

ACUTE FATTY LIVER OF PREGNANCY

ANAESTHESIA TUTORIAL OF THE WEEK 191

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QUESTIONS

Before reading the article, try and decide whether the following statements are true or false. The answers can be found at the end of the article.

True or False

1. Acute fatty liver of pregnancy is a benign, self-limiting condition.
2. Acute fatty liver of pregnancy can be difficult to distinguish from other causes of liver disease in pregnancy.
3. Maternal mortality from acute fatty liver of pregnancy is in excess of 90%.
4. Everyone suspected of acute fatty liver of pregnancy should have a liver biopsy.
5. The main principle of treatment remains prompt delivery.

INTRODUCTION

Acute fatty liver of pregnancy (AFLP) is a rare but potentially fatal complication of late pregnancy. First described in 1934 as “Acute Yellow Atrophy of the Liver” it was associated with a maternal and foetal mortality of approximately 85%. Although it still carries a significant risk, early diagnosis, recognition of less serious cases and better management have improved the prognosis with an estimated maternal mortality of around 10-20% and a perinatal mortality of 20-30%.

PATHOPHYSIOLOGY

AFLP is histologically and clinically similar to Reye’s Syndrome and Jamaican Vomiting Sickness, both diseases of microvesicular fatty infiltration. It is thought to be caused by abnormal oxidation of mitochondrial fatty acids, although the exact pathophysiology remains unclear. The condition is associated with an inherited deficiency of a mitochondrial enzyme – long chain 3-hydroxyacetyl coenzyme-A dehydrogenase (LCHAD). This enzyme catalyses a reaction in the β -oxidation of fatty acids and so deficiency allows the build-up of long chain fatty acids. These fatty acids are incorporated into triglycerides within the hepatocytes, until accumulation in the cells causes the typical microvesicular deposition seen on histology. Subsequent impairment of mitochondrial function results in hepatocyte failure.

Deficiency of LCHAD does not account for all cases of AFLP and other enzyme deficiencies have also been implicated. One hypothesis suggests that a combination of specific genetic defects causing a

complete deficiency of a trifunctional protein (responsible for the final steps in mitochondrial fatty acid oxidation) may also be to blame.

LCHAD deficiency is an autosomal recessive disorder and often the mother will be heterozygous for the abnormal gene with a homozygous foetus producing the excessive toxic metabolites. However not all women who carry foetuses with the abnormal genotype will go on to develop liver disease. It is thought that other stressors, such as pre-eclampsia, increase the risk of developing AFLP.

EPIDEMIOLOGY

Acute fatty liver of pregnancy is rare, with an approximate incidence of 1 in 7,000 to 1 in 20,000 pregnancies. It is more common in first and multiple pregnancies and there is a higher incidence associated with male foetuses (3:1 ratio).

It does not appear to have any racial or geographical predilections. A comprehensive review of the UK Obstetric Surveillance System (UKOSS) found 57 cases in 1,132,964 maternities. Nearly a fifth of these were in twin pregnancies, confirming a much greater risk.

Unlike the fatty liver of non-pregnant patients, normally associated with obesity, there is some dispute in pregnancy with some specialists believing that it is more commonly seen in underweight women.

CLINICAL FEATURES

Signs and Symptoms

Acute fatty liver of pregnancy usually presents after 30 weeks gestation and often near term. Although an antepartum condition it may only become apparent after delivery.

The condition normally presents following a brief prodromal illness of one to two weeks with right upper quadrant discomfort and generalised malaise followed by worsening abdominal pain, anorexia, increasing nausea and vomiting. Approximately half of the patients will exhibit features of pre-eclampsia but the proteinuria and hypertension are usually mild. Liver function is abnormal with a 3-10 fold elevation in transaminase levels and a raised alkaline phosphatase. Jaundice, with or without ascites, usually appears within the first two weeks of the onset of symptoms. A common presenting feature is thirst and there is a well described association between AFLP and diabetes insipidus.

Investigations and Diagnosis

Laboratory tests can assist in the diagnosis of AFLP. Various conditions such as HELLP syndrome (**H**aemolysis, **E**levated **L**iver enzymes and **L**ow **P**latelets) can produce raised liver function tests and it may be difficult to differentiate between them. AFLP tends to produce a greater rise in bilirubin, causing a jaundice not normally seen in other pregnancy related liver diseases. Marked hyperuricaemia (out of proportion to the other features of pre-eclampsia), would normally favour AFLP as the diagnosis. Viral hepatitis tends to produce a more significant rise in ALT whilst paracetamol overdose will cause gross derangements in LFTs.

The liver dysfunction with AFLP can cause significant hypoglycaemia which may help in its distinction from pre-eclampsia and HELLP syndrome. As liver function worsens, coagulation may become impaired and eventually disseminated intravascular coagulopathy (DIC) can occur. Other useful indicators include a raised ammonia level and tests indicative of pancreatitis ie. raised amylase and lipase levels.

Radiological imaging (MRI, CT or ultrasound) may show hepatic steatosis but, unfortunately, findings are inconsistent as the fat deposits are microvesicular and the liver can appear normal. Ultrasound imaging is a helpful, but not definitive, test as approximately twenty percent of the general population will demonstrate a hepatic echogenic appearance suggestive of fatty changes to the liver.

Liver biopsy is the gold standard diagnostic test but, given the potential for coagulopathy, biopsy should only be used where the diagnosis is unclear and where delivery will not be delayed. The characteristic findings on biopsy are of microvesicular fatty infiltration, fibrin deposition and haemorrhage.

Diagnosis is usually made clinically. This can be aided by the “Swansea Criteria” which is a collection of signs and symptoms. This method suggests that a diagnosis can be made where there are six or more of the following criteria in the absence of another cause.

Six or more criteria required in the absence of another cause

- Vomiting
- Abdominal pain
- Polydipsia/ polyuria
- Encephalopathy
- Elevated bilirubin $> 14 \mu\text{mol/l}$
- Hypoglycaemia $< 4 \text{ mmol/l}$
- Elevated urea $> 340 \mu\text{mol/l}$
- Leucocytosis $> 11 \times 10^9 /\text{l}$
- Ascites or bright liver on ultrasound scan
- Elevated transaminases (AAT or ALT) $> 42 \text{ IU/l}$
- Elevated ammonia $> 47 \mu\text{mol/l}$
- Renal impairment; creatinine $> 150 \mu\text{mol/l}$
- Coagulopathy; prothrombin time > 14 seconds or APPT > 34 seconds
- Microvesicular steatosis on liver biopsy

Values as used by Knight et al.

Figure 1. Swansea Criteria for diagnosis of Acute Fatty Liver of Pregnancy

MANAGEMENT

Treatment is usually supportive and similar to that of other causes of hepatic dysfunction. The optimal management of AFLP involves expeditious delivery of the baby and this practice has led to improved outcomes for both mother and child. Severe cases should be admitted to an intensive care unit where they can be observed by a multidisciplinary team, as multisystem failure requiring ventilation and dialysis may occur. There should be careful monitoring of coagulation with aggressive correction of coagulopathies by the administration of appropriate clotting factors. Large volumes of 50% glucose may be required to correct hypoglycaemia. As with pre-eclampsia, careful fluid balance is essential as both renal dysfunction and pulmonary oedema are complications of the condition.

Plasmapheresis is recommended in some reports and *N*-acetylcysteine (a glutathione precursor and antioxidant) may be used to promote the selective inactivation of free radicals in hepatic failure. In the most severe cases involving fulminant hepatic failure and encephalopathy the patient should be urgently transferred to a specialist liver unit and orthotopic liver transplantation considered.

A rapid and dramatic reversal of both clinical condition and laboratory abnormalities usually follows delivery but morbidity can still occur, usually related to a severe coagulopathy. A full recovery, however, with no long term sequelae is the normal outcome should the mother survive the initial episode.

Key points in management

- Correction of altered coagulation
- Monitoring and treatment of hypoglycaemia
- Careful fluid balance
- **Early delivery**

Figure 2. Key management points

ANAESTHESIA and AFLP

There remain limited case reports regarding anaesthetic care for women with AFLP. It seems logical that an anaesthetist should be part of multi-disciplinary approach to the care of a woman with AFLP even if there is a desire to deliver vaginally.

As with many obstetric conditions, the main concern for anaesthetists involved in operative delivery is balancing the risks of general and regional techniques. General anaesthesia may worsen or confuse the clinical appearance of encephalopathy. Regional techniques, however, may not be appropriate in those patients with worsening coagulation, and waiting for correction of any coagulopathy could lead to further deterioration in clinical condition. Regional anaesthesia can also cause hypotension and decrease hepatic blood flow although whether this directly worsens the condition is not known. There are case reports of successful delivery using either technique.

Analgesia

Analgesia following an operative delivery is challenging. Paracetamol is normally safe in liver disease when given in normal doses. Non-steroidal anti-inflammatory drugs are contraindicated, both for their antiplatelet function and the possibility of exacerbating renal dysfunction. Hepatic dysfunction will impair the metabolism of most opioids and reduce their plasma clearance. Any accumulation of opioids may confuse the clinical picture regarding encephalopathy. Remifentanyl (which is metabolised by plasma esterases) may be a suitable alternative, especially if available in a patient controlled analgesia regimen.

FOLLOW-UP and FUTURE PREGNANCIES

Most women will make a full recovery from AFLP. However those that do not may demonstrate significant morbidity and case reports include women developing pancreatitis in the postpartum period and proceeding to liver transplantation. Acute fatty liver of pregnancy can recur in future pregnancies, even with no obvious genetic predisposition (i.e. a normal LCHAD gene) although the risk of recurrence is not known. All women who have had AFLP should be made aware of the potential for recurrence and counselled regarding future pregnancies. Any future pregnancies should be managed in a specialist setting.

SUMMARY

Acute fatty liver of pregnancy is a rare but potentially fatal disease. Although mortality has improved in recent years, careful management should be given to these patients preferably in a specialist centre.

ANSWERS TO QUESTIONS

1. False: Acute fatty liver of pregnancy is a potentially fatal condition and carries a significant mortality.
2. True: AFLP may present with features of pre-eclampsia. Blood tests and clinical suspicion help distinguish it from other causes of hepatic dysfunction.
3. False: Maternal mortality from AFLP was at one time estimated to be approximately 85% but with earlier and better diagnosis and prompt treatment it has been reduced to 10-20%.
4. False: Liver biopsy may not be appropriate given the potential for abnormal clotting and should be made on an individual case basis.
5. True: Despite improving mortality, early recognition and prompt delivery remain the mainstay of management.

SUGGESTED FURTHER READING

Knight M, Nelson-Piercy C, Kurinczuk JJ, Spark P and Brocklehurst P, A prospective national study of acute fatty liver of pregnancy in the UK; *Gut*; 2008; 57; 951-956

Gregory TL, Hughes S, Coleman MA, De Silva A, Acute fatty liver of pregnancy; three cases and discussion of analgesia and anaesthesia; *Int J Obstet Anesth*; 2007; 16; 175-179

Bacq Y, Acute fatty liver of pregnancy; UpToDate; www.uptodate.com