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Case Report

Analysis of seven consecutive cases of acute fatty liver of pregnancy: single center experience in China

Xu-Dong Han[1*], Xia Cao[2*], Gui-Fang Gu[2], Gang Qin[3]

[1]Intensive Care Unit, [2]Department of Obstetrics and Gynaecology, [3]Center for Liver Diseases, The Nantong Third People's Hospital, Nantong University, Nantong, China. [*]Equal contributors.

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Abstract: *Objectives:* To summarize the clinical characteristics, and maternal and neonatal outcomes in patients who were diagnosed with acute fatty liver of pregnancy (AFLP). *Methods:* A retrospective case series study over 10 years was conducted at the Nantong Third People's Hospital, Nantong University, China. Seven cases diagnosed as AFLP were included. The medical records were reviewed for clinical presentations, laboratory tests, and maternal and neonatal outcomes. *Results:* All patients presented with nausea, vomiting, malaise, and abdominal pain at a median of 34 weeks of gestation, then progressive jaundice subsequently. Four cases were diagnosed in the antepartum period, and three cases in early postpartum period. Complications revealed with acute renal failure in 4 patients (57.1%). Hepatic encephalopathy, pancreatitis, sepsis and multiple organ dysfunction syndrome were seen in 2 patients (28.6%). Delivery occurred by caesarean section in 5 patients (71.4%) and vaginally in 2 patients (28.6%). There were two maternal death (28.6%) and one neonatal death (12.5%). *Conclusions:* AFLP is still a potentially lethal complication of pregnancy. All patients suspected with such diagnosis should undergo screening for the laboratory tests. Early recognition and timely termination of pregnancy are essential to improve pregnancy outcomes.

Keywords: Acute fatty liver of pregnancy, liver failure, case series

Introduction

Acute fatty liver of pregnancy (AFLP) is an uncommon severe complication of pregnancy, with an estimated incidence of 1/6,000-1/20,000 pregnancies [1, 2]. At first, Ogston *et al.* reported the acute yellow atrophy of the liver in pregnancy in 1870s [3]. Then Sheehan *et al.* described the pathology of obstetric acute yellow atrophy in 1940 [4]. Usually occurring in late pregnancy with unknown etiology, AFLP is characterized as sudden onset of liver failure due to hepatic microvesicular steatosis [5]. The maternal and neonatal mortality rates have been estimated at 10-40% [6, 7]. With early diagnosis and prompt treatment, outcomes and survival have improved.

The aim of the present study was to report our experience on AFLP with the clinical features, laboratory findings, diagnosis, management and the pregnancy outcome of AFLP in all cases over the past 10 years.

Materials and methods

We performed a retrospective case series study of patients with AFLP at the Nantong Third People's Hospital, Nantong University between January 2007 and December 2016. The diagnosis of AFLP was made on the basis of clinical and laboratory findings. All patients exhibited six or more of the Swansea criteria proposed by Ch'ng *et al.* to objectively confirm the diagnosis of AFLP: (1) vomiting, (2) abdominal pain, (3) polydipsia/polyuria, (4) encephalopathy, (5) elevated bilirubin, (6) hypoglycemia, (7) elevated urate, (8) leukocytosis, (9) ascites or bright liver on ultrasound scan, (10) elevated transaminases, (11) elevated ammonia, (12) renal impairment, and (13) coagulopathy [8].

Data including maternal age, gestational age, symptoms, laboratory findings, clinical course, and pregnancy outcomes were reviewed. We had taken the permission from the Institutional Review Board of Nantong Third People's

Table 1. Maternal characteristics

Case	Year	Age	Gravida and parity	GA at diagnosis (wks)	GA at delivery (wks)	Delivery method
1	2007	24	G3P2	32 1/7	31 6/7	CS
2	2009	29	G1P0	30 1/7	30 2/7	CS
3	2012	26	G1P0	37 4/7	37 5/7	VD
4	2012	23	G1P0	36	36 1/7	CS
5	2013	21	G1P0	34 4/7	34 3/7	CS
6	2014	24	G2P1	38 4/7	38 3/7	VD
7	2016	38	G4P1	28	30 4/7	CS

GA, gestational age; CS, caesarean section; VD, vaginal delivery.

Hospital for this study. All participants were informed of the potential and future prospects of this survey and their informed consent was taken. All respondents were assured of strict confidentiality of their identity.

Results

Seven AFLP cases had been identified during the past 10 years (**Table 1**). The frequency of AFLP in our hospital is 1 in 1,435 pregnancies. The median (range) age was 24 (21-38) years old. Four (57%) were primiparous women, while the other three were multiparous women. The median gestational age at delivery was 34.4 (range, 30.3-38.4) weeks. All AFLP cases occurred during the third trimester of pregnancy or immediate postpartum. Four cases were diagnosed during the antepartum period, while the other three cases were diagnosed within 2 days post-delivery.

The seven cases had quite similar clinical manifestations. Non-specific insidious onset compromised nausea, vomiting, abdominal pain and general malaise. Then fever and jaundice appeared subsequently.

The liver function indexes included elevated serum total bilirubin (TBIL = 93.2 μmol/L, ranged 36.6-362 μmol/L), elevated serum aspartate aminotransferase (AST = 152 IU/L, ranged 61-775 IU/L), alanine aminotransferase (ALT = 197 IU/L, ranged 22-976 IU/L), lactic dehydrogenase (LDH = 632 IU/L, range 409-1451 IU/L). Leucocytosis (> 11 × 10^9/L), prolonged prothrombin time (PT > 14 s) and elevated urate (> 430 μmol/L) was found in 6 (85.7%), 5 (71.4%), 6 (85.7%) of the patients respectively at diagnosis. Hypoglycaemia (< 4 mmol/L) and renal impairment (creatinine > 150 μmol/L) occurred in 5 (71.4%) and 4 (57.1%) of the cases respectively during the course (**Table 2**). A transient excess of fat in the liver or bright liver was detected in 5 cases during hospitalization with ultrasound scan, thus confirming the diagnosis of AFLP. The notable disappearance of the excess of fat in the liver several days after the initi al ultrasound scan paralleled the improvement in liver function tests.

Delivery was expedited in all patients after admission to the hospital or once a steroid course was completed, with the exception of one patient who was treated expectantly for more than two weeks before delivery. Delivery occurred by caesarean section in 5 patients (71.4%) and vaginally in 2 patients (28.6%) (**Table 1**). Artificial liver support systems (ALSS), plasma exchange (PE) combined with continuous renal replacement therapy (CRRT) here, was performed in 2 of these patients (**Table 3**).

Two patients died at day 4 and day 10 after diagnosis of AFLP (**Figure 1**). Five patients had severe morbidities, including two with hepatic encephalopathy, four with acute renal failure (ARF), one with disseminated intravascular coagulation (DIC), two with severe pancreatitis, three with sepsis and two with multiple organ dysfunction syndrome (MODS). In total, these patients were treated for a median of 15 days (ranged 3-34). Five women (71.4%) were admitted to intensive care unit for a median of 3 days (ranged 2-11).

The median birth weight of infants was 1825 g (ranged 1100-2850 g), and 5 of the 8 infants were male. There was no stillbirth and one neonatal death among the 8 infants (case fatality 12.5%). Six neonates from 5 mothers were delivered in preterm birth. Intrauterine fetal distress (42.9%) was the most common neonatal complication, and only three neonates had an Apgar score of 10 at 5 min (**Table 4**).

Discussion

Acute fatty liver of pregnancy is a rare but severe complication which usually occurs in the third trimester of pregnancy or immediate puerperium. Our series has higher incidence rate compared with others reports, because most of these patients were referred to our Liver Unit

Table 2. Laboratory values

Case	WBC (10^9/L)	PLT (10^9/L)	ALT (IU/L)	AST (IU/L)	TBIL (μmol/L)	PT (s)	LDH (IU/L)	GLU (mmol/L)	BUN (mmol/L)	CREA (μmol/L)	UA (μmol/L)	Ammonia (μmol/L)
						At diagnosis						
1	15.3	62	22	61	362	22.3	690	5.29	9.77	147	437	37.7
2	18.89	117	50	64	76.3	13.8	409	6.55	7.2	106.1	102.1	31
3	12.79	91	295	382	73.3	17.3	1451	3.3	5.7	124.4	434	24
4	16.54	71	89	80	329.5	21.2	1149	11.7	7.7	192.2	474	10
5	16.30	312	976	775	93.2	18.5	558	4.57	4.16	121.4	510.7	30.9
6	10.79	40	197	152	103.5	16.7	632	1.9	6.5	209	471	8.9
7	26.11	240	270	460	36.6	18.5	472	3.97	5	124	458	64.2
						Peak/Nadir range						
1	12.3-15.3	31-62	20-25	61-73	210.7-362.0	15.3-29.3	619-707	5.29-8.90	6.23-9.77	21-147	82-431	37.7-102.5
2	5.14-23.21	80-329	23-61	30-86	17.3-86.4	10.8-17.1	239-566	3.63-7.80	5.83-8.10	58.5-121.0	102.1-398.0	31-31
3	7.08-15.86	91-163	21-295	25-488	11.6-73.3	11.8-17.3	214-1451	3.83-5.05	2.52-6.37	61-1244	181.9-434	24-24
4	13.6-35.46	15-210	16-89	32-187	70.6-329.5	14.9-34.2	295-1933	5.62-14.71	2.97-8.08	89.2-193.8	54-474	10-849
5	3.67-36.64	49-352	36-976	37-775	30.2-232.8	11.4-32.9	191-1058	3.30-8.31	3.5-9.55	48.3-146.4	127.1-532.9	30.9-40.4
6	2.6-10.79	40-323	18-46	30-48	10.7-103.5	10.8-17.1	166-632	1.9-6.87	2.14-6.5	42.7-222.3	143-485	5.9-16.5
7	4.84-29.41	54-404	14-292	45-458	45.8-211.9	11.6-27.1	287-1492	2.93-15.24	4.03-14.52	45.6-190.8	55-458	25.3-64.2

WBC, white blood cell; PLT, platelet; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TBIL, total bilirubin; PT, prothrombin time; LDH, lactic dehydrogenase; GLU, glucose; BUN, blood urea nitrogen; CREA, creatinine; UA, uric acid.

Table 3. Maternal complications and outcomes

Case	HE	ARF	DIC	Pancreatitis	Sepsis	MODS	Hospital days	ICU days	ALSS	Death
1	Yes	Yes	No	No	Yes	Yes	3	3	Yes (PE+CRRT)	Yes
2	Yes	Yes	No	No	No	No	15	2	No	No
3	No	No	No	No	No	No	14	0	No	No
4	No	Yes	No	Yes	Yes	Yes	8	8	Yes (PE+CRRT)	Yes
5	No	No	No	No	No	No	24	3	No	No
6	No	No	Yes	No	No	No	29	0	No	No
7	No	Yes	No	Yes	No	No	34	11	No	No
Overall	28.6%	57.1%	14.3%	28.6%	28.6%	28.6%	15 (3-34)		28.6%	28.6%

HE, hepatic encephalopathy; ARF, acute renal failure; DIC, disseminated intravascular coagulation; MODS, multiple organ dysfunction syndrome; ICU, intensive care unit; ALSS, artificial liver support system; PE, plasma exchange; CRRT, continuous renal replacement therapy.

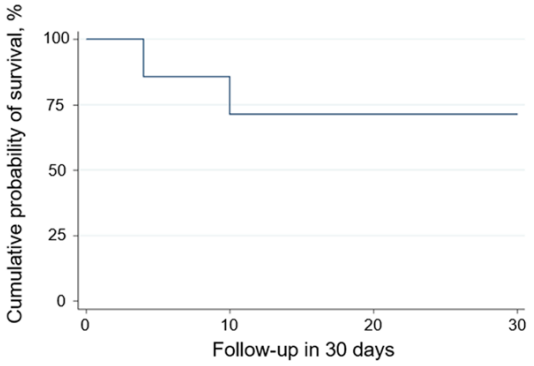

Figure 1. Cumulative survival in AFLP patients over follow-up of 30 days.

after unsuspected liver disease had been found at other hospitals.

The complicated manifestations and insufficient understanding of the disease make early diagnosis and effective treatment challenging. The classic attack of AFLP is preceded by a prodrome which lasts from a few days to several weeks. The initial non-specific symptoms includes nausea and vomiting, malaise, and abdominal pain sometimes. These various prodromal symptoms herald the onset of jaundice, which is often preceded by darkening of the urine. Once jaundice appears during the third trimester of pregnancy, AFLP should be considered. The main differential diagnoses include viral hepatitis, autoimmune hepatitis, drug-induced liver injury, preeclampsia and HELLP syndrome. In earlier years, liver biopsy was the only means to exclude viral hepatitis in cases of AFLP. Yet, with the advent of accurate viral serologic tests, liver biopsy has fallen out of favor. Moreover, magnetic resonance imaging (MRI)-based liver fat quantification has been suggested as a new diagnostic tool to identify AFLP [9]. In our center, ultrasound scan still remains an effective tool to a secure diagnosis of AFLP without performing liver biopsy.

Maternal and fetal mortality rates were reported to be as high as 80% in the first half of the last century [10]. In recent years, the prognosis of AFLP has improved due to early diagnosis, prompt termination of pregnancy and advances in critical care medicine. If the diagnosis is delayed, however, the patient can progressively deteriorate and develop severe liver dysfunction, encephalopathy, sepsis and multiple organ failure, eventually leading to death. In our study, acute renal failure which occurred in approximately 57.1% of patients was the leading cause of morbidity and mortality. There were 2 maternal deaths (28.6%) in our study. One postpartum patient, who had severe hepatic coma, progressed quickly and finally died of multiple organ failure. Another patient who developed acute liver and renal failure, severe pancreatitis and sepsis, died of multiple organ failure despite expeditious delivery and supportive treatment.

A few data described pancreatitis as a complication in women with AFLP [11]. It should be noted that 2 of 7 cases here were diagnosed with acute pancreatitis and one died. Pancreatitis may be a potentially lethal complication of AFLP. We suggest that all patients with AFLP should undergo screening for serum lipase and amylase.

Artificial liver support system has been an effective tool for patients with acute-on-chronic liver failure in our center [12]. It has been reported that timely application of PE combined

Table 4. Fetal and neonatal outcomes

Case	No. of fetus	Fetal sex	Preterm	Intrauterine Fetal distress	Neonatal apnea	Birth weight (g)	Apgar score	Death
1	1	M	Yes	Yes	No	1350	8	No
2	1	M	Yes	No	No	1100	10	No
3	1	M	No	No	Yes	2750	10	No
4	1	M	Yes	Yes	Yes	1500	7	No
5	2	F/F	Yes	No	No	2100/2150	9/10	No
6	1	F	No	No	No	2850	9	No
7	1	M	Yes	Yes	Yes	1550	3	Yes
Overall	8		71.4%	42.9%	42.9%	1825 (1100-2850)	9 (3-10)	14.3%

with CRRT or plasma perfusion (PP) in the early phase of AFLP was beneficial to facilitating hepatic and renal recovery. Thus ALSS may be a promising therapy to halt or reverse the progression of AFLP [13, 14]. However, the maternal outcome we observed with the ALSS treatment was poor, mainly because the two cases were at late phase of AFLP.

In summary, AFLP remains a rare but potentially lethal complication of pregnancy. Early recognition and immediate termination of pregnancy are essential to improve maternal and fetal outcomes.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Gang Qin, Center for Liver Diseases, The Nantong Third People's Hospital, Nantong University, 9 Seyuan Road, Nantong 226019, Jiangsu, China. Tel: +86 189 1228 8106; E-mail: tonygqin@ntu.edu.cn

References

[1] Castro MA, Fassett MJ, Reynolds TB, Shaw KJ, Goodwin TM. Reversible peripartum liver failure: a new perspective on the diagnosis, treatment, and cause of acute fatty liver of pregnancy, based on 28 consecutive cases. Am J Obstet Gynecol 1999; 181: 389-395.

[2] Knight M, Nelson-Piercy C, Kurinczuk JJ, Spark P, Brocklehurst P; System UKOS. A prospective national study of acute fatty liver of pregnancy in the UK. Gut 2008; 57: 951-956.

[3] Ogston A. Acute yellow atrophy of the liver, abortion, and post mortem examination of mother and foetus. Br Med J 1873; 1: 57.

[4] Sheehan HL. The pathology of acute yellow atrophy and delayed chloroform poisoning. J Obstet Gynaecol Br Emp 1940; 47: 49-62.

[5] Rajasri AG, Srestha R, Mitchell J. Acute fatty liver of pregnancy (AFLP)--an overview. J Obstet Gynaecol 2007; 27: 237-240.

[6] Vigil-De Gracia P, Lavergne JA. Acute fatty liver of pregnancy. International Journal Of Gynaecology and Obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2001; 72: 193-195.

[7] Fesenmeier MF, Coppage KH, Lambers DS, Barton JR, Sibai BM. Acute fatty liver of pregnancy in 3 tertiary care centers. Am J Obstet Gynecol 2005; 192: 1416-1419.

[8] Ch'ng CL, Morgan M, Hainsworth I, Kingham JG. Prospective study of liver dysfunction in pregnancy in Southwest Wales. Gut 2002; 51: 876-880.

[9] Chatel P, Ronot M, Roux O, Bedossa P, Vilgrain V, Bernuau J, Luton D. Transient excess of liver fat detected by magnetic resonance imaging in women with acute fatty liver of pregnancy. Am J Obstet Gynecol 2016; 214: 127-129.

[10] Varner M, Rinderknecht NK. Acute fatty metamorphosis of pregnancy. A maternal mortality and literature review. J Reprod Med 1980; 24: 177-180.

[11] Moldenhauer JS, O'Brien J M, Barton JR, Sibai B. Acute fatty liver of pregnancy associated with pancreatitis: a life-threatening complication. Am J Obstet Gynecol 2004; 190: 502-505.

[12] Qin G, Shao JG, Wang B, Shen Y, Zheng J, Liu XJ, Zhang YY, Liu YM, Qin Y, Wang LJ. Artificial liver support system improves short- and long-term outcomes of patients with HBV-associated acute-on-chronic liver failure: a single-center experience. Medicine 2014; 93: e338.

[13] Ding J, Han LP, Lou XP, Geng LN, Liu D, Yang Q, Gao S. Effectiveness of combining plasma exchange with plasma perfusion in acute fatty liver of pregnancy: a retrospective analysis. Gynecol Obstet Invest 2015; 79: 97-100.

[14] Yu CB, Chen JJ, Du WB, Chen P, Huang JR, Chen YM, Cao HC, Li LJ. Effects of plasma exchange combined with continuous renal replacement therapy on acute fatty liver of pregnancy. Hepatobiliary Pancreat Dis Int 2014; 13: 179-183.