Acute fatty liver of pregnancy: the multidisciplinary approach

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In the article defined the modern views on the etiology and pathogenesis of acute fatty liver. The main clinical features of the course of the disease in pregnant women were obtained. It highlighted the need for the formation of a multidisciplinary approach to address the tactics of patients with this pathology and describes the main differential laboratory and clinical criteria for acute fatty degeneration and HELLP-syndrome. The article shows the need for genetic studies of the parents and child to identify the genes responsible for disease development. A case of pregnancy, childbirth and the postpartum period in patients with acute fatty liver was described.
Key words: *acute fatty liver, pregnancy, diagnostics, treatment.*

Nevertheless the impressive achievements in the diagnostics and intensive care the acute fatty liver of pregnancy (AFLP) remains to be potentially life-threatening complication manifesting in the third trimester of pregnancy and ***early postpartum period***. The high risk group for AFLP includes: primigravida, multiple pregnancy, and pregnancies carrying a male fetus. The data concerning the maternal mortality is now estimated to be 12.5–36%, but a neonatal mortality rate of 7–66% [1, 2].

According to the most recent data the incidence of AFLP is being considered as 1:7,000 to 1:16,000 pregnancies. The latest prospective research study in the United Kingdom, performed in 229 centers confirmed 57 cases of AFLP in 1132964 pregnancies, and according to this trial, the incidence of AFLP is 5 in 100 000 pregnancies. It means that the inadequate awareness for this rare and sometimes fulminant developing pathology could become the crucial challenge for the perinatal, neonatal and intensive care teams. In the same study the majority of cases (74%) were proceded at a median gestational age of 36 weeks, and in 60% of cases the immediate delivery performed within 24 h of the diagnosis statement. The abdominal delivery rate was 74% [3, 4].

The «underwater rocks» of AFLP.

1. The pathology is rare.

2. The etiology is not still completely clear.

3. The delay of the diagnosis and «crisis team reaction» could become fatal for mother and child.

This the **key point**: the etiology of AFLP has nothing mutual with the hypertensive disorders of pregnancy (preeclampsia and HELLP-syndrome), so, the clinical strategy in AFLP should be more aggressive, more rapid and more specialists in other fields (surgery, hepatology, transplantation) has to be involved. We have to emphasize that the etiology of AFLP remains unknown, but the evident data confirm the hepatic damage caused by defects in the activity of long chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD) and this fact absolutely explains the difference between AFLP and preeclampsia origins [5, 6].

The rarity of the disease and it's rapid progression could be explained by the interaction between an LCHAD activity-deficient female and similarly deficient fetus, because the toxins produced from aberrant fatty acid oxidation aggressively damage the maternal liver with the development of hepatic microvesicular steatosis [5, 6].

The clinical presentation.

We analyzed the retrospective comparison of the seven cases from the Chinese study and the pregnancy outcomes of the 126 cases from the Medline-based Knowledge Infrastructure search for the period 2000–2008 from the available database. The incidence of the main clinical symptoms in the Chinese study is presented in the Table 1. The total demographic data and pregnancy outcomes from the Medline-based Knowledge Infrastructure search are presented in the Table 2. The detailed information about the pregnancy period and perinatal outcomes from the Indian study is represented in Table 3 [3, 4].

We revealed the most common clinical complications in AFLP: renal insufficiency in all patients; hepatic failure and multiple organ dysfunction syndrome (MODS), hypoglycemia, disseminated intravascular coagulation (DIC) failure in 4 patients (57.1%), hemorrhagic shock, acute respiratory distress syndrome (ARDS), and hepatic encephalopathy were seen in 3 patients (42.8%) [3, 4].

According to the presented data, 109 (86.5%) deliveries performed by abdominal approach, and maternal mortality rate was 12.8%. Among the patients vaginally, 35.2% women died. Concerning the perinatal outcomes we have to evaluate, that 8,9% neonates died after the cesario section (CS) and 28% - after the vaginal deliveries [3, 4].

The complications associated with AFLP in the Chinese study are presented in Table 4.

The clinical and laboratory tests in AFLP.

The pattern of necessary laboratory tests for diagnosis of AFLP should include at least six or more of the following features if there is no other explanation: vomiting, abdominal pain, polydipsia/polyuria, encephalopathy, elevated bilirubin (>14 mmol/L), leukocytosis (>11×10^9/L), elevated uric acid (>340 mmol/L), low glucose (<4 mmol/L), ascites on ultra-

Table 1

Clinical manifestations of AFLP in the Chinese study

Symptoms	Patient I	Patient II	Patient III	Patient IV	Patient V	Patient VI	Patient VII
Vomiting (85,7%)	+		+	+	+	+	+
Epigastric pain (85,7%)	+	+	-	+	+	+	+
Jaundice (100%)	+	+	+	+	+	+	+
Polydipsia (57,1%)	+	+	-	+	-	-	+
Pruritis (42,8%)	+	-	-	+	-	+	-
Encephalopathy (stage 0-IV)	II	0	0	0	III	0	II

Table 2

The overall summary of the 126 cases of AFLP (Medline-based Knowledge Infrastructure search)

Particulars	cases	cases	value	test
Maternal age (years)	26 years (Range, 21-32)	27 years (Range, 21-37)		
Mean gestational age (weeks)	36 weeks (Range, 32-38)	36 weeks (Range, 28-38)		
Primigravida	85.7 (6/7)	74.6 (94/126)	0.837	0.045
Multigravida	14.2 (1/7)	25.4 (32/126)		
Mode of delivery				
Cesarean section	71.4 (5/7)	86.5 (109/126)	0.579	0.308
Vaginal delivery	28.5 (2/7)	13.4 (17/126)		
Complications				
Hypoglycemia	57.1 (4/7)	41.2 (52/126)	0.664	0.189
Acute renal insufficiency	100 (7/7)	50.7 (64/126)	0.031	4.626
ARDS	42.8 (3/7)	40.4 (51/126)	1	0
Coagulopathy	57.1 (4/7)	78.5 (99/126)	0.392	0.732
Encephalopathy	42.8 (3/7)	46 (58/126)	1	0
MODS	57.1 (4/7)	30.1 (38/126)	0.281	1.16
Outcomes				
Maternal death				
Cesarean section	20 (1/5)	12.8 (14/109)	0.513	
Vaginal delivery	0 (0/2)	35.2 (6/17)	1	
Perinatal/postnatal death				
Cesarean section	28.5 (2/7)	8.9 (12/134)	0.144	
Vaginal delivery	66.6 (2/3)	28 (7/25)	0.234	

ARDS: Acute respiratory distress syndrome; MODS: Multiple organ dysfunction syndrome

Table 3

The peculiarities of the pregnancy period and perinatal outcomes the Chinese study

Patient Number	Age (years)	Gravida and parity	Onset of symptoms (gestational weeks	Interval between first symptoms and delivery (days)	Mode of delivery	Fetal sex	Fetal weight (g)	Apgar score at one and five minutes
I	27	G_{1P0}	34	14	CS	M M	1800 1850	4-7 3-7
II	25	G_{1P0}	36	3	V	F F	2110 2385	Stillborn Postnatal death
III	21	G_{1P0}	36	10	V	M	2150	5-7
IV	22	G_{1P0}	38	6	CS	M	2950	Stillborn
V	32	G_{4P3}	32	9	CS	M M	1620 1420	5-7 4-7
VI	29	G_{1P0}	38	5	CS	M	2600	Stillborn
VII	26	G_{1P0}	38	8	CS	M	2510	3-7

V: vaginal delivery; CS: caesarean section

sound scan, increase in the level of transaminases (aspartate aminotransferase or alanine aminotransferase >42 IU/L), renal impairment (creatinine >150 мmol/L), elevated ammonia (>47 mmol/L), coagulopathy (prothrombin time >14 sec or activated partial thromboplastin time >34 sec), and microvesicular steatosis on liver biopsy. The results of the laboratory tests in the Chinese study are represented in Table 5 [3, 4].

We have to emphasize that the most importatnt peculiarity of AFLP (opposite to HELLP-syndrome) is a high level of bilirubin associated with moderate increases of AST, ALT. The thrombocytopenia could be seen with or without other signs of disseminated intravascular coagulation (DIC).

As to the published data, nearly 90% of the women with AFLP had an abdominal ultrasound examination with classical signs of ascites or bright liver seen in 25% of cases. So, hepatic ultrasound is considered like not sufficiently sensitive or specific to make a definite diagnosis of AFLP [7, 8].

The challenge of the diagnosis of AFLP could be explained by nospecificity of the initial clinical presentation, so the symptoms and biochemical abnormalities may be similar for such conditions as acute viral hepatitis, pre-eclampsia, HELLP syndrome, intrahepatic cholestasis or gull-stone disease [1, 7, 8].

The AFLP is rare and uncommon, so the best approach to any pregnant women with the evidence of any liver dysfunction is to rapid excluding other causes. Women with AFLP can also have pre-eclampsia, but patients with only pre-eclampsia do not present jaundice and hypoglycemia usually. The development of AFLP is more acutely than pre-eclampsia, and patient with pre-eclampsia rarely presents with severe coagulopathy (DIC). In cases of viral hepatitis, patients usually have much higher levels

Table 4

Complications associated with AFLP from the Chinese study

Findings	Number of patients ( )	Percentage (%)
Hypoglycemia	4	57.1
Acute renal insufficiency	7	100
DIC	4	57.1
Ascites	2	28.5
Liver failure	4	57.1
Hepatic encephalopathy	3	42.8
ARDS	3	42.8
Hemorrhagic shock	3	42.8
Pulmonary Edema	1	14.2
Sepsis	1	14.2
Metabolic acidosis	2	28.5
MODS	4	57.1
IGT	1	14.2
Maternal death	1	14.2

Table 5

Results of blood biochemistry and hematology during acute phase of AFLP

Findings	Mean±S.D	Range
Aspartate aminotransferase (U/L)	175,7±48,8	119-246
Alanine aminotransferase (U/L)	112,3±34,1	60-178
Lactic dehydrogenase (U/L)	315,7±73	234-428
Total bilirubin (mol/L)	327,1±173	158.2-526
Direct bilirubin (mol/L)	182,6±60,2	110-246
Blood urea nitrogen	24±3,4	20-29
Prothrombin time (INR)	17±7,3	6.2-26.4
Thrombin time	29,3±3,8	25.5-35.4
Partial thromboplastin time (s)	52,4±9,0	36.2-60.4
Fibrinogen (g/L)	0,9±0,4	0.6-1.5
Total Protein (g/L)	40,3±4,7	34-48
Creatinine (mol/L)	306±83,7	218-441
Uric acid (mol/L)	671,5±56	598-788
Glucose (mmol/L)	3,1±1,5	0.9-5.1
WBC ($\times 10^9$/L)	15,4±3,8	10.3-18.8
Platelets ($\times 10^9$/L)	39,5±9,3	33-56

of serum transaminases, (>1000 U/L), and serology tests for hepatitis would be positive,but uric acid levels are rarely elevated in fulminant hepatitis,as well as signs of pre-eclampsia are absent in viral hepatitis. In case of ICP (intrahepatic cholestasis of pregnancy) the jaundice could be presented, but ICP is characterized by intense pruritus and elevated alkaline phosphatase, but abdominal pain, nausea, vomiting, liver failure or disseminated intravascular coagulation are uncommon in this pathology [7, 8].

Case-report

Patient S., 29 years of old was transferred from the Oblast Hospital with the diagnosis: Pregnancy 33 weeks, hepatosis of pregnant, toxic hepatitis. G4P1 (cesario section 5 years ago, HELLP-syndrome in 38 weeks of pregnancy, male neonate 2620 g – 48 sm, died in 3 months), missed abortion 8 weeks, miscarriage 5 weeks.

The onset of symptoms was at 33 weeks of pregnancy: nausea, vomiting, weakness. On the 5-th day the AST (2N) and ALT (3N) were elevated, with further rapid augmentation for 5N and 6N respectively. The elevation of bilirubin was detected as well as the first signs of coagulation disorders, thrombocytopenia. Taking into consideration the history of the patient, rapid worsening of the laboratory parameters, raising weakness, the decision about the urgent cesario section was established and the surgeon-hepatologist from the National Institute of the surgery and transplantation was included to the obstetric team. The perinatal outcomes are presented in the Table 6.

The postpartum period was complicated by coagulation disorders, she wastreated in ICU with adequate aggressive supportive therapy: correction of liver function, therapy to impact on the jaundice reduction, therapy to diminish liver enzymes, correction for coagulation dysfunction, including human prothrombin complex for intravenous injection (Octaplex), and antibiotic therapy (carbapenems). The patient was discharged from the ICU on the 7-th day and from the hospital with the child on the 22-th day.

According to the data of the genetic testing of the child, the LCHAD deficiency (HADHA gene, coding alpha subunit long chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD) in the common mutation c.1528G>C (Glu474-Gln, p.E474Q) was proved, it means that a gene was inherited from both parents,

Table 6

The peculiarities of the pregnancy period and perinatal outcomes in our case of AFLP

Patient	Age (years)	Gravida and parity	Onset of symptoms (weeks of pregnancy)	Interval between first symptoms and delivery (days)	Mode of delivery	Fetal sex	Fetal weight (g)	Apgar score at one and five minutes
S.	29	G_4P_1	33	6	CS	M	2030	4-5

Table 7

The algorithm for the AFLP management

	Pre-delivery	Delivery	Post-partum
Emergency care Department	+ – stabilization of maternal state – rapid diagnostics (at least six clinical and laboratory criteria) – urgent pregnancy termination	+ – If there is no time for cervix preparedness – Cesario section The risk of postpartum hemorrhage in AFLP is high, so the hysterectomy and uterine artery embolization should be considered in case of emergency delivery (abdominal or vaginal)	+ – The improvement of the majority of AFLP patients is being observed soon after delivery – If the hepatic encephalopathy has developed the recovery is more long – Patients with encephalopathy, deep jaundice, or prothrombin times less than 40% of control, patients with any extrahepatic complication should be under observation in the ICU – The risk of sudden hypoglycemia can occur at any time,so the glucose infusions should be supplied – Patients with thrombocytopenia would require platelets trasfusion and fresh frozen plasma infusions – Nota Bene! Prothrombin time and blood glucose levels should be monitored daily or twice per day – All the other supportive care should be provided according to evident clinical symptoms
Multidisciplinary approach	«Crisis reaction team» – obstetrician, specialized on high risk pregnancy, anesthesiologist, neonatologist, surgeon, specialized in liver disease, transplantologist (in rare cases)		
Gene test for partners and child	HADHA gene, mutation c.1528G>C (Glu474-Gln, p.E474Q)		
Family planning	– After any episode of AFLP, women and her family should be informed about the risk of it's recurrence – The regular monitoring of the main biomarkers (AST,ALT, BIL, GLU) should be performed during the next pregnancy **even if the gene test result of HADHA gene mutation is negative**		

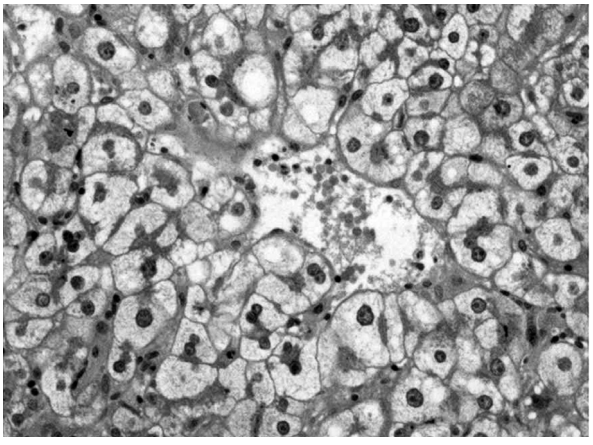
because the LCHAD deficiency is a rare autosomal recessive disorder. The special recommendations for feeding were given to the child, considerably to his impossibility to metabolize fats. The additional gene test proved the presence of this pathology in woman and her partner. So, we can suppose retrospectively, that the first pregnancy was affected not by the HELLP-syndrome, but it was the late onset of the AFLP, resulted in the birth of the child with inherited LCHAD deficiency and mitochondrial pathology.

It should be explained by the negative impact of toxic products of LCHAD deficiency, which are accumulated in the mitochondria and can become the cause of degeneration and fatty infiltration of muscle fibres, which would affect both skeletal and cardiac muscle development. The liver of the child becomes enlarged with lipid depositions within the hepatocytes and the progressive jaundice is associated with impaired bilirubin metabolism. This inherited LCHAD deficiency presents clinically in the neonatal period with severe liver failure, cardiomyopathy and hypoketotic hypoglycemic encephalopathy. All these symptoms may be irreversible. So, the diet with low long-chain fatty acids and supplemented with medium-chain triglycerides is recommended. Such dietary correction can lead to the long-term prognosis, but not in preventing irreversible changes.

As to the data obtained during last decades men and women often do not know whether they are a carriers of this changed (mutated) gene, because their metabolism is able to continue to metabolize fatty acids normally. But, when both partners carry the gene and both genes are passed on to the baby, the baby is then unable to metabolize some fatty acids and a build-up can occur in the womb, then the un-metabolized free fatty acids return from the baby, crossing the placenta, to the maternal blood stream, being the cause of the hepatic stress for the mother, fat infiltrations to build up in the liver (Picture) [5, 6].

KEY POINTS IN AFLP MANAGEMENT (see Table 7).

There are very few cases of liver transplantation performed for AFLP. The data from the American United Network for Organ Sharing (UNOS) database for the HELLP syndrome proved that within the period between 1987 and 2003, there were only eight liver transplants performed for this pregnancy-associated condition. The authors suggested that orthotopic liver transplantation should be performed [7] for those women with fulminant hepatic failure due to AFLP, who manifest signs of irreversible liver failure despite delivery and aggressive supportive care and for those patients with hepatic encephalopathy, severe metabolic acidosis, worsening coagulopathy with liver rupture complicated by hepatic necrosis as indicated by computed tomography.



Acute fatty liver, micrivesicular steatosis (bioptate)

Острая жировая дистрофия печени при беременности: мультидисциплинарный подход

Ю. Давыдова, Р. Ткаченко, А. Лиманская, А. Огородник

В статье приведены современные взгляды на этиологию и патогенез развития острой жировой дистрофии печени. Определены основные клинические особенности течения данного заболевания у беременных. Выделена необходимость формирования мультидисциплинарного подхода для решения вопросов тактики ведения пациентов с данной патологией, а также описаны основные дифференциальные лабораторные и клинические критерии острой жировой дистрофии и HELLP-синдрома. Определена необходимость генетических исследований как родителей, так и ребенка, для определения генов, ответственных за развития этого тяжелого осложнения беременности. Описан случай ведения беременности, родов и послеродового периода у пациентки с острой жировой дистрофией печени.

Ключевые слова: *острая жировая дистрофия, беременность, диагностика, лечение.*

Гостра жирова дистрофія печінки при вагітності: мультидисциплінарний підхід

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У статті наведені сучасні погляди на етіологію та патогенез розвитку гострої жирової дистрофії печінки. Визначено основні клінічні особливості перебігу даного захворювання у вагітних. Виділена необхідність формування мультидисциплінарного підходу для вирішення питань тактики ведення пацієнтів з даною патологією, а також описані основні диференціальні лабораторні та клінічні критерії гострої жирової дистрофії і HELLP-синдрому. Визначено необхідність генетичних досліджень як батьків, так і дитини, для визначення генів, відповідальних за розвиток цього важкого ускладнення вагітності. Описаний випадок ведення вагітності, пологів та післяпологового періоду у пацієнтки з гострою жировою дистрофією печінки.

Ключові слова : *гостра жирова дистрофія, вагітність, діагностика , лікування.*

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Статья поступила в редакцию 11.09.2015