampsia, the HELLP syndrome (haemolysis, elevated liver tests, low platelets), acute fatty liver of pregnancy (AFLP) , hyperemesis gravidarum and intrahepatic cholestasis). Gestational timing is a key factor in making the right diagnosis, although exceptions and overlap may occur.

In this overview we will focus on the presentation of pregnancy-related liver diseases in the third trimester without pre-eclampsia, with special attention on the differential diagnosis of HELLP syndrome versus acute fatty liver of pregnancy. These conditions mostly arise in the third trimester but may also occur postpartum. Prior to 1980, the mortality associated with AFLP was in excess of 80% and > 25% for the HELLP syndrome. Due to earlier recognition, prompt effective treatment and referral to specialist centers, mortality was reduced. Given the complexity of these disorders and the potential risks to both mother and foetus, it is important that obstetricians and gastroenterologists/hepatologists collaborate closely to provide optimal care.

HELLP

HELLP syndrome occurs in 0,5-0,9% of pregnancies and 2-12% of cases of severe pre-eclampsia are complicated by the HELLP syndrome. This is a disorder defined by the triad of haemolysis, elevated liver enzymes and low platelets (2). This multisystem disorder basically occurs in the last trimester of pregnancy but can also manifest itself during postpartum. Maternal mortality rates vary from 1 to 5% and the perinatal mortality ranges from 7 to 22%.

Clinical findings can be non-specific including nausea, vomiting, right upper quadrant pain, oedema and weight loss. Hypertension and proteinuria can be present or absent. A subset of patients with severe pre-eclampsia can present with visual disturbances or headache. Less commonly associated findings include renal failure, diabetes insipidus, antiphospholipid syndrome, DIC, pulmonary oedema, placental abruption and retinal detachment.

There is an increased incidence of HELLP syndrome in Caucasian patients and multiparas.

There are no unequivocal diagnostic criteria. Several studies have tried to define the HELLP syndrome based on laboratory parameters. By definition, laboratory tests include 1/ haemolysis (indirect bilirubin usually less than 5 mg/dL and LDH levels greater than 600 IU/L in association with decreased haptoglobin levels), 2/ moderately elevated transaminases (200 IU/L to 700 IU/L) and 3/ thrombocytopenia below 100 x 10^9/L. Various diagnostic criteria for HELLP syndrome have been proposed. The two most commonly used classifications were developed at the universities of Mississippi and Tennessee (3-4-5)

(Table 1). The Tennessee System classification is based on the following parameters: AST > 70 IU/L, LDH > 600 IU/L and platelets < 100 x 10^9/L. Accordingly, there are two forms: complete and partial HELLP syndrome. The Mississippi classification relies on the nadir of platelet counts: class 1 (< 50 x 10^9/L), class 2 (50-100 x 10^9/L) and class 3 (100-150 x 10^9/L) (4). Prothrombin time is normal unless associated DIC is present with increased levels of fibrin degradation products, d-dimers and thrombin-antithrombin complexes. Liver imaging may show subcapsular haematomas, intraparenchymal haemorrhage, infarction or hepatic rupture.

The pathogenesis is thought to be a micro-angiopathic haemolytic anaemia with vascular endothelial damage, fibrin deposition in the blood vessels and activation and overconsumption of platelets resulting in severe bleeding disorders. The precipitating injury is not well known. An association witch a defect in long-chain 3 hydroxyacyl-coenzyme A dehydrogenase (LCHAD-deficiency) has been described, suggesting a possible overlap of HELLP syndrome and AFLP, although this is much less established for the former than for the latter (10).

Table 1.— **Classification of HELLP syndrome**

Mississippi 3 classification (11)	**Tennessee classification (13-14)**
Class 1	*Complete syndrome*
Platelets < 50.000/mm^3	Haemolysis on peripheral blood smear
LDH > 600 IU/L	LDH > 600 IU/L , bilirubin > 1,2 mg/dL
AST or ALT > 70 IU/L	AST > 70 IU/L Platelets < 100.000/mm^3
Class 2	
Platelets 50.000 – 100.000/mm^3	
Class 3	*Incomplete syndrome*
Platelets 100.000 – 150.000/mm^3 LDH > 600 IU/L AST or ALT > 40 IU/L Haemolysis	1-2 features of HELLP

Hepatic damage is caused by intravascular fibrin deposition and sinusoidal obstruction syndrome leading to hepatic haemorrhage and infarction. Histologically one can see microthrombi, and fibrin deposits. As the disease progresses, hepatocyte necrosis, periportal haemorrhage and eventually hepatic rupture can be seen.

Hospitalisation for antepartum stabilisation of hypertension, DIC, seizure prophylaxis and foetal and maternal monitoring is mandatory, as progressive and sudden deterioration is possible. The only effective treatment option is immediate induction. If gestational age is between 24 en 34 weeks, a National Institutes of Health Consensus Development Panel recommends administration of steroids to accelerate foetal lung maturity. Platelet transfusion will be required for mothers with platelet counts < 50 x 10^9/L prior to delivery or any surgical procedure. If platelet count drops < 30 x 10^9/L, transfusion is required to reduce spontaneous haemorrhage. Prophylactic antibiotics are recommended. After induction, close monitoring during the next 48 hours is mandatory, as data have shown worsening thrombocytopenia and increasing LDH levels. Liver transplantation is rarely indicated in case of 1/ persisting bleeding from hepatic rupture or 2/ liver failure from extensive necrosis (11).

The recurrence of HELLP in subsequent pregnancies has been investigated and is thought to be 3-27%, or even higher if the pregnancy was ended before 32 weeks (12).

AFLP

Acute fatty liver of pregnancy is an uncommon but potentially fatal disorder occurring in the third trimester of pregnancy, usually between 30 and 38 weeks of gestation or early postpartum. Several retrospective studies indicate an incidence of 1 in 7000 and 1 in 20,000 pregnancies (13). Although initially thought to be universally fatal, early diagnosis and prompt delivery have dramatically improved the prognosis with reduction of maternal and foetal mortality rates to 5% and 25% respectively (14).

The most frequent initial symptoms are nausea or vomiting, epigastric pain, anorexia and jaundice. About one-half of patients have signs of pre-eclampsia with hypertension and oedema. As the disease progresses, liver failure with coagulopathy and encephalopathy develops. Extra-hepatic complications as infection, intra-abdominal bleeding, pancreatitis and central diabetes insipidus can occur. Renal insufficiency is often seen. If metabolic acidosis secondary to impaired clearance of serum lactate by damaged liver cells is present, it directly effects foetal acid-base status (15).

This disorder is more common in twin pregnancies, nulliparous mothers and mothers carrying a male foetus.

Diagnosis is complicated by a large clinical and biochemical overlap between AFLP and HELLP syndrome (Table 2). AFLP usually occurs later in gestation and causes, in contrast to the HELLP syndrome, a true hepatic dysfunction resulting in hypoglycaemia due to impaired hepatic glycogenolysis, elevated ammonia and coagulopathy. Platelet count can be decreased with or without DIC which is associated with marked reduction in antithrombin III. Transaminases can raise from modest up to 1000 IU/L. Alkaline phosphatase is 3-4 times normal. Radiologic imaging (ultrasound, CT or MRI) may show hepatic steatosis but unfortunately findings are inconsistent, especially on ultrasound, as the fat deposits are microvesicular and the liver can appear normal. In addition, 20% of the general population has fatty liver nowadays.

Although liver biopsy showing microvesicular fatty infiltration of the hepatocytes is diagnostic, it is not routinely performed because of the invasive character and coagulopathy. In general there is no inflammation or necrosis seen unless in more severe cases. The Swansea

Table 2. — **Differential clinical and biochemical diagnostic tools of AFLP and HELLP syndrome (10)**

	AFLP	HELLP
Symptoms	malaise fatigue vomiting	abdominal pain
Jaundice	variable > 5 mg/dL severe cases	rare, if present < 5 mg/dL
Liver failure	yes	no
-hypoglycaemia	yes	no
-mental status	NH3↑	headache, seizure
PT↑	liver failure	DIC
Trombocytopenia	no	yes
Transaminases	variable up to 10XULN	up to 10XULN
Haemolysis	no	yes
Hypertension	25-50%	85%

Table 3. — **Swansea criteria for diagnosis of AFLP**

Swansea criteria for diagnosis of AFLP (16)
Vomiting Abdominal
Pain
Polydypsia/polyuria
Encefalopathy
Elevated bilirubin > 1.46 mg/dL (25 μmol/L)
Hypoglycaemia < 72 mg/dL (4 mmol/L)
Elevated uric acid > 5.7 mg/dL (340 μmol/L)
Leucocytosis > 11 x 10^9/L
Ascites or bright liver on ultrasound
Elevated transaminases (AST or ALT) > 42 IU/L
Elevated ammonia > 65 μg/dL (47 μmol/L)
Renal impairment; creatinine > 1.7 mg/dL (150 μmol/L)
Coagulopathy; prothrombin time > 14 seconds or aPTT > 34
Seconds Microvesicular steatosis on liver biopsy

diagnostic criteria are a collection of signs and symptoms that can be used as an alternative to liver biopsy. Six or more criteria in the absence of another cause are sufficient to diagnose AFLP (16) (Table 3). Despite a sensitivity and negative predictive value of 100%, the rather low specificity of 57% limits its usefulness (17).

Although the exact pathogenesis is not well known, a number of studies illustrated the association with foetal long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD) deficiency. In approximately 20% of cases a LCHAD-deficiency can be identified in the foetus. A diet low in long-chain fatty acids and supplemented with medium chain triglycerides is recommended as infants with LCHAD-deficiency can develop fatal non-ketotic hypoglycaemia, cardio- or neuromyopthy. The transfer of non-oxidated long chain fatty acids from the foetus is most likely the cause of toxic liver damage of the mother. As genetic counseling is nowadays available, testing all women with acute fatty liver of pregnancy, their infants and fathers (as inheritance is recessive) is mandatory.

Early diagnosis, prompt delivery and intensive supportive care are the cornerstones in the management of AFLP. Before induction, maternal stabilization with glucose infusion and reversal of coagulopathy is mandatory. Attention needs to be paid to fluid status because low plasma oncotic pressure can lead to pulmonary oedema. There is no unified conclusion as to the selected mode of pregnancy termination. Vaginal birth is probably the best approach although caesarean delivery is often performed because of rapid deteriorating maternal-foetal status. In addition, before surgery supplementation of fresh frozen plasma, platelets and packed red blood cells to correct coagulation and to reduce blood loss is important. Liver tests and coagulopathy usually start to normalize shortly after delivery. Sometimes a transient worsening of liver and renal function is seen. Most patients recover and have no sequelae of the condition. However, liver transplantation may be indicated in those patients with hepatic encephalopathy, severe metabolic acidosis or worsening coagulopathy, or those with liver rupture complicated by hepatic necrosis as indicated by computed tomography (18).

Even if the search for LCHAD is negative, acute fatty liver of pregnancy can recur. The exact risk of recurrence is unknown (19).

Concluding remarks

We presented a case report of a first twin pregnancy presenting with severe anicteric hepatitis and renal failure in its third trimester. There were no signs of pre-eclampsia. Laboratory testing could exclude viral hepatitis. Symptoms and biochemical alterations on admission could not differentiate between HELLP syndrome and AFLP. Further clinical course was complicated by hypoglycaemia and severe coagulopathy with possible associated DIC syndrome. Although our patient was not homozygote for the most common G1528C mutation seen in LCHAD-deficiency patients, the absence of haemolysis and the true hepatic dysfunction resulting in hypoglycaemia, severe coagulopathy and decreased levels of antithrombine III favour the diagnosis of AFLP.

Although relatively uncommon, hepatic disorders during pregnancy are important because of their potentially detrimental effects on both mother and foetus. Diagnosis can be challenging and early recognition will allow better outcomes and counseling for future family planning. Therefore obstetricians and gastroenterologists/hepatologists need to collaborate to ensure the best possible outcome in patients.

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