Acute fatty liver of pregnancy and concomitant medical conditions: A review of cases at a quaternary obstetric hospital

Annabelle Lamprecht^{1,2} , Adam Morton^{2,3} ,
Josephine Laurie^{2,3} and Winnifred Lee²

Abstract

Acute fatty liver of pregnancy is a rare complication of pregnancy that may result in fulminant hepatic failure. We present a review of all patients presenting to a quaternary obstetric hospital over a 15-year period, with particular regard to biochemical changes, results of gene testing, and pre-existing conditions. Seventeen patients with acute fatty liver of pregnancy were identified. Six patients were documented to have pre-existing gastrointestinal disease; five with inflammatory bowel disease, and one with influenza A hepatitis. Antithrombin III levels were low in this study, consistent with previously published data. There were no recurrences of acute fatty liver of pregnancy in nine subsequent pregnancies to seven mothers. The authors are not aware of any literature addressing pre-existing medical conditions which may predispose to acute fatty liver of pregnancy.

Keywords

Acute fatty liver of pregnancy, inflammatory bowel disease

Received 22 December 2017; accepted 13 February 2018

Background

Acute fatty liver of pregnancy (AFLP) is a rare mitochondrial hepatopathy estimated to complicate 5–30 per 100,000 pregnancies. The disorder is associated with maternal mortality of up to 12.5%, a risk of stillbirth of 100–120 per 1000 births and considerable maternal morbidity including complications such as disseminated intravascular coagulation and haemorrhage, sepsis, acute kidney injury requiring dialysis, and fulminant hepatic failure necessitating liver transplantation.¹ Management consists of urgent delivery of the fetus and supportive maternal care.

AFLP has been attributed to a defect in mitochondrial β -oxidation of fatty acids, and is characterised by hepatic microvesicular steatosis. Several fetal fatty oxidation defects have been reported to be associated with AFLP. The most common gene mutation is defects in long-chain 3-hydroxyacyl-CoA dehydrogenase/mitochondrial trifunctional protein (LCHAD/MTP). Other associated gene mutations include fetal deficiency of carnitine palmitoyl transferase I, short and medium chain acyl-CoA dehydrogenase. There have, however, been many case reports and series where AFLP was not associated with a detectable gene mutation. The authors are not aware of any literature addressing pre-existing medical conditions which may predispose to AFLP.

Mater Health is a quaternary referral obstetric hospital with approximately 10,000 deliveries per year.

Methods

An audit of women diagnosed with AFLP over a 15-year period was performed specifically addressing underlying medical conditions and the incidence of LCHAD gene mutations. Patients were identified

through patient coding of diagnosis-related groups and interrogation of the pathology database for patients with elevated hepatic transaminases with subsequent review of medical records.

Results

Seventeen patients were diagnosed over 15 years with AFLP with a mean maternal age of 31 years and 14 (82%) were nulliparous; 10 women were of Caucasian ethnicity, 4 of Asian background, 2 from India, and one woman was Colombian. The median gestation at diagnosis was 37 weeks (range 26–38 weeks' gestation) and one woman was diagnosed postpartum.

With regard to symptoms, 9 women had vomiting, 12 complained of abdominal pain, and 4 manifested features of encephalopathy. One woman manifested polyuria and excessive thirst. All of the women displayed at least six of the Swansea criteria.² Laboratory data are

¹Department of Obstetrics and Gynaecology, Sunshine Coast University Hospital, Birtinya QLD, Australia

²Faculty of Medicine, University of Queensland, Brisbane, Australia

³Mater Misericordiae Health Service Ltd, Raymond Tce, South Brisbane, QLD, Australia

Corresponding author:

Annabelle Lamprecht, Sunshine Coast University Hospital, Doherty St, Birtinya QLD, Australia.

Email: Annabelle.lamprecht@health.qld.gov.au

summarised in Table 1. Five patients (29%) had symptomatic hypoglycaemia with plasma glucose less than 2.5 mmol/L and 15 patients (88%) had renal dysfunction evidenced by serum creatinine greater than 90 µmol/L. Four women had serum sodium less than 130 mmol/L. Fifteen women were tested for mutations in the LCHAD gene and all were negative. Liver biopsy was not performed in any of the women. Six of the women had pre-existing gastrointestinal disease, summarised in Table 2. In two women, AFLP developed subsequent to a diagnosis of intrahepatic cholestasis of pregnancy (ICP).

Delivery was by caesarean section in 80% of cases. Meconium-stained liquor was present in 67% of deliveries and there was one stillbirth. There were no maternal deaths and none of the women required liver transplantation. Two women required haemodialysis during admission. Average inpatient and intensive care unit stay were 13.4 days (range 4–38) and 4.9 days, respectively (range 0–13). One woman whose AFLP was complicated by acute pancreatitis presented subsequently three weeks postpartum with acute pulmonary oedema due to peripartum cardiomyopathy (left ventricular ejection fraction 25%). Nine subsequent pregnancies were identified in seven mothers without recurrence of AFLP.

Discussion

The audit was remarkable for the proportion of women who developed AFLP in the setting of pre-existing gastrointestinal disorders,

the uniform negative testing for LCHAD gene mutation, and the absence of recurrence of AFLP in subsequent pregnancies.

Liver disease occurs in approximately 10–20% of patients with inflammatory bowel disease (IBD).³ Non-alcoholic fatty liver disease is the most common hepatic complication and primary sclerosing cholangitis the most specific for IBD. Other hepatic complications include cholelithiasis, IgG-4 cholangitis, PSC-autoimmune hepatitis, hepatic amyloid, granulomatous hepatitis and portal vein thrombosis. Pregnant women with IBD may be at increased risk for antepartum haemorrhage, low birth weight infants, premature delivery, caesarean section, postpartum haemorrhage and severe maternal morbidity.^{4,5} To the best of the authors' knowledge, an association between IBD and AFLP has not been previously described.

An association between ICP and later Crohn's disease, but not ulcerative colitis (UC) has been described in a population-based cohort study.⁶ Two cases of AFLP occurring subsequent to the diagnosis of ICP have been reported.^{7,8} It is important for clinicians to recognise that elevated serum bile acids and pruritus may occur in a number of disorders other than ICP including non-alcoholic fatty liver disease, AFLP, acute viral hepatitis, chronic active hepatitis and primary biliary cirrhosis.^{9,10}

A common feature in IBD, ICP and influenza infection is elevated levels of inflammatory cytokines. An excessive T(H)1 T-cell response in Crohn's disease leads to increased levels of pro-inflammatory cytokines including interferon-gamma (IFN-γ), interleukin(IL)-12, IL-1 and IL-6 and tumour necrosis factor-alpha(TNF-α).¹¹ UC is associated with a T(H)2 T-cell response. ICP is associated with an

Table 1. Summary of investigations in the 17 patients reviewed.

	Abnormal (%)	Median	Interquartile range	Range
Laboratory parameter (Swansea criteria cutoff ²)				
Bilirubin µmol/L (>14 µmol/L)	100	87	62–141	34–214
AST u/L (>42 u/L)	100	329	151–411	71–4320
ALT u/L (>42 u/L)	100	253	155–390	89–4815
Prothrombin time seconds (>14 s)	100	20.3	19–25	15.3–>120
Plasma glucose mmol/L (<4 mmol/L)	71	3.2	2.4–8.4	1.1–4.9
Urate mmol/L (>0.34 mmol/L)	80	0.46	0.35–0.60	0.14–0.72
White blood cells cells/µL (>11 cells/µL)	94	16.1	14.2–22.1	8.8–39.4
Serum creatinine µmol/L(>150 µmol/L)	53	155	111–220	46–549
Ammonia µmol/L (>47 µmol/L)	35	37	16–55	5–95
Other significant laboratory parameters				
Serum bicarbonate mmol/L (<16 mmol/L)	24	19	14.75–21	11–25
Serum lactate mmol/L (>2.2 mmol/L)	58	4	2.3–5.3	1.3–7.8
Fibrinogen g/L (<3 g/L)	82	1.7	1.2–3.45	<0.1–5.6
Antithrombin III % (<82%)	100	22	12.5–27.3	1.6–51
Cholesterol mmol/L(no defined cutoff)	-	2.2	2–3.95	1.5–5.1
Serum albumin g/L (<24 g/L)	82	22	21–23	16–34
Serum sodium mmol/L (<130 mmol/L)	24	132	131–135	122–137
Fatty liver present on ultrasound	25	–	–	–

Table 2. Details of pre-existing gastrointestinal/liver disease in women with AFLP.

Case	Diagnosis	Treatment	Other conditions
1	Crohn's disease	6-mercaptopurine	ICP 15 days prior to AFLP
2	Ulcerative colitis	6-mercaptopurine, mesalazine	ICP 6 days prior to AFLP
3	Ulcerative colitis	Sulfasalazine	Hyposplenic blood film; familial hidradenitis suppurativa
4	Crohn's disease	Infliximab, purinethol, allopurinol, prednisone, mesalazine	Hyposplenic blood film
5	IBD – not specified		
6	Influenza hepatitis		Preceded AFLP by 28 days

ICP: intrahepatic cholestasis of pregnancy; IBD: inflammatory bowel disease; AFLP: acute fatty liver of pregnancy.

increase of type 1 cytokines (TNF- α , IFN- γ), and a reduction in type 2 cytokines.¹² With influenza infection, massive expansion of virus specific CD8⁺ cells and activation of Kupffer cells lead to the release of inflammatory cytokines mediating reduced hepatic fatty acid oxidation and hepatocyte injury.¹³ Hepatic mitochondrial β -oxidation is increased following administration of tetradecylthioacetic acid, an anti-inflammatory bioactive fatty acid. Similarly, anti-TNF- α antibody treatment improves mitochondrial function in ob/ob mice.¹⁴ An immunohistopathological study of hepatic tissue sections from two patients with AFLP, however, found only weak staining for anti-TNF- α and neutrophil elastase antibody, whereas liver tissue from two patients with the syndrome of haemolysis, elevated liver enzymes and low platelets stained strongly for TNF- α and neutrophil elastase.¹⁵

Hyposplenism has been reported to complicate 40% of patients with extensive UC, and 35% of patients with Crohn's disease of the colon.¹⁶ Hyposplenism in individuals with IBD may be associated with an increased risk of sepsis, high rates of postoperative infection having been reported after surgery for hyposplenic UC patients.¹⁷

A retrospective study of 10 women with pregnancies complicated by AFLP found that none harboured the common LCHAD mutation (G1528C), suggesting the metabolic basis of AFLP to be more heterogeneous than previously thought.¹⁸ Supporting this, there have been cases of AFLP associated with other disorders of fatty acid oxidation, such as fetal deficiency of carnitine palmitoyl transferase I or short or medium chain acyl-CoA dehydrogenase and pregnancies with a fetus affected by a disorder of fatty acid oxidation demonstrate an 18-fold increase in maternal liver disease compared to matched controls.^{19,20} In another study, mutations causing paediatric LCHAD deficiency were detected in 19% of families with a maternal history of AFLP.²¹

Results from the audit support the value of low ATIII levels in distinguishing between AFLP and severe preeclampsia with haemolysis, elevated liver enzymes and low platelets (HELLP syndrome). Review of the 61 cases published in the literature, where ATIII levels were measured in AFLP disclosed a mean level of 16.1% (range 0–69%). Mean levels of ATIII in preeclampsia and HELLP syndrome range between 60 and 85%.^{22–28} ATIII levels are unlikely to be of benefit in distinguishing between AFLP and other causes of acute hepatic failure in pregnancy, given that a mean ATIII level of 14% was reported in seven non-pregnant patients with acute severe hepatic failure of unknown cause.²⁹ Values in non-pregnant individuals with end-stage hepatic failure due to alcoholic cirrhosis were significantly higher with a mean ATIII level of 51%.

The presence of hyponatraemia in several patients is perhaps surprising given that AFLP may be associated with hypernatremia due to transient diabetes insipidus as a result of reduced hepatic breakdown of vasopressinase. Severe hyponatraemia has been reported in three previous cases of AFLP.^{7,30,31} Hyponatraemia in hepatic failure is likely due to limitation of free water clearance as a result of enhanced release of antidiuretic hormone with tissue hypoperfusion together with reduced renal function.³² Hypothalamic-pituitary-adrenal axis insufficiency in acute hepatic failure may be an additional factor.³³

One previous case of biopsy-proven AFLP complicated by PPCM has been reported.³⁴ The incidence of these disorders suggests that a chance association should occur in only 1 in 100 million pregnancies. The pathophysiology linking the two conditions is unknown.

The risk of recurrent AFLP in a subsequent pregnancy is unknown. One study reported 2 cases of recurrence among 28 pregnancies to women with previous AFLP.³⁵

Conclusion

This audit raises the possibility of an increased risk of AFLP in women with IBD. Investigation of pregnancy registries containing

significant numbers of women with IBD would be worthwhile to explore this further. In addition, further studies with regard to possible mechanisms linking IBD with an increased risk of pregnancy-unique liver diseases would be worthwhile. Investigations as to whether there are other unidentified genetic mutations increasing the risk of AFLP would be informative. The audit supports previous evidence regarding the utility of low ATIII levels in the diagnosis of AFLP, and differentiation from HELLP syndrome. Clinicians caring for women with AFLP should be aware of PPCM as a rare complication of the disorder. A registry of the outcome of subsequent pregnancies to women with AFLP would be valuable to assist women in making an informed decision regarding the risk of recurrence.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Ethical approval

Ethics approval for the review of medical records was obtained.

Guarantor

AM.

Contributorship

All authors were involved in the identification of patients. AL and JL performed chart review and data collection, AM performed the literature review and manuscript preparation. AM, JL and AL edited and reviewed the manuscript for publication.

ORCID iD

Annabelle Lamprecht <http://orcid.org/0000-0003-0712-3823>

Adam Morton <http://orcid.org/0000-0001-9887-714X>

References

1. Xiong HF, Liu JY, Guo LM, et al. Acute fatty liver of pregnancy: over six months follow-up study of twenty-five patients. *World J Gastroenterol* 2015; 21: 1927–1931.
2. Knight M, et al. A prospective national study of acute fatty liver of pregnancy in the UK. *Gut* 2008; 57: 951–956.
3. Wieser V, Gerner R, Moschen AR, et al. Liver complications in inflammatory bowel diseases. *Dig Dis* 2013; 31: 233–238.
4. Shand AW, Chen JS, Selby W, et al. Inflammatory bowel disease in pregnancy: a population-based study of prevalence and pregnancy outcomes. *BJOG* 2016; 123: 1862–1870.
5. Abdul Sultan A, West J, Ban L, et al. Adverse pregnancy outcomes among women with inflammatory bowel disease: a population-based study from England. *Inflamm Bowel Dis* 2016; 22: 1621–1630.
6. Wikstrom Shemer EA, Stephansson O, Thuresson M, et al. Intrahepatic cholestasis of pregnancy and cancer, immune-mediated and cardiovascular diseases: a population-based cohort study. *J Hepatol* 2015; 63: 456–461.
7. English N and Rao J. Acute fatty liver of pregnancy with hypoglycaemia, diabetes insipidus and pancreatitis, preceded by intrahepatic cholestasis of pregnancy. *BMJ Case Rep* 2015; 2015: 1–4.

8. Vanjak D, Moreau R, Roche-Sicot J, et al. Intrahepatic cholestasis of pregnancy and acute fatty liver of pregnancy. An unusual but favorable association? *Gastroenterology* 1991; 100: 1123–1125.
9. Puri P, Daita K, Joyce A, et al. The presence and severity of nonalcoholic steatohepatitis is associated with specific changes in circulating bile acids. *Hepatology* 2017; 67: 534–548.
10. Kim MJ and Suh DJ. Profiles of serum bile acids in liver diseases. *Korean J Intern Med* 1986; 1: 37–42.
11. McClane SJ and Rombeau JL. Cytokines and inflammatory bowel disease: a review. *JPEN J Parenter Enteral Nutr* 1999; 23: S20–S24.
12. Yayi H, Danqing W, Shuyun L, et al. Immunologic abnormality of intrahepatic cholestasis of pregnancy. *Am J Reprod Immunol* 2010; 63: 267–273.
13. Tarasenko TN, Singh LN, Chatterji-Len M, et al. Kupffer cells modulate hepatic fatty acid oxidation during infection with PR8 influenza. *Biochim Biophys Acta* 2015; 1852: 2391–2401.
14. Garcia-Ruiz I, Rodriguez-Juan C, Diaz-Sanjuan T, et al. Uric acid and anti-TNF antibody improve mitochondrial dysfunction in ob/ob mice. *Hepatology* 2006; 44: 581–591.
15. Halim A, Kanayama N, El Maradny E, et al. Immunohistological study in cases of HELLP syndrome (hemolysis, elevated liver enzymes and low platelets) and acute fatty liver of pregnancy. *Gynecol Obstet Invest* 1996; 41: 106–112.
16. Palmer KR, Sherriff SB, Holdsworth CD, et al. Further experience of hyposplenism in inflammatory bowel disease. *Q J Med* 1981; 50: 463–471.
17. Muller AF and Toghil PJ. Hyposplenism in gastrointestinal disease. *Gut* 1995; 36: 165–167.
18. Maitra A, Domati-Saad R, Yost N, et al. Absence of the G1528C (E474Q) mutation in the alpha-subunit of the mitochondrial trifunctional protein in women with acute fatty liver of pregnancy. *Pediatr Res* 2002; 51: 658–661.
19. Browning M, Levy H, Wilkins-Haug L, et al. Fetal fatty acid oxidation defects and maternal liver disease in pregnancy. *Obstet Gynecol* 2006; 107: 115–120.
20. Roth K. Hepatic carnitine palmitoyltransferase I deficiency presenting as maternal illness in pregnancy. *Clin Pediatr* 2000; 39: 437–438.
21. Yang Z, Zhao Y, Bennett MJ, et al. Fetal genotypes and pregnancy outcomes in 35 families with mitochondrial trifunctional protein mutations. *Am J Obstet Gynecol* 2002; 187: 715–720.
22. Paternoster DM, Stella A, Simioni P, et al. Coagulation and plasma fibronectin parameters in HELLP syndrome. *Int J Gynaecol Obstet* 1995; 50: 263–268.
23. Weiner CP, Kwaan HC, Xu C, et al. Antithrombin III activity in women with hypertension during pregnancy. *Obstet Gynecol* 1985; 65: 301–306.
24. Demir C and Dilek I. Natural coagulation inhibitors and active protein c resistance in preeclampsia. *Clinics* 2010; 65: 1119–1122.
25. de Boer K, Buller HR, ten Cate JW, et al. Coagulation studies in the syndrome of haemolysis, elevated liver enzymes and low platelets. *Br J Obstet Gynaecol* 1991; 98: 42–47.
26. Marietta M, Simoni L, Pedrazzi P, et al. Antithrombin plasma levels decrease is associated with preeclampsia worsening. *Int J Laborat Hematol* 2009; 31: 227–232.
27. Chen Y and Lin L. Potential value of coagulation parameters for suggesting preeclampsia during the third trimester of pregnancy. *Am J Med Sci* 2017; 354: 39–43.
28. Vigil-De Gracia P. Acute fatty liver and HELLP syndrome: two distinct pregnancy disorders. *Int J Gynaecol Obstet* 2001; 73: 215–220.
29. Boks AL, Brommer EJ, Schalm SW, et al. Hemostasis and fibrinolysis in severe liver failure and their relation to hemorrhage. *Hepatology* 1986; 6: 79–86.
30. O'Loughlin S, Sweeney EC and Keelan P. Persistent hypoglycaemia and severe hyponatraemia in a case of acute fatty liver of pregnancy. *J Irish Med Assoc* 1971; 64: 45–49.
31. Djibre A, Zohar S and Assy N. Acute fatty liver of pregnancy [Internet]. Oxford: GastroHep.com; 2010. Available at: <https://www.gastrohep.com/classcases/classcases.asp?id=49>
32. Lo R, Austin A and Freeman J. Vasopressin in liver disease – should we turn on or off? *Curr Clin Pharmacol* 2008; 3: 156–165.
33. Harry R, Auzinger G and Wendon J. The clinical importance of adrenal insufficiency in acute hepatic dysfunction. *Hepatology* 2002; 36: 395–402.
34. Keyser EA, Reed BG, Gonzalez-Brown V, et al. Peripartum cardiomyopathy and acute fatty liver of pregnancy: one patient with two zebras. *Mil Med* 2012; 177: 470–473.
35. Zurcher K. Uncomplicated second pregnancy following acute pregnancy fatty liver. *Schweizerische Medizinische Wochenschrift* 1996; 126: 1224.