Acute Fatty Liver of Pregnancy: Incidence and Clinical Evolution in Toluca, Mexico

José Meneses-Calderón, MD*†; Jazmin Meneses-Figueroa, MD†;
Jesús Carlos Briones-Garduño, MD, MSc*; María José Vargas-Contreras, MD†;
Cecilia Veneranda Contreras-Herrera, MD†; Hugo Mendieta-Zerón, MD, MSc, PhD*†

Objective: The objective of this study was to determine the incidence and evolution of patients with acute fatty liver of pregnancy (AFLP) over a period of 18 years in the city of Toluca, Mexico.

Methods: This was a descriptive and retrospective study of eighteen years. All women with AFLP confirmed by biopsy were included and the incidence, laboratory test values and complications were registered.

Results: AFLP incidence was of 1 case for every 8,451 deliveries. The main complications were bleeding, infections and neurological compromise. The mortality was of 33.33%.

Conclusion: It can be concluded that AFLP has a slightly lower incidence in Mexico than that reported in other countries but with a higher survival. This condition deserves a multidisciplinary team to improve the survival rate.

[P R Health Sci J 2024;43(4):221-225]

Key words: Acute fatty liver of pregnancy, Diagnosis, Incidence, Survival

Pregnant woman with jaundice represents a diagnostic challenge, and identifying the causal factors and making an early diagnosis to establish early management and avoid complications in the maternal-fetal state are the priority. Interestingly, 3 to 5% of pregnant women may manifest liver function tests abnormalities, however, only 0.1% present with jaundice (1).

In 1843, Rokitansky originally described AFLP as an "acute yellow atrophy" of the liver in an autopsy case upon observing a significant decrease in the organ size, however, it was Sheehan in 1940, who identified the fat accumulation in hepatocytes and reported that this process was inevitably fatal and constituted a distinct clinicopathological entity (2). Currently, the normal fat content in the liver is approximately 5% in women, however, with AFLP it increases to 13 to 19% (3). Until 1983, 135 histologically proven cases in the world literature had been published (4). In the 1980s, the AFLP incidence was 1 in every 13,000 pregnancies (5).

Abnormalities in fatty acid oxidation (FAO) at the intramitochondrial level have been implicated in AFLP etiology (6,7). Long-chain 3-hydroxyacyl-CoA-dehydrogenase (LCHAD) deficiency was identified in 20% of children with mothers with AFLP; however, FAO abnormalities were noted in 15 of 27 children born to mothers with AFLP (8). Furthermore, during the steroidogenesis process, the placenta produces fatty acids that significantly increase its presence in the maternal circulation, thereby leading to deleterious effects (9). Moreover, the deficiency of other enzymes that participate in beta-oxidation, including carnitine palmitoyltransferase has been implicated as a cause of AFLP-like liver failure. These enzyme deficiencies increase the levels of long-chain fatty acids and their deposit within the hepatocyte (10). Defects in beta-oxidation are reflected by urinary organic acid and plasma carnitine and acylcarnitine level elevation following an overnight fast (11).

AFLP is a diagnosis of exclusion supported by identifying 6 or more of the 14 Swansea criteria (12, 13) listed in the next groups: A) Clinical criteria: abdominal pain, encephalopathy, polydipsia/polyuria and vomiting, B) Paraclinical: ascites or bright liver on ultrasound scan, coagulopathy (prothrombin time (PT) >14 seconds and/or activated partial thromboplastin time (APTT) > 34 seconds), hyperammonemia >47 μmol/L, hyperbilirubinemia >14 μmol/L, hyperuricemia >340 μmol/L, hypoglycemia < 4 mmol/L, renal impairment (increased creatinine >150 μmol/L), increased transaminase level (aspartate aminotransaminase or alanine aminotransferase > 42 U/L), leukocytosis > 11 000/mm3 and C) Histopathological criteria: microvesicular steatosis on liver biopsy.

In pathological studies before the Swansea criteria were published, the biopsy identification of the microvesicular fat deposit in hepatocytes, in the absence of significant inflammation or necrosis were associated with AFLP. In severe cases alterations in the lobular architecture, hepatocyte loss, reticulin collapse, and inflammation of the portal spaces with varying degrees of necrosis are observed. Moreover, microvesicular steatosis can be visualized using special stains for fat (oil red O or Sudan black) on frozen tissue sections (14). Isolated reports of electron microscopy with microvesicular steatosis as well as the presence of osmophilic droplets and giant mitochondria are available (15); therefore, several authors have suggested mitochondrial dysfunction as part of AFLP (16). Nowadays, liver biopsy is rarely indicated.

*"Mónica Pretelini Sáenz" Maternal Perinatal Hospital, Health Institute of the State of Mexico, Av. Paseo Tollocan, Poniente 201, Universidad, 50010, Toluca, Mexico; †Faculty of Medicine, Autonomous University of the State from Mexico, Av. Paseo Tollocan, Moderna de la Cruz, 50180, Toluca, Mexico

The authors have no conflict of interest to disclose.

Address correspondence to: Hugo Mendieta-Zerón, MD, PhD. Research Department "Mónica Pretelini Sáenz" Maternal-Perinatal Hospital. Paseo Tollocan s/n. Col. Universidad, Toluca, Mexico, C.P. 50010. Email: drmendietaz@yahoo.com

Early diagnosis, early resolution of pregnancy, and intensive care unit (ICU) support are involved in AFLP management. Once the patient is stabilized, fetal extraction by vaginal delivery, if tolerated, is the priority; however, cesarean section is the most common interruption owing to the rapid maternal–fetal state deterioration. Postpartum consumption coagulopathy, acute kidney failure, pancreatic pseudocyst, fulminant liver failure, and hepatic rupture secondary to massive necrosis are the most common complications (14,17,18,19,20). This study aimed to determine the evolution of patients with this disease over an 18-year period in Toluca, Mexico.

Methods

This was a descriptive and retrospective study performed in the following two periods over 18 years: the first in the ICU of the "Lic. Adolfo López Mateos" General Hospital (1992–2008) and the second in the obstetric ICU of the "Mónica Pretelini Sáenz" Maternal Perinatal Hospital (HMPMPS) (2009–2010), Health Institute of the State of Mexico (ISEM), Toluca, Mexico.

During the period of review, all women with AFLP confirmed by biopsy were included and those who died within the first 24 hours of arriving at our hospital were excluded. The Ethics in Research Committee of the HMPMPS approved the study protocol (November 2021). Informed consent was waived as medical data were obtained from historical files. Statistical analysis was performed using Excel software.

Table 1. General characteristics of six patients with acute fatty liver of pregnancy

Variable	Case number and year of presentation					
	1 (1992)	2 (1994)	3 (1996)	4 (1999)	5 (2004)	6 (2010)
Age (years)	17	18	23	31	23	25
Gestational age (weeks)	38	38	32	35	29.3	36.2
Sex or the baby	Female	Female	Male	Female	Male	Female
Maternal Body Mass Index (kg/m^2)	27.1	29.0	33.8	31.3	24.7	33.8
P/V/A/C	1/1/0/0	5/3/0/2	3/2/0/1	5/4/0/1	1/1/0/0	1/0/0/1
Maternal death	+	+	-	-	-	-
Fetal death	+	+	-	-	+	-
Abdominal pain	+	+	+	+	+	+
Acute renal failure	+	-	+	+	+	+
Coagulopathy	+	+	+	+	+	+
Edema	+	-	+	+	+	+
Encephalopathy	+	+	+	+	+	+
Hypoglycemia	+	+	+	+	+	+
Jaundice	+	+	+	+	+	+
Nausea and vomiting	+	+	-	+	+	+
Preeclampsia/Eclampsia	+	+	-	-	-	+
Premature abruption of a normoinserted placenta	-	+	-	+	-	-
Rhythm and heart-conduction disorders	-	-	Heart-conduction disorders	Rhythm disorder	-	-
Transvaginal bleeding	+	+	+	-	+	-
Upper gastrointestinal bleeding	+	-	+	-	-	+

P/V/A/C: pregnancies/vaginal deliveries/abortions/cesareans.

Results

For 18 years, 50,709 deliveries were attended, and six cases of AFLP were confirmed. All six AFLP cases were corroborated by histopathological study, leading to an incidence of 1 case in every 8,451 deliveries. The general characteristics of the patients are presented in Table 1.

Laboratory tests showed the following values, as expressed in means (ranges albumin, 1.5 (0.9–2.1) g/dL; alkaline phosphatase, 410 (167–792) IU/L; alanine aminotransferase, 543 (87–1,100) IU/L; aspartate aminotransferase, 1,483 (115–4,630) IU/L; bilirubin, 15.2 (7.4–26.8) mg/dL; creatinine, 3.2 (1–4.5) mg/dL; glucose, 51 (39–63) mg/dL; hemoglobin, 8.0 (5.3–9.7) g/dL; leukocytes, 24.4 (16–30.3) × 103 cells/μL; platelets, 75.6 (20–427) × 103 cells/μL; PT, 9.9 (5.4–14.5) s; and uric acid, 13.7 (11.9–18.4) mg/dL.

The main complications (in number of events) included bleeding, 21; infections, 8; neurological compromise, 7; lung damage, 6; metabolic alterations, 3; rhythm and heart conduction disorders, 3; ascites, 3; hypovolemic shock, 3; and others, 9. The time wherein the laboratory alterations were normalized in the four surviving patients is shown in Table 2.

Discussion

As this study included patients since 1992, it is important to note that the Swansea criteria had not been published during this time and that liver biopsy was performed for confirming AFLP diagnosis. A study by Goel et al. in 2012 (20 years after the first group of patients included in our study) still expressed doubts regarding using the Swansea criteria for AFLP diagnosis without liver biopsy (21). The AFLP incidence reported in the present study (1 case in every 8,451 pregnancies) was slightly less than that reported in a previous study (1 case in every 6,659 pregnancies) (22).

Most patients with AFLP are in the third trimester of pregnancy with a mean gestational age of 35.5 (range, 28–40) weeks (23); isolated reports in later periods such as the immediate postpartum are available (24). In our patients, the mean gestational age was 34.75 weeks, which is consistent with prior reports.

Table 2. Time to laboratory normalization after pregnancy resolution (days) in four surviving AFLP patients

Number of case	1 (1996)	2 (1999)	3 (2005)	4 (2010)	Mean
Protrombin time (≤ 3 seconds)	1	1	1	1	1
Platelet (≥ 100 000 x mm^3)	11	7	6	7	7.7
Aspartate aminotransferase (≤ 40 IU/L)	65	7	20	29	30.2
Alanine aminotransferase (≤ 35 IU/L)	65	7	20	29	30.2
Glucose (≥ 110 mg/dl)	33	5	6	14	14.5
Albumin (≥ 3.4 g/dl)	19	10	13	13	13.7
Creatinine (≤ 1.2 mg/dl)	25	27	3	16	18.5

AFLP: acute fatty liver of pregnancy.

AFLP shows a certain predilection for nulliparous women, multiple pregnancies, and when the product of conception is a male (25). In this study, the finding that three of our patients were primiparous and three were multigravida women supports this notion.

The initial manifestations of AFLP are nonspecific and frequently misinterpreted, including nausea and vomiting (70%), pain in the right upper quadrant or epigastrium (50%–80%), or a syndrome virus-like with headache, malaise, fatigue, anorexia and abdominal pain that usually precede by one to two weeks, as a prodromal period to the jaundice phase; itching is rare (26,27). On physical examination, fever and jaundice are common and as the condition progresses they occur in >70% of the patients. Hypersensitivity in the right upper quadrant or epigastrium is frequently observed; however, the liver is not palpable (28). Conversely, in this study, the following variables showed 100% frequency: abdominal pain, coagulopathy, encephalopathy, hypoglycemia and jaundice. AFLP deserves special attention because without appropriate treatment, it can complicate with multisystem involvement, including fulminant liver failure, kidney failure, coagulopathy with uncontrollable uterine or gastrointestinal bleeding, pancreatitis, seizures, coma, and death (29); despite severe affliction, our patients had a 66.66% survival rate. An aspect that may influence this last data is that the regulations in Mexico establish that the mortality of an ICU is attributed to patients who complete at least a 24 h stay.

Some women may develop preeclampsia, edema, and hypertension. Furthermore, hemolysis, elevated liver enzyme levels, and low platelet (HELLP) syndrome; thrombotic thrombocytopenic purpura; and AFLP can be a spectrum of the same disease. Transient diabetes insipidus can also occur, but is very rare (30). Special care must be taken when hypofibrinogenemia as well as PT and APTT lengthening with decreased antithrombin III levels simultaneously develop, which is common in the pathology progression (31); this scenario indicates disseminated intravascular coagulation installation, an ominous sign that significantly contributes to the high morbidity and mortality of these patients.

A review by Ko et al., reported that, abnormalities in liver function tests generally include elevation in aminotransferase levels from 300 to 500 IU/L; however, an average of 1,000 IU/L and an upper range of up to 3,600 IU/L are also reported. Hyperbilirubinemia is significant with a mean of 10 mg/dL, in addition to serum ammonia elevation, lactic acidosis, and hypoglycemia secondary to liver glycogenolysis failure. Alkaline phosphatase can rise up to 10 times its normal value and blood urea nitrogen and creatinine levels increase when acute renal failure has complicated the disease progression. Surprisingly, one of our patients reached an extreme aspartate aminotransferase level (4,630 IU/L), and the mean value of bilirubin was one-third higher than that reported previously (32).

Furthermore, PT normalized within the first 24 h following the resolution of pregnancy, and platelets returned to normal levels on the eighth day following pregnancy interruption. The laboratory parameter with the longest time to return to the normal range was bilirubin (>1 month). Of note, our patients remained hypoglycemic for an average of 15 days following delivery, and one patient remained hypoglycemic for 33 days, reflecting functional liver damage. Finally, all patients had elevated creatinine levels, which took an average of 18.5 days to return to normal levels. The abovementioned data confirm the severity of liver involvement of this complication and the corresponding care to avoid major problems once the pregnancy is resolved (6).

The presence of rhythm and conduction disorders in three patients– one with a heartbeat ectopic disease that led to strokes of ventricular tachycardia (Figure 1), another with only sporadic ectopic beats, and the third with second-degree atrioventricular block–requires attention. These abnormalities may be because of myocardial microvesicular fat infiltration. The images of liver biopsies performed in our patients are shown in Figures 2 and 3.

In a previous 5-year study, the main characteristics of 86 pregnant women (50 primiparas [58.1%]; 36 multiparas [41.9%]) with AFLP included age of 30.8 ± 5.4 years and body mass index of 21.0 ± 2.5 kg/m^2. Gastrointestinal symptoms including epigastric pain (68.6%), nausea (47.7%), anorexia (46.5%), and vomiting (39.5%) were the main complaints. Jaundice of the skin and/or sclerae (54.7%), edema (38.4%), fatigue (19.8%), bleeding tendency (16.3%), polydipsia or polyuria (14.0%), and skin itching (8.1%) were the main nongastrointestinal symptoms. Only 24 cases (27.9%) showed fatty liver by imageological examination (33).

Finally, artificial liver support is an effective measure to improve severe patients' prognosis (34). As a preventive strategy,

Figure 1. Patient with AFLP and ventricular tachycardia that raced two hours after cesarean section.

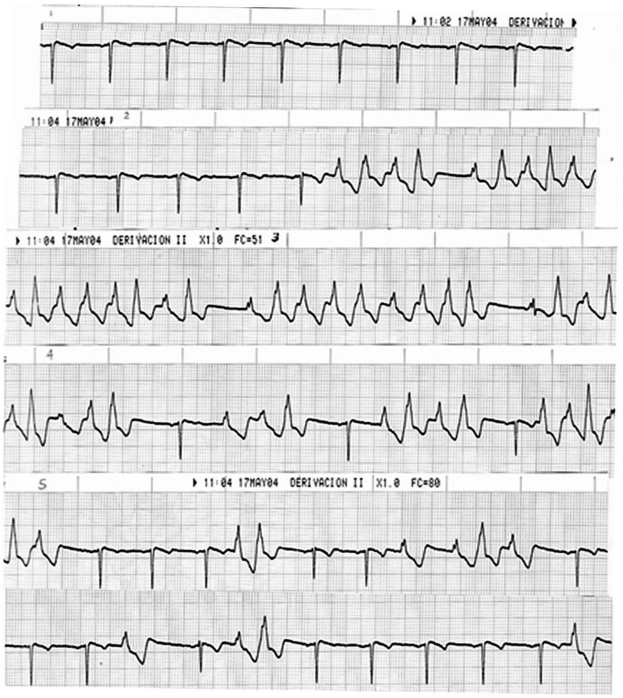


Figure 2. Hepatic biopsies of the survival patients 2 and 4. Hematoxylin-eosin staining showing fat accumulation in microvesicles with central cytoplasm.

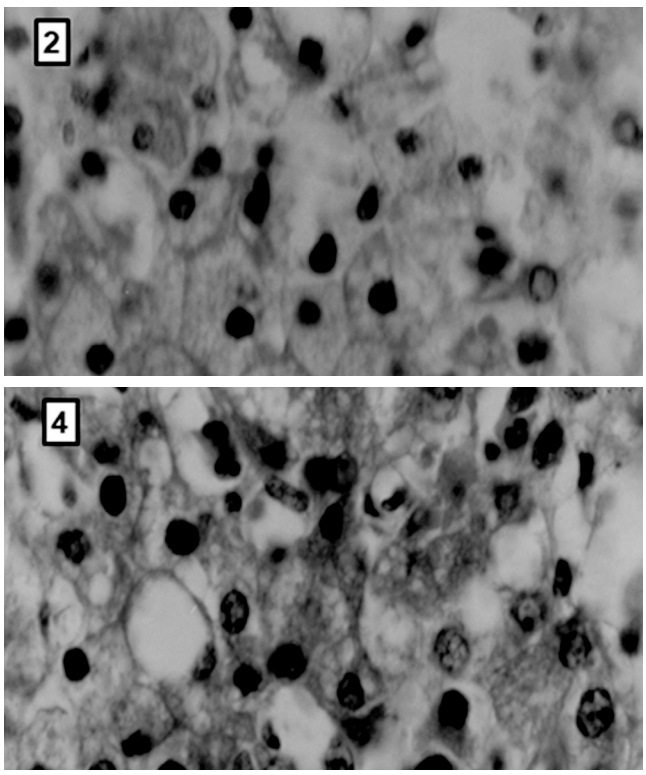
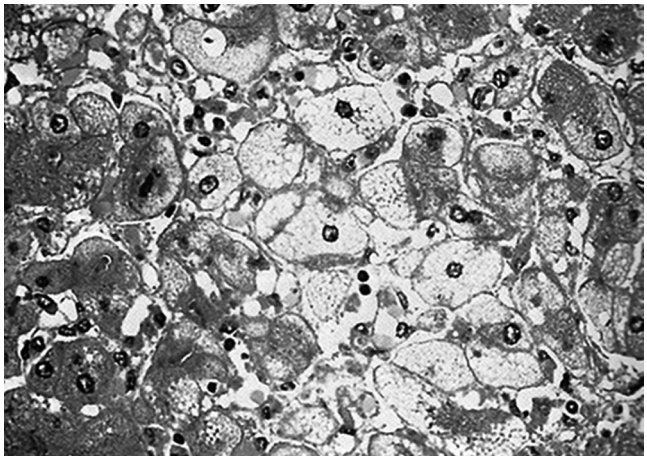


Figure 3. Hepatic biopsies of the survival patient 6 with oil red staining showing fat accumulation in the cytoplasm with multiple microvesicles and the nucleus remaining central.



usual genotyping of infants can be considered a prevention option as LCHAD deficiency in infants can be associated with maternal AFLP. The use of elastography instead of liver biopsy would also be an innovative aspect. A limitation of this study is that the exclusion criteria led to an underestimate of the actual number of AFLP cases during the studied period (35).

Conclusion

AFLP has a low incidence but a high mortality index that deserves a multidisciplinary team to improve the survival rate, which in our experience was at 66.66%.

Resumen

Objetivo: El objetivo de este estudio fue determinar la evolución de pacientes con hígado graso agudo del embarazo (HGAE) durante un período de 18 años en la ciudad de Toluca, México. Métodos: Este fue un estudio descriptivo y retrospectivo de dieciocho años. Se incluyeron todas las mujeres con HGAE confirmada por biopsia y se registró la incidencia, valores de laboratorio y complicaciones. Resultados: La incidencia de HGAE fue de 1 caso por cada 8,451 partos. Las principales complicaciones fueron hemorragias, infecciones y compromiso neurológico. La mortalidad fue del 33.33%. Conclusión: Se puede concluir que la AFLP tiene una incidencia ligeramente menor en México que la reportada en otros países pero con una mayor sobrevida. Esta condición amerita un equipo multidisciplinario para mejorar la tasa de supervivencia.

Acknowledgments

Authors thank ENAGO for the English style and grammar revision.

References

1. Hay JE. Liver disease in pregnancy. Hepatology. 2008;47(3):1067-76.
2. Sheehan H. The pathology of acute yellow atrophy and delayed choroform poisoning. J Obstet Gynaecol Brit Emp. 1940;47:49-62.
3. Vigil-De Gracia P, Lavergne JA. Acute fatty liver of pregnancy. Int J Gynaecol Obstet. 2001;72(2):193-195.
4. Hague WM, Fenton DW, Duncan SL, Slater DN. Acute fatty liver of pregnancy. J R Soc Med. 1983;76(8):652-661.
5. Pockros PJ, Reynolds TB. Acute fatty liver of pregnancy. Dig Dis Sci. 1985;30(6):601-602.
6. Sims HF, Brackett JC, Powell CK, et al. The molecular basis of pediatric long chain 3-hydroxyacyl-CoA dehydrogenase deficiency associated with maternal acute fatty liver of pregnancy. Proc Natl Acad Sci U S A. 1995;92(3):841-845.
7. Liu J, Ghaziani TT, Wolf JL. Acute Fatty Liver Disease of Pregnancy: Updates in Pathogenesis, Diagnosis, and Management. Am J Gastroenterol. 2017;112(6):838-846.
8. Treem WR, Shoup ME, Hale DE, et al. Acute fatty liver of pregnancy, hemolysis, elevated liver enzymes, and low platelets syndrome, and long chain 3-hydroxyacyl-coenzyme A dehydrogenase deficiency. Am J Gastroenterol. 1996;91(11):2293-300.
9. Natarajan SK, Thangaraj KR, Goel A, Eapen CE, Balasubramanian KA, Ramachandran A. Acute fatty liver of pregnancy: an update on mechanisms. Obstet Med. 2011;4(3):99-103.
10. Innes AM, Seargeant LE, Balachandra K, et al. Hepatic carnitine palmitoyltransferase I deficiency presenting as maternal illness in pregnancy. Pediatr Res. 2000;47(1):43-45.
11. Guntupalli SR, Steingrub J. Hepatic disease and pregnancy: an overview of diagnosis and management. Crit Care Med. 2005;33(10 Suppl):S332-S339.
12. Ch'ng CL, Morgan M, Hainsworth I, Kingham JG. Prospective study of liver dysfunction in pregnancy in Southwest Wales. Gut. 2002;51(6):876-80. doi: 10.1136/gut.51.6.876. Erratum in: Gut. 2003;52(2):315.
13. Rolfes DB, Ishak KG. Acute fatty liver of pregnancy: a clinicopathologic study of 35 cases. Hepatology. 1985;5(6):1149-1158.
14. Reyes H, Sandoval L, Wainstein A, et al. Acute fatty liver of pregnancy: a clinical study of 12 episodes in 11 patients. Gut. 1994;35(1):101-106.
15. Wanders RJ, Vreken P, den Boer ME, Wijburg FA, van Gennip AH, IJlst L. Disorders of mitochondrial fatty acyl-CoA beta-oxidation. J Inherit Metab Dis. 1999;22(4):442-487.
16. Pereira SP, O'Donohue J, Wendon J, Williams R. Maternal and perinatal outcome in severe pregnancy-related liver disease. Hepatology. 1997;26(5):1258-1262.
17. Wu Z, Huang P, Gong Y, Wan J, Zou W. Treating acute fatty liver of pregnancy with artificial liver support therapy: Systematic review. Medicine (Baltimore). 2018;97(38):e12473.
18. Shi Y, Wu H, Zhou X, et al. Analysis of clinical characteristics and genetic testing in patients with acute fatty liver of pregnancy: a retrospective study. BMC Pregnancy Childbirth. 2021;21(1):617.
19. Ye R, Mai Z, Pan X, Cai S, Deng L. Acute fatty liver of pregnancy causes severe acute pancreatitis and stillborn fetus: A case report. Medicine (Baltimore). 2021;100(16):e25524.
20. Brooks RR, Feller CM, Maye JP. Acute fatty liver of pregnancy: a case report. AANA J. 2002;70(3):215-217.
21. Goel A, Ramakrishna B, Zachariah U, Ramachandran J, Eapen CE, Kurian G, Chandy G. How accurate are the Swansea criteria to diagnose acute fatty liver of pregnancy in predicting hepatic microvesicular steatosis? Gut. 2011;60(1):138-9; author reply 139-40. doi: 10.1136/gut.2009.198465.
22. 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(2):389-395.
23. 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(5):1416-1419.
24. Jwayyed SM, Blanda M, Kubina M. Acute fatty liver of pregnancy. J Emerg Med. 1999;17(4):673-677.
25. Riely CA, Latham PS, Romero R, Duffy TP. Acute fatty liver of pregnancy. A reassessment based on observations in nine patients. Ann Intern Med. 1987;106(5):703-706.
26. Riely CA. Acute fatty liver of pregnancy. Semin Liver Dis. 1987;7(1):47-54.
27. McNulty J. Acute fatty liver of pregnancy. In: Foley MR, Strong TH, Garite TJ, editors. Obstetric Intensive Care Manual. 2. New York: The MacGraw-Hill Companies Inc 2004. pp.207.
28. Simpson KR, Luppi CJ, O'Brien-Abel N. Acute fatty liver of pregnancy. J Perinat Neonatal Nurs. 1998;11(4):35-44.
29. Kaplan MM. Acute fatty liver of pregnancy. N Engl J Med. 1985;313(6):367-370.
30. Kennedy S, Hall PM, Seymour AE, Hague WM. Transient diabetes insipidus and acute fatty liver of pregnancy. Br J Obstet Gynaecol. 1994;101(5):387-391.
31. Castro MA, Goodwin TM, Shaw KJ, Ouzounian JG, McGehee WG. Disseminated intravascular coagulation and antithrombin III depression in acute fatty liver of pregnancy. Am J Obstet Gynecol. 1996;174(1 Pt 1):211-216.
32. Ko H, Yoshida EM. Acute fatty liver of pregnancy. Can J Gastroenterol. 2006;20(1):25-30.
33. Liu CL, Chen DJ, Chen CY, Zhou XH, Jiang Y, Liu JY, Chen YE, Hu CR, Dong JJ, Li P, Wen M, Li YH, Zhang HL. [Clinical analysis of 86 cases of acute fatty liver of pregnancy]. Zhonghua Fu Chan Ke Za Zhi. 2023;58(12):896-902.
34. Peng Q, Zhu T, Huang J, Liu Y, Huang J, Zhang W. Factors and a model to predict three-month mortality in patients with acute fatty liver of pregnancy from two medical centers. BMC Pregnancy Childbirth. 2024;24(1):27.
35. Lim SM, Kim SU. Acoustic radiation force impulse elastography is useful to exclude nonliver-related ascites. Eur J Gastroenterol Hepatol. 2011;23(11):1080-1.