CASE REPORT

Acute fatty liver of pregnancy with hypoglycaemia, diabetes insipidus and pancreatitis, preceded by intrahepatic cholestasis of pregnancy

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Accepted 25 March 2015

SUMMARY

We present the case of a 33-year-old woman in her first pregnancy. She presented with pruritus at 34 weeks gestation. A diagnosis of intrahepatic cholestasis of pregnancy was made based on elevated bile acids and elevated liver transaminases. She re-presented 4 days later, jaundiced with abdominal pain and nausea, and was hypertensive. Her bilirubin was now elevated and her creatinine had doubled. The differential diagnosis included pre-eclampsia and Hemolysis Elevated Liver enzymes Low Platelet count (HELLP) syndrome, and delivery was expedited. Postnatally, the patient became coagulopathic, though not thrombocytopenic; she had persistent hypoglycaemia, hyponatraemia, developed acute pancreatitis and had profound ascites and peripheral oedema. Management was supportive with multidisciplinary care and over a period of 3 weeks she made a full clinical and biochemical recovery.

BACKGROUND

Conditions unique to pregnancy that cause liver dysfunction include intrahepatic cholestasis of pregnancy, pre-eclampsia, Hemolysis Elevated Liver enzymes Low Platelet count (HELLP) syndrome and acute fatty liver of pregnancy. While cholestasis and pre-eclampsia are frequently seen, HELLP syndrome and acute fatty liver of pregnancy are both rare, and potentially life-threatening conditions. This case highlights the clinical and biochemical overlap between these conditions, and the potential difficulty in differentiating between them. We also found this case interesting due to the patient's relatively innocuous initial presentation, which, over a short number of days, progressed to severe multi-organ impairment. Acute fatty liver of pregnancy presenting with apparent intrahepatic cholestasis of pregnancy is not something we have previously seen.

CASE PRESENTATION

A 33-year-old woman presented at 34 weeks gestation in her first pregnancy, with pruritus. She was otherwise well and the pregnancy up to that point had been low risk and uncomplicated. The working diagnosis was intrahepatic cholestasis of pregnancy based on an elevated fasting bile acid result of 47 µmol/L and elevated liver transaminases: γ -glutamyltransferase (γ GT) 81 U/L, alanine transaminase (ALT) was over 11 times normal at 392 U/L. Bilirubin was normal, 14 µmol/L. She re-presented 4 days later with abdominal pain and

nausea. She was noted to be slightly icteric. She was afebrile, though tachycardic at 125 bpm and had an elevated blood pressure, for the first time in this pregnancy, of 160/90 mm Hg. On examination, she had a soft, non-tender abdomen, her reflexes were normal and there was no proteinuria. She was feeling normal fetal movements and had a reactive cardiotocography.

INVESTIGATIONS

Biochemistry tests demonstrated significant changes in the liver profile and dramatic impairment of renal function. Notably, bilirubin was now elevated, λ GT had increased and ALT had dropped. Her creatinine had doubled from previously and uric acid was elevated (table 1).

Given the sudden and severe nature of the hepatorenal impairment, labour was induced. This resulted in a non-elective caesarean section following unsuccessful attempt at instrumental delivery. The patient was transferred to the high-dependency unit postoperatively.

Day one after delivery, the patient was profoundly jaundiced with a distended abdomen and significant bilateral lower limb oedema. She was haemodynamically stable and her blood pressure was normal. Biochemically, her liver function remained stable but creatinine continued to rise to 205 µmol/L. She was now hyponatraemic at 119 mmol/L and was polyuric with dilute urine. Her urinary protein creatinine ratio was elevated for the first time. Her haemoglobin had dropped from a preoperative 135 to 65 g/L and platelets were now down to 136×10^9 /L. A blood film, however, did not show signs of haemolysis. She had become coagulopathic with international normalised ratio (INR) 1.4 and fibrinogen 0.8 g/L. Vitamin K, fresh frozen plasma, cryoprecipitate and packed red blood cells were administered, along with an intravenous loop diuretic and 20% albumin infusion.

An abdominal ultrasound demonstrated fatty infiltration of the liver, normal kidneys and pancreas, with a moderate amount of free fluid in the abdomen and pelvis.

On day two, a non-contrast CT of the abdomen was performed to investigate increasing abdominal pain. This showed extensive free fluid within the abdomen, a large rectus sheath haematoma and features suggestive of acute pancreatitis. The patient's serum lipase at this point was markedly elevated at 2894 IU/L.

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To cite: English N, Rao J. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2015-209649

Table 1 Blood results at second presentation

	Value	Normal range		Value	Normal range
Haemoglobin	139 g/L	115–155 g/L	Creatinine	185 µmol/L	30–100 mol/L
White cell	19×10 ⁹ /L	4–11×10 ⁹ /L	Bilirubin	112 µmol/L	<16 mol/L
Platelet	241×10 ⁹ /L	150–400×10 ⁹ /L	AST	45 U/L	<31 U/L
Sodium	134 mmol/L	134–146 mmol/L	ALT	54 U/L	<31 U/L
Potassium	4.5 mmol/L	3.4–5.5 mmol/L	Albumin	31 g/L	38–50 g/L
Bicarbonate	20 mmol/L	22–32 mmol/L	Uric acid	0.40 mmol/L	0.12–0.38 mmol/L
Urea	8.6 mmol/L	3–8 mmol/L	LDH	645 U/L	<450 U/L

ALT, alanine transaminase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.

DIFFERENTIAL DIAGNOSIS

The patient's initial liver enzyme abnormalities were attributed to intrahepatic cholestasis of pregnancy, however, when she re-presented the differential diagnoses included pre-eclampsia, HELLP syndrome and acute fatty liver of pregnancy. Postnatally, acute fatty liver of pregnancy was the working diagnosis because of her coagulopathy in the presence of normal platelets and hypoglycaemia, as well as the radiological finding. Hepatitis serology was negative.

TREATMENT

Following the administration of blood products, the patient's haemoglobin remained stable with no evidence of active haemorrhage. She was haemodynamically stable but remained coagulopathic with INR now 1.6. Post operatively, she experienced low-grade temperatures with neutrophilia of up to 35.5×10^9 /L. She was started on a regime of intravenous antibiotics as prophylaxis to spontaneous bacterial peritonitis. On day three, she became hypoglycaemic to 1.9 mmol/L, which proved extremely difficult to control, and she eventually required a dextrose infusion. During this time, liver function remained impaired and she remained coagulopathic and hypoglycaemic with persistent ascites and peripheral oedema, however, she did not become encephalopathic. Peak bilirubin level reached was eight times normal at 141 µmol/L; Alk Phos reached 262 U/L whereas ALT and aspartate aminotransferase levels reached modest peaks of 47 U/L and 55 U/L, respectively. Creatinine had been trending down since day one post delivery and had normalised by day seven. Throughout this prolonged course, management remained supportive, with priorities being management of fluid balance, correction of electrolyte abnormalities and close monitoring of coagulopathy. The dextrose was ceased after 7 days of continuous infusion. By day 12, liver impairment was resolving, and the patient was no longer coagulopathic and had normal albumin levels. Bilirubin continued to

rise and she remained jaundiced though she was now stable enough to leave the high-dependency unit. At this stage, she began to have persistent fevers and a 1.5 L abscess was drained from below the caesarean section scar.

OUTCOME AND FOLLOW-UP

By day 18, the patient's liver function had almost completely normalised and her bilirubin had started to trend down. On review 3 weeks later, she was feeling well and had clinically improved. Apart from a mildly elevated λ GT, liver enzymes were normal; bilirubin and lipase had also returned to normal levels (table 2).

The male baby was born in good condition, breathing without assistance and with normal blood gases, and weighing 2.49 kg at 36 weeks. He was taken to special care nursery for observation and treated with prophylactic antibiotics, though inflammatory markers were not elevated and his bilirubin and glucose levels remained within normal limits. He was transferred to the general nursery at day one of life for feeding and was discharged home well on day 6.

Genetic analysis for LCHAD deficiency mutations showed the patient was negative for the common variant. The patient required a thorough debrief on the events of her pregnancy and was counselled regarding possible recurrence in future pregnancies.

DISCUSSION

Acute fatty liver of pregnancy is a rare cause of liver dysfunction and is unique to pregnancy. It has an estimated incidence of 5 per 100 000 pregnancies but many more cases may go undiagnosed.¹ It was first described in 1940 and was considered a fatal condition at the time. It is still associated with significant maternal morbidity though mortality from the condition is decreasing, and for every one patient who dies from the disease, 70 will survive.²

Histologically, it is characterised by microvesicular fatty infiltration of hepatocytes. This causes hepatic impairment and an

Table 2 Trend from day one postcaesarean section

Normal value	Day 1	Day 2	Day 3	Day 4	Day 7	Day 14	Day 21	Day 28
Haemoglobin 115–155 g/L	100	86	78	76	92	86	94	101
White cell count 4–11×10 ⁹ /L	30	35	32	35	40	25	14	14
Creatinine 30–100 µmol/L	202	170	115	80	61	49	33	34
Sodium 134–146 mmol/L	118	124	130	131	130	129	135	138
Bilirubin <16 µmol/L	88	97	133	137	121	128	68	38
λ GT <31 U/L	99	86	78	71	41	46	70	58
ALT <31 U/L	30	14	13	14	12	34	27	14
INR 0.8–1.2	1.5	1.6	1.4	1.3	1.3	1.3	1.3	1.2

ALT, alanine transaminase; INR, international normalised ratio; λ GT, λ glutamyltransferase.

array of extrahepatic complications such as hepatorenal syndrome, pancreatitis, diabetes insipidus and coagulopathy.³ Owing to the rarity of the condition, much of our knowledge comes from case series and population studies. While there are no clear predisposing factors, it is more common in first pregnancies, multiple pregnancies, male fetuses, and in women with low body mass index. In terms of genetic predisposition, there have been reports suggesting an association with inherited deficiency of long-chain 3-hydroxyacyl dehydrogenase (LCHAD) deficiency resulting in toxic build-up of metabolites. This has also been seen in some cases of HELLP syndrome.⁴

Difficulty in diagnosing acute fatty liver of pregnancy can occur because of the clinical overlap with other conditions, so much so that some authors suggest it behaves as though part of a spectrum of conditions along with pre-eclampsia and HELLP syndrome.⁵

Fifty per cent of acute fatty liver of pregnancy cases will present with pre-eclampsia and then go on to develop additional features. In this case, the initial presentation with intrahepatic cholestasis of pregnancy was unusual. There have been reported cases of intrahepatic cholestasis of pregnancy preceding HELLP syndrome; however, we can find few other cases where it has been associated with acute fatty liver of pregnancy.⁶

Differentiating AFLP from HELLP syndrome remains difficult due to similarities in clinical and in biochemical features such as patterns of liver function impairment. In this case, the persisting hypoglycaemia, the dramatically elevated creatinine and, in particular, the coagulopathy in the absence of haemolysis, were more suggestive of acute fatty liver of pregnancy.

Difficulties in standardising diagnosis has led to the development of scoring criteria. The most commonly used is the Swansea criteria, described by Ch'ng *et al*⁵ (box 1).

Hepatorenal impairment is a frequent feature in other reported cases of acute fatty liver of pregnancy. The presence of hypoglycaemia and acute pancreatitis are rare and tend to be markers of a more severe disease process.⁷

The management of AFLP, once the diagnosis is suspected, is expediting delivery and providing supportive therapy for the mother with multidisciplinary input from intensivists, haematologists and hepatologists. In this case, only supportive therapy was required; the patient's good outcome in the presence of significant illness is likely due to the early presentation initially with pruritus and then abdominal pain, allowing delivery to be expedited prior to the onset of further complications.

Box 1 Swansea criteria

Six of the following features.

- ▶ Vomiting
- ▶ Abdominal pain
- ▶ Polydipsia/polyuria
- ▶ Raised bilirubin
- ▶ Hypoglycaemia
- ▶ Encephalopathy
- ▶ Elevated uric acid
- ▶ Leucocytosis
- ▶ Ascites or bright liver on ultrasound scan
- ▶ Elevated AST and ALT
- ▶ High ammonia
- ▶ High creatinine
- ▶ Coagulopathy
- ▶ Microvesicular steatosis on liver biopsy

Patient's perspective

- ▶ Leading up to my admission I had a normal healthy pregnancy!
- ▶ The week starting 07/09/14, I had severe itchy hands & feet so I went to the antenatal clinic for a check up, and the doctor did a general check up and took bloods. A few days later the doctor asked me to come back to the clinic to discuss the results, which confirmed that I had obstetric cholestasis.
- ▶ The reason I went to the hospital on 14/09/14 was due to having severe constipation, where the midwife was able to relieve me of my pain after a few hours. While in the bathroom I noticed the yellow in my eyes, I had no idea! But the midwife was concerned about my baby, and me, so I was monitored and kept in overnight. The following morning I was induced and given an epidural, and the waiting began. Unfortunately, I was unable to have my baby naturally, so forceps were used but unsuccessfully, so an emergency c section was performed and my beautiful baby boy was born! I really don't remember much after the c section, but I do remember being wheeled into the High Dependency Unit (HDU), the corridors of the hospital and going into the lifts.
- ▶ During my time in HDU (2 weeks) I was treated as the most important person in the unit and I cannot fault the care I received, they felt like family after I was discharged from HDU. The doctors and nurses were amazing with everything they did and they explained everything & anything I asked, as I had no idea what had happened due to illness. The support the staff gave my family was amazing! The encouragement I received to get up and walk was amazing, without it I don't think I would have, as it was 9 days after I was admitted to HDU!
- ▶ Eventually, I was discharged from HDU and moved to the Maternity Ward, where I spent another 2 & ½ weeks recovering from the illness. The encouragement from all the staff was appreciated, as they all wanted me to get better and go home to Samuel, to enjoy being a new mother! The best time of being in hospital was when the doctors said that I could get Day Release...go home and relax, be a mum!
- ▶ This illness has had a huge impact on me mentally, physically and emotionally. I spent 33 days in hospital, where I missed out on the first month of my baby's life and I missed out on taking him home with my partner to enjoy being a family and being a full-time mum!
- ▶ It has impacted on my body as I have lost a lot of muscle weight, which is going to take 2–3 months to gain back, and my appetite was also affected. Today I was discharged from seeing the dieticians, as they are happy with where I am, even though I haven't gained or lost weight since being discharged. I also became allergic to adhesive tape and I was sick of being a pincushion! I have extra stretch marks due to having a c section and from the fluid.
- ▶ Mentally, it's been really tough. My room at the hospital started to become a prison and there seemed to be no end to my time there. I felt like I wasn't going anywhere and I couldn't see any improvement, I was getting easily upset as all I wanted was to go home! I am still in contact with the hospital's psychologist, where I have regular chats. It's going to take me a while to get over this illness mentally as I think I've been robbed of my time/life, as I am only 33 years old. I am a very healthy person who doesn't get sick and who leads an active life, which currently I can't!
- ▶ As the years go past I will never forget this time in my life and I don't wish this illness on my worst enemy.

Learning points

- ▶ Acute fatty liver of pregnancy has an incidence of 5 per 100 000 pregnancies and is associated with significant maternal morbidity.
- ▶ Abnormal liver function can be a frequent finding in pregnancy, and a high index of clinical suspicion is required to out-rule serious underlying pathology.
- ▶ Patients who have suspected Hemolysis Elevated Liver enzymes Low Platelet count syndrome or acute fatty liver of pregnancy can deteriorate quickly. Delivery of the baby must be expedited in the safest manner possible, to ensure better maternal and neonatal outcomes.

Contributors JR was the Obstetric Consultant who admitted the patient. NE was involved with the inpatient management of the patient.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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