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Acute fatty liver with pancreatitis in pregnancy after *in vitro* fertilization – literature review and case report

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ABSTRACT. – BACKGROUND: Acute fatty liver disease in pregnancy (AFLP) is a low-incidence condition that usually affects women in the third trimester of pregnancy or the early postpartum period. This article reviews recent advances in the diagnosis and treatment of AFLP with pancreatitis in pregnancy induced by *in vitro* fertilization (IVF).

CASE REPORT: A rare case of AFLP and pancreatitis occurred in a pregnant woman with an IVF-induced twin pregnancy delivered by cesarean section. Diagnosis of this condition is difficult, and delay in accurate diagnosis and timely and appropriate treatment can lead to serious complications such as acute pancreatitis or extensive damage to multiple organs and systems, which can have significant consequences. The main therapeutic approach was the rapid administration of drugs accompanied by therapeutic measures to support liver function and pancreatic complications.

CONCLUSIONS: We would like to reemphasize the importance of multidisciplinary management and rapid intervention in AFLP with acute pancreatitis after IVF.

Key Words:
Acute fatty liver, Pregnancy, Pancreatitis, *In vitro* fertilization.

Introduction

Liver dysfunction in pregnancy can occur for a variety of reasons and its incidence can widely vary geographically. In general, liver disease can be divided into pregnancy-specific liver disease, pregnancy-associated liver disease, and liver disease during pregnancy[1].

Acute fatty liver disease in pregnancy (AFLP) is defined as a rapidly progressive icteric syndrome that occurs predominantly in the third trimester of pregnancy or immediately after delivery and is characterized by hepatic microsteatosis, hepatocytic flatulence, minimal necrosis or hepatocellular inflammation[2,3]. The initial symptoms in patients are jaundice of the skin and sclera, abdominal pain, nausea, and vomiting. Clinically, AFLP is a syndrome characterized by a rapid deterioration of liver function with the appearance of encephalopathy and coagulopathy in a patient who has not been diagnosed with pre-existing liver disease[4].

This clinical picture was first described by Sheehan[5] in 1940 as "acute yellow atrophy" of the liver and was initially considered fatal due to coagulopathy and multiple organ dysfunction. However, thanks to scientific advances in medicine, it has recently become possible to diagnose AFLP as early as possible, improving prognosis and maternal mortality through the timely initiation of appropriate treatment[3].

Today, maternal mortality is estimated at 12.5% to 18%, but the perinatal survival rate of newborns is only between 23% and 66%[6,7].

Case Presentation

This study is based on a comprehensive literature search of PubMed, Google Scholar, Scopus, and MEDLINE databases to determine the eti-

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ology, pathogenesis, diagnosis, and treatment of AFLP.

The search terms used were "AFLP", "pancreatitis" and "IVF". We analyzed all papers published up to January 2024 and mainly considered case reports, case-control studies, systematic cohort studies and reviews. The information relevant to this article was extracted from 50 articles and medical books.

We begin by describing our experience with the development of a case of AFLP with pancreatitis in pregnancy after IVF. We then summarize the characteristics of this pathology from the current literature.

A 25-year-old female patient presented to the emergency department of the obstetrics and gynecology department complaining of painful uterine contractions and itchy skin. She was 37 weeks pregnant with twins; both fetuses were viable and had intact membranes. The pregnancy had been induced by *in vitro* fertilization and the patient was monitored and documented by a specialist throughout the pregnancy. Specific pregnancy-related investigations were performed, and no medical problems were noted during the pregnancy. The medical history also indicated that the patient had had a cesarean delivery with no medical problems and a normal puerperium. She had not been traveling, nor was she taking any medications or herbal remedies except for progesterone supplements, which are usually administered in the first 7 weeks after egg retrieval in IVF.

The tests performed on the day of admission revealed no significant changes, except for alanine aminotransferase (ALT), which showed a value of approximately 117 UI/L. We also mention that on the day of admission, the patient presented a result for the summary urinalysis with no pathological changes, a negative urine culture, infectious markers negative for hepatitis C virus (HCV), hepatitis B virus (HBV), human immunodeficiency virus (HIV) 1 and 2 antibodies and rapid plasma reagin (RPR) latex. Examination of the vaginal secretion culture showed no development of pathogenic flora. Table I summarizes all the results of the paraclinical examinations performed on this patient.

On the second day, the patient complains of systematic uterine contractions and abdominal pain. Because of the imminent risk of uterine rupture due to a scarred uterus, a transverse segmental cesarean section was decided. Two live male infants were delivered, G1-2,350 g and G2-2,400 g, who developed well immediately and in the following days. The immediate postoperative development of the patient was favorable. In the first few hours, the patient was clinically and hemodynamically stable and had no fever.

24 hours after delivery, the patient showed a slightly altered general condition, marked jaundice with yellow skin and sclera, colicky pain in the right hypochondrium, and elevated blood pressure. Further paraclinical examinations were carried out. We found an increase in leukocytosis, transaminase, bilirubin, and fibrinogen. On the same day, an abdominal ultrasound was performed, showing an elongated gallbladder with transonic contents, without stones, a common bile duct of 3.9 mm, a right kidney with a regular outline with a slightly dilated upper ureter, a pancreas with normal margins, a spleen of 120 mm, a spherical, weathered abdomen with an echogenic liver image.

However, the patient's symptoms worsened from one day to the next with anorexia, persistent nausea, vomiting, and epigastric pain. The patient was transferred to the intensive care unit for monitoring. The jaundice worsened, and polyuria and polydipsia were observed. The patient complained of malaise with drowsiness and signs of encephalopathy. Objectively, she showed edema and moderate hypertension. In Table I, the laboratory analyses show moderate to severe liver dysfunction with hypofibrinogenemia, hypoalbuminemia, and prolonged clotting time. An increase in direct bilirubin to over 5 mg/dl indicates the presence of intrahepatic cholestasis. Hypoglycemia was noted but was corrected with medication. Coagulopathy is evident by the prolongation of the activated partial thromboplastin time (aPTT) and the Quick time; the international normalized ratio (INR) is also elevated above normal. Although the hemolysis is not severe, it is manifested by the occurrence of leukocytosis, moderate thrombocytopenia, and elevated levels of lactic dehydrogenase (LDH). Elevated creatinine levels also indicate some degree of renal insufficiency. Gradually, a disorder of the pancreas with elevated amylase and lipase levels was noted.

This clinical and paraclinical context prompted us to make the diagnosis of AFLP. This was made according to the Swansea criteria in Table II. The diagnosis of AFLP is made when at least 6 of the 15 Swansea criteria are met[8].

Once the diagnosis was confirmed, treatment was initiated, including antibiotics, antispasmodics, analgesics, vitamins, anticoagulants, glucocorticoids, and infusions of albumin and arginine

Table I. Evolution of maternal laboratory data.

Medical analysis	On the 1st day	After 48 hours	After 72 hours	On 6th day	On 7th day	On 8th day	On 13th day	On discharge from hospital
Hemoglobin (mg/mL)	10.2	9.2	9	9.3	10.1	10.5	11	12.3
Leucocytes (x10^3/µL)	8.2	23.71	24.41	14.19	15.79	15.29	12.95	11.82
Platelets (x10^3/µL)	300	192	198	191	238	194	243	288
Blood sugar (glucose) (mg/dL)	71	56	53	76	69	86	66	77
Aspartate aminotransferase (AST) (UI/L)	55	197	179	150	117	127	122	112
Alanine aminotransferase (ALT) (UI/L)	117	233	181	130	181	146	154	135
Amylase (UI/L)	-	35	300	88	195	761	837	290
Lipase (UI/L)	-	36	128	211	550	1200	640	342
Gamma glutamyl transferase (GGT) (UI/L)	-	80	76	77	136	225	737	523
Albumin (g/dL)	3.2	3.1	3.0	3.2	3.3	3.2	3.4	3.5
Lactate dehydrogenase (UI/L)	-	562	580	542	530	508	384	223
Alkaline phosphatase (ALP) (UI/L)	-	418	376	321	366	288	324	223
INR: International normalized ratio (s)	1	1.7	1.67	1.44	1.41	1.35	1.2	1.1
C reactive protein (CRP) (mg/dL)	-	4.92	5.23	2.7	2.11	2.05	1.86	1.72
Urea(mg/dL)	10.3	38	48	65	54	-	16	17
Creatinine (mg/dL)	0.8	1.46	1.22	1.07	0.88	0.81	0.62	0.6
Direct bilirubin (mg/dL)	-	6.4	6.3	5.8	7	7.4	6.49	2.1
Total bilirubin (mg/dL)	-	8.6	8.3	8	9.5	8.3	7.2	2.9
D-dimer (mg/mL)	-	17.34	13.2	8.93	8.57	6.72	5	0.5
Fibrinogen (mg/dL)	150	179	152	129	151	184	300	200
Quick time (s)	13	19	18.6	16.1	15.7	15	15	11
Activated partial thromboplastin (aPTT) (s)	40	44.7	45.9	55.7	57.1	60.9	55	40
Fibrin monomer test	Negative	Positive	Positive	Positive	Positive	Positive	Negative	Negative
Sodium (mmol/L)	128	140	150	141	139	139	140	128
Chloride (mmol/L)	102	114	107	110	107	112	106	100
Potassium (mmol/L)	4.5	4.8	3.5	3.6	3.5	-	3.38	4.5

solution. This comprehensive treatment approach aims to treat the underlying disease, relieve symptoms, provide nutritional support, and minimize potential complications associated with the diagnosed condition. On the fifth day, remarkable biological changes were detected at the pancreatic level, characterized by a rapid increase in lipase and amylase levels. An MRI examination was decided and performed, in which the pancreas, liver, and gallbladder were examined in normal size and appearance. No pathological changes were found, except for a bilateral pleural effusion with a maximum thickness of 6 mm on the right side and 12 mm on the left side.

Two days later, the patient complained of diffuse abdominal pain, mainly in the right hypochondrium and periumbilical area. Amylase and lipase levels began to rise rapidly. A CT scan was

Table II. Swansea criteria for the diagnosis of AFLP.

Criteria	Parameter
Clinical	Vomiting
	Abdominal pain
	Polydipsia/polyuria
	Encephalopathy
Laboratory	Bilirubin (> 0.8 mg/dL)
	Hypoglycemia (< 72 mg/dL)
	Leukocytosis (> 11,000 cells/μL)
	Elevated transaminase level (> 42 IU/L)
	Serum ammonia (> 47 μmol/L)
	Uric acid (> 5.7 mg/dL)
	Acute kidney injury (AKI) or creatinine (1.7 mg/dL)
	Coagulopathy (PTT > 14 s or aPTT > 34 s)
Imaging findings	Ascites or pale liver on ultrasound imaging
	Microvesicular steatosis on hepatic biopsy

requested but could not be performed for technical reasons.

The patient was then transferred to the surgical department of the trauma surgery clinic due to complications of the pancreas. On admission, local examination revealed an abdomen with mobile fatty tissue that was painful on palpation in the epigastric region, jaundiced skin, and a liver whose upper edge was located in the fifth rib.

On the eighth day, a native CT scan with contrast medium was performed, which showed the following: bilateral pleural effusion with a thickness of 13.5 mm on the left side and 4.3 mm on the right side. Liver with homogeneous parenchyma, without localized processes, spleen homogeneous, with normal bipolar diameter. Cholecystitis with thin walls without radiopaque stones. Homogeneous pancreas with increased volume (pancreatic head AP diameter = 54 mm, corporal = 3.31 mm, caudal 26.7 mm), possibly in the context of reactive pancreatitis, which can be classified in a Balthazar B score with a necrosis score of 0. Morphologic integrity of the adrenal glands and morphologic integrity of the renal and biliary tracts, except for right pleuroureteral hypotension. Perihepatic, perisplenic abdominal effusion in Morrison's space, at the level of the cholecystic bed, bilaterally parietal-colic and minimally through the intestinal loops with a maximum thickness of 9.5 mm perisplenic and 18 mm perihepatic. The pelvic CT, native and with contrast, showed a uterus with physiologic involution after cesarean section and minimal pelvic overflow at the level of the iliac fossa.

The gastroenterological examination revealed that the biliary obstruction was not confirmed by imaging, and it was recommended that treatment with ursodeoxycholic acid (UDCA) and a drug derived from milk thistle extract be continued.

During hospitalization, the patient was treated with antibiotics, hepatoprotectants, gastroprotectants, antiemetics, Ringer's solution, glucose, vitamins, and glucocorticoids. The clinical condition and biological constants gradually improved. The patient was discharged on day 17 on request with the recommendation to continue the hepatoprotective treatment and the hygienic diet and to be examined by a gastroenterologist.

Discussion

Definitions of Terms

To understand liver disease during pregnancy, we need to understand the adaptive function of the liver during pregnancy. Normal pregnancy is characterized by adaptive changes in lipid metabolism to meet the needs of the placenta and the glucose and lipid requirements of the growing fetus: increased glucose production, progesterone synthesis, and lipogenesis, and decreased lipolysis. We have tried to summarize the most important adaptive changes during pregnancy and have come to the following conclusion:

- Serum levels of ALT and AST do not change during pregnancy. Serum levels of AST or ALT activity above the upper limit of the prenatal norm should be considered pathologic.
- Liver function tests remain largely unchanged during pregnancy, except for elevated ALP levels. ALP is physiologically produced by the placenta. The ALP serum level increases, especially in the third trimester of pregnancy, due to the placental isoenzyme.
- The total bilirubin concentration is low in all three trimesters of pregnancy.
- GGT activity usually remains normal during pregnancy.
- Pregnancy can lead to an increase in cholesterol levels and a decrease in bile acids and phosphatidylcholine.
- The pregnancy-specific reduction in gallbladder motility is mediated by progesterone. There is an increased risk of gallstone formation during pregnancy, a risk that remains elevated for up to five years after pregnancy

and then returns to baseline[8-10].

Jaundice is defined as the clinical manifestation of hyperbilirubinemia caused by the deposition of bile pigments in the skin, resulting in a yellowish discoloration of the skin and mucous membranes. The normal serum bilirubin concentration in adults is less than 1 mg/dL; however, clinical jaundice does not occur until the serum bilirubin level exceeds 2 mg/dL. The incidence of jaundice in pregnancy, including underlying chronic liver disease, is 3-5%[8].

There is no single liver function test to quantify liver disease. The term "liver function tests" describes a group of laboratory tests that can be used to provide a discrete profile of liver function. Liver cell damage or necrosis is measured by determining aspartate aminotransferase (AST) and alanine aminotransferase (ALT), while synthetic liver function (cirrhosis or severe acute liver disease) is quantified by determining albumin levels and prothrombin time. Cholestasis and biliary obstruction are determined by measuring alkaline phosphatase (ALP), bilirubin, 5'-nucleotidase or gamma-glutamyl transferase (GGT)[8,11].

Pregnancy-specific liver dysfunctions include pre-eclampsia, hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome, acute fatty degeneration of pregnancy, cholestasis of pregnancy, and hyperemesis gravidarum. Pre-existing liver diseases during pregnancy, such as hemolytic anemia, liver pathologies such as acute viral hepatitis, drug-induced hepatitis, Budd-Chiari syndrome, and Wilson's disease, can be clinical causes of hyperbilirubinemia during pregnancy. Pathologies such as bile duct obstruction, gallstones, choledochal cysts, and pancreatitis can also lead to clinical jaundice during pregnancy. Liver dysfunction associated with pre-eclampsia and viral hepatitis are the most common causes of jaundice in pregnancy[8,10].

AFLP is a rare disease with high morbidity and mortality[12]. Most cases of AFLP are diagnosed in the third trimester or immediately after birth[13,14]. Isolated cases occurring in the second trimester have been reported[15].

Epidemiology

AFLP only occurs during pregnancy and, therefore, only affects women. It can affect any woman of childbearing age. From the studies[16,17] published so far, the incidence of AFLP in pregnancy is rare: 1 in 7,000 to 16,000 deliveries, with a higher incidence in nulliparous women and women with multiple pregnancies; the male fetus is a risk factor. The incidence of this disease can vary greatly depending on the geographical region. In India, for example, the incidence is estimated at around 30 cases per 100,000 pregnancies. In North America, the incidence varies, with a rate of 5.6 per 100 AFLP cases among Latina women in Los Angeles. These incidence rates illustrate the geographic diversity and demographic factors that influence the prevalence of AFLP in different populations[8].

Several risk factors were identified, with a higher prevalence observed in nulliparous women with multiple pregnancies and in women carrying male fetuses. This hypothesis is supported by the increased incidence in women with male fetuses, which is also consistent with the case we reported in which the patient gave birth to two male children[8,18]. Other risk factors include acute fatty liver in pregnancy, multiple pregnancies, a body mass index below 20 kg/m^2, fetal deficiency of long-chain acyl hydroxy-CoA dehydrogenase (LCHAD), and pre-eclampsia[11,19,20]. It is already known that multiple pregnancies are more frequently achieved by IVF (as in our case). However, there are also cases in the literature[21] that do not meet these criteria, as described by de Oliveira et al[3]. Publications from the 1980s indicate a high mortality rate of around 70%; however, more recent studies[3,15] suggest lower mortality rates: around 20% in some centers in low-income countries or even less than 10% in high-income countries. The reduction in mortality rates is attributed to a better understanding of the disease, easier recognition of its manifestations, early intervention and timely delivery, and proactive management of complications. In addition, the introduction of new treatments, such as artificial liver support therapy (ALST), which includes techniques such as plasma exchange (PE), has contributed to better outcomes in the treatment of the disease[9].

Pathophysiology

The pathophysiology of AFLP is still unknown. The causes of AFLP are associated with mitochondrial dysfunction in fat oxidation processes. It is also associated with a deficiency of LCHAD, which leads to abnormal β-oxidation of long-chain fatty acids[2]. It is an autosomal recessive gene mutation; outside of pregnancy, women have normal fatty acid oxidation under normal physiological conditions. If the fetus is homozygous for this mutation, it is unable to oxidize fatty acids, which are passed on to the mother, who is unable to metabolize the extra fatty acids due to

reduced enzyme function[22]. In pregnancies with LCHAD-deficient fetuses, AFLP occurs in up to 79% of cases[23].

Fetal homozygosity for the LCHAD enzyme includes the placenta. Incomplete mitochondrial beta-oxidation leaves a residual substrate that is catalyzed by alternative pathways in peroxisomes and microsomes. In contrast to mitochondrial beta-oxidation, peroxisomal beta-oxidation does not produce ATP. Instead, peroxide radicals and other prooxidant species are formed from the by-products of the blocked pathways, further impairing placental mitochondrial function. Because the fetal and maternal placental circulations are adjacent, the toxic byproducts pass unimpeded to the maternal circulation, where the effects on fetal subcellular metabolism are reflected in the maternal organs. The maternal LCHAD heterozygote may be more susceptible to mitochondrial dysfunction, including beta-oxidation[24]. Impaired hepatic mitochondrial function likely underlies AFLP[25]. Other maternal organs may also be affected. Pancreatitis, renal dysfunction, and cerebral effects may occur[24]. Other hypotheses for the pathogenesis of this disease include quantitative variations in serum levels of steroidal sex hormones but also genetic factors such as mutations in the *ABCB4* gene encoding multidrug resistance protein 3 (MDR3), which is associated with progressive familial intrahepatic cholestasis of pregnancy (ICP)[8].

In pregnancy, the main causes of acute liver failure (ALF), which are very similar to AFLP, are pre-eclampsia/eclampsia (often with liver infarction), hemolysis syndrome, HELLP syndrome, acute liver rupture, viral hepatitis, drug-induced liver disease and food poisoning (associated with fungi). Budd syndrome is also recognized as a contributing factor in certain cases[9,26]. However, the role of various medications in the development of ALF should not be underestimated. These include drugs such as paracetamol, hormones such as dydrogesterone, and antibiotics such as the combination of sulfamethoxazole and trimethoprim, ciprofloxacin, amoxicillin, and nitrofurantoin. ALF in India is mainly caused by viral hepatitis, while in Western countries, an overdose of paracetamol is punishable by law[4]. It is crucial to be aware of possible drug-related factors in the development of ALF disease, such as AFLP, and consider them in the overall assessment and treatment[27]. In our case, we were unable to definitively determine the cause of the onset of this condition.

Symptomatic

Liver dysfunction occurs in pregnancy, with a prevalence of around 3%. In liver disease (especially AFLP), the severity of symptoms (nausea and vomiting) correlates with high liver enzyme levels[28]. We observed a similar phenomenon in our case, where the patient had a worsening of symptoms with a concomitant change in liver enzyme levels. Patients with acute obesity in pregnancy often present with symptoms such as malaise, itchy skin, loss of appetite, nausea, vomiting, abdominal pain, and jaundice of the skin and sclera[3,19].

Clinical and Paraclinical Diagnosis

Early diagnosis is a challenge due to its rarity and differential diagnoses[29]. Investigations in a newly admitted patient with suspected ALF, which includes AFLP, are based on clinical assessment and serve several purposes:

(a) Confirmation of the diagnosis and exclusion of other diseases:

- Liver function tests: determination of liver enzyme levels (ALT, AST), bilirubin, and coagulation parameters.
- Imaging examinations: use of imaging techniques such as ultrasound (US) or magnetic resonance imaging (MRI) to assess liver morphology.
- Serology of viral hepatitis: examination for markers of viral hepatitis.

(b) Determination of the cause of ALF:

- Detailed history: identify possible causes, including recent medications, viral infections, and exposure to hepatotoxins.
- Serologic testing: screen for autoimmune markers and metabolic abnormalities.
- Imaging: perform additional imaging studies to detect structural abnormalities or tumors.

(c) Assessment of severity, risk of complications, and prognosis:

- Assessment of severity: use of scoring systems such as the Model for End-Stage Liver Disease (MELD) or King's College criteria.
- Coagulation tests: screening for coagulopathy and bleeding risk.
- Arterial blood gas analysis: assessment of acid-base status and severity of metabolic disorder.
- Neurological examinations: monitoring for hepatic encephalopathy.
- Prognostic markers: measurement of factors such as serum lactate, ammonia, and creatinine for prognostic assessment[8,29].

Overall, these tests help to confirm the diagnosis of ALF, identify the underlying cause, and assess the severity of liver failure. The information obtained forms the basis for appropriate management decisions and measures to optimize patient care[4].

Clinical examination may reveal epigastric tenderness or even guarding, a decrease in bowel sounds due to reflex ileus, and Murphy's sign[29]. The diagnosis is often confirmed by measuring the lipase level, which is more than three times the normal value. AST and ALT levels are usually elevated by 5 to 10 times the upper limit. Platelet counts may be decreased with or without additional signs of disseminated intravascular coagulation, along with a marked decrease in antithrombin III. Patients with severe impairment may have elevated sodium levels, prolonged prothrombin time, or hypoglycemia caused by liver failure[3,29]. All of these paraclinical signs were present in our AFLP case. An ultrasound or MRI examination of the liver primarily serves to exclude other diagnoses such as hepatic infarction, hematoma, or biliary obstruction[3,8,29]. In our case, we were unable to detect any biliary obstruction. We observed a liver with increased echogenicity like Cao et al[30] in a similar case of AFLP in pregnancy after IVF.

A definitive and unequivocal confirmation of this pathology is achieved by histologic examination. However, a liver biopsy is not always performed due to the hemorrhagic complications typical of this disease[15]. In AFLP, the pathognomonic sign of the liver biopsy is microvesicular fatty infiltration in the hepatocytes, a specific alteration in this disease. The fat droplets are centrally distributed around the cell nuclei and give the cytoplasm a foamy appearance[3]. We did not have the time to perform such an examination. Screening tests for viral hepatitis A, E, and B should not be neglected and should be performed routinely. If atypical causes are suspected, other tests such as IgM anti-HSV, tests for tropical infections, serum ceruloplasmin, autoimmune markers, and an echocardiogram can also be considered. In immunocompromised patients, additional tests for Varicella zoster virus (VZV), Cytomegalovirus (CMV), and Epstein-Barr virus (EBV) may be required[4]. In our case, all tests were negative.

As there is no universal approach to the diagnosis and clinical, laboratory, and imaging findings, the Swansea criteria, in Table II, have been proposed to be considered when AFLP is clinically suspected[8,18,19]. However, Swansea's criteria are not specific enough for this[31,32]. Like Cao et al[30], we cannot use the entire Swanson algorithm to diagnose AFLP[28]. To simplify and facilitate the diagnosis of early-stage AFLP, Vigil-de Gracia and Montufar Rueda[33] have attempted to summarize the features and compiled the "AFLP triad", which includes the following:

- Clinical symptoms (nausea/vomiting, jaundice, stomach pain),
- Laboratory findings (functional liver abnormalities, coagulopathy, renal dysfunction, hypoglycemia),
- Complications (encephalopathy, ascites, coagulopathies, renal failure)[32,33].

Recently, Zhong et al[34] showed that the sensitivity and specificity of the association of gastrointestinal symptoms, ALT, bilirubin, bile acids, and aPPT/PT in AFLP diagnosis were 97.6% and 97.1%, respectively, while several markers may not be suitable for differential diagnosis[32,34]. All these criteria were also met in our case.

Differential Diagnosis

Clinical manifestations and laboratory tests are the most important tools for the diagnosis and differentiation of AFLP from common pregnancy disorders such as ICP, HELLP syndrome, and pre-eclampsia[18,19]. It should also be noted that 20-40% of patients with AFLP are simultaneously diagnosed with pre-eclampsia/HELLP syndrome[35]. In the differential diagnosis, the possibility of SARS-CoV-2 infection, which can cause an increase in liver enzymes, should also be considered[19,53].

In ICP, the predominant symptom is pruritus with a serum bilirubin level of less than 5 mg/dL and elevated bile acids. One of the typical features of ICP is elevated serum bile acids. Generally, the symptoms in the mother disappear with delivery. In rare cases, the symptoms persist in the woman, and she develops cholestatic disease. These cases may be related to a genetic MDR3 deficiency, which should be suspected in young women with cholestasis of unknown cause who develop severe ICP. Ursodeoxycholic acid (UDCA) at a dose of 10-15 mg/kg/day is effective in reducing pruritus, improving liver tests in women with ICP, and improving fetal outcome[36].

As in our case, AFLP can be distinguished from HELLP syndrome and pre-eclampsia by hypoglycemia, marked jaundice with elevated bilirubin, and signs of systemic liver dysfunction such as mild to moderately elevated transaminases, hepatic encephalopathy, and disseminated intravascular coagulation. In HELLP syndrome,

however, the values are significantly lower. The incidence of AFLP is significantly higher in twin pregnancies than in HELLP syndrome[37]. If hepatic encephalopathy occurs, AFLP should be strongly suspected. The PT is prolonged, fibrinogen levels are reduced, and lactate dehydrogenase is elevated. Disseminated intravascular coagulation is found in 10% of patients. These laboratory abnormalities help to differentiate between pre-eclampsia and AFLP. Viral hepatitis usually shows elevated aminotransferase levels, which have been ruled out by negative serologies. The use of medication or herbal remedies must also be excluded by the medical history[18].

Treatment

AFLP during pregnancy is a medical emergency as it can lead to increased maternal-fetal morbidity and mortality[9]. Every effort should be made to determine the etiology of AFLP, as treatment depends on the etiology[26]. A patient with pregnancy-related ALF should not be denied potentially life-saving therapy, as the risks of untreated or fulminant AFLP are generally higher than those of fetal harm following therapy[9].

The most important treatment for AFLP is timely termination of pregnancy and supportive therapy. It is estimated that in AFLP, maternal mortality is 48% lower, and perinatal mortality is 44% lower when a cesarean section is performed compared to vaginal delivery[14]. In our case, immediate cesarean section was a curative measure. Patients with AFLP, whether mild or severe, must be transferred to the intensive care unit for further treatment. In case of infectious complications of AFLP, a low-dose antibiotic therapy is recommended. Hepatoprotective agents, blood transfusions, albumin infusions, infection control, fluid and electrolyte balance, and nutritional support are essential components to support the liver, facilitate recovery, and mitigate potential complications[10,38]. Artificial liver support therapies (ALST), including blood transfusion, plasma exchange (PE), molecular adsorbent recirculation system (MARS), and dual molecular plasma adsorption (DPMAS), are used in AFLP patients. However, it is unclear whether these measures can improve the prognosis or shorten the recovery time after birth in patients with AFLP. Cryoprecipitate and plasma infusion do not improve the prognosis of AFLP patients[38]. Further studies are needed to identify specific biomarkers for the gestational period to minimize maternal and fetal complications and to determine risk factors such as environmental risks, maternal conditions, and hereditary factors[10]. As already mentioned, there is no specific treatment for AFLP. The first step is to terminate the pregnancy and deliver the baby, usually after stabilizing the mother and ensuring fetal maturity[3]. Because hypoglycemia is common and dangerous, blood glucose levels must be carefully monitored. Hypoglycemia is usually treated with a continuous infusion of a 10% glucose solution. In some patients with severe hypoglycemia, an additional bolus infusion of 50% glucose may be required[3].

Previous studies[32] have shown that the recovery time of liver function depends on the severity of the disease, with liver enzyme levels improving within 1 to 2 days, cholesterol and bilirubin levels within 4 to 6 days, and acute kidney injury within 7 to 10 days after birth. Extracorporeal life support systems can be used as a last resort for organic system failure. Artificial liver support therapy may also be approved for women with persistent liver failure. If end-stage liver failure is present, liver transplantation should be considered[23]. Therapeutic management is also based on the classical recommendations for any pancreatitis complication, as in our case: digestive rest, parenteral rehydration, analgesia, antibiotic therapy, and drainage of infected necrotic foci. Etiologic treatment may include cholecystectomy for biliary pancreatitis and a low-fat diet in conjunction with lipid-lowering medications for secondary pancreatitis due to hypertriglyceridemia[29].

It is important to emphasize that the diagnostic and therapeutic management of AFLP is a multidisciplinary process that requires the active and rapid intervention of gastroenterologists, anesthesiologists, surgeons, obstetricians, and neonatologists in a tertiary center with an intensive care unit[39]. The multifunctionality of the liver requires multidisciplinary and pluralistic interventions for its preservation or treatment. A multidisciplinary approach can be defined as a program that integrates different disciplines to address problems or issues from different perspectives. This allows a deepening of knowledge about the topic from different angles to provide effective answers. A pluralistic approach promotes mutual understanding and collaboration around a topic or issue, similar to a multidisciplinary approach[40].

Complications

Approximately half of patients diagnosed with hepatic steatosis during pregnancy experience signs of preeclampsia either at the onset or

at some point during the illness, a circumstance observed in our case and documented in other reported cases. Life-threatening complications of AFLP include ALF, disseminated intravascular coagulation, postpartum hemorrhage, acute renal failure, gastrointestinal bleeding, liver rupture, and hepatic infarction[3,16]. Prothrombin time has been found[41] to correlate with maternal complications and gestational age at delivery is associated with increased fetal and neonatal complications.

In addition, extrahepatic complications such as pancreatitis can occur, which can be severe and life-threatening. The occurrence of acute pancreatitis during pregnancy is rare, with a reported incidence between 0.02% and 0.1%[42]. Acute pancreatitis associated with pregnancy-induced hypertension is a rare situation with an unfavorable outcome[29]. Acute pancreatitis in pregnant patients is often treated in the same way as in non-pregnant patients. It is usually self-limiting, and most patients respond to initial conservative measures, including intravenous fluids, analgesics, gastric decompression, antispasmodics, and antibiotics. The surgical approach remains controversial[20].

Pseudocysts of the pancreas can lead to complications in 5% of pancreatitis cases and can be detected by CT scans. However, serious complications can occur in about 10% of patients, manifesting as necrosis and multiple organ failure, including the cardiovascular, pulmonary, and renal systems[20].

In less than 2 cases, intrahepatic bleeding or liver rupture may occur[43].

Investigations to determine the risk of complications and prognosis include blood count, determination of procalcitonin levels, blood, urine, and sputum/bronchoalveolar lavage cultures, tests to assess renal function, blood glucose, serum electrolytes, amylase/lipase, and blood gas analysis[4]. Based on our own experience and study of the literature, we can state the following:

- PT/INR should be checked at least once a day.
- Blood glucose levels should be checked every 1-4 hours.
- Sodium levels should be checked every 12 hours and maintained between 145 and 150 mmol/L.
- Urine output should be measured every hour.
- Surveillance cultures should be sent every 48 hours or when infection is suspected.
- Continuous blood pressure monitoring with a MAP target of 70-80 mmHg is recommended.
- Continuous monitoring of central body temperature should be performed.

Cardiomyopathy, neuropathy, myopathy, non-ketotic hypoglycemia, liver failure, and death associated with neonatal fatty acid oxidation defects may occur in the infant. Neonates with LCHAD deficiency can be treated with dietary modification, resulting in reduced morbidity and mortality[44].

Prognosis and Aftercare

Prognosis depends on the quality and speed of therapeutic care[4,29,45,46]. Complications, due to advances in diagnostic strategies and supportive care, maternal mortality and perinatal morbidity in AFLP have decreased. In the 1980s, Kaplan[47] reported maternal and fetal mortality rates of approximately 85%. Today, maternal mortality is estimated at 12.5% to 18%, and neonatal mortality at 7% to 66%[48].

While laboratory abnormalities may persist after birth, in rare cases, liver failure may occur, necessitating liver transplantation. Usually, liver function tests begin to normalize after birth; however, a transient worsening of renal and liver function may be observed after the first few days, followed by a marked improvement, as reported by us and other authors[3]. In severe cases, especially if the diagnosis is made late, monitoring of the patient in the intensive care unit may be necessary. Mechanical ventilation, dialysis, parenteral nutrition, or surgical interventions may be steps in the treatment of these patients[3].

It should be noted that AFLP may recur in subsequent pregnancies. However, the exact risk of recurrence is not known and affected women should be informed of this possibility[3,26,44]. One study[49] found that the likelihood of recurrence in a future pregnancy was 21%, with 80% of recurrences occurring in a milder form.

The maternal-fetal prognosis is favorable if the diagnosis is made early and the associated risk factors are identified. A multidisciplinary team must always make the decisions for this patient and the pregnant woman should be referred to a specialized tertiary center for high-risk pregnancies[28,44].

Adverse fetal outcomes have been observed[50] more frequently in pregnant women diagnosed with this pathology in the third trimester than in pregnant women presenting postpartum. When AFLP is diagnosed in pregnancy in the second trimester, the severity is comparable to the manifestation in the third trimester, although with a lesser association with arterial hypertension, which is rare[51]. The management of this condition in the second trimester presents a major challenge for obstetricians as they must decide how best to terminate the

pregnancy, considering the potential neonatal impact of premature delivery. All newborns born to mothers with AFLP should be screened at birth for LCHAD deficiency or other fatty acid oxidation defects due to the risk of metabolic crisis and death within the first year of life. Genetic counseling is indicated for affected families[41,52].

Conclusions

More attention should be paid to mothers who become pregnant through *in vitro* fertilization, as more and more cases of AFLP are appearing in the medical literature. Despite its rare occurrence, this condition is important as it can increase maternal and/or fetal morbidity and mortality. Early diagnosis and performance of the necessary laboratory tests to detect complications are the most important factors for effective treatment. Timely diagnosis and prompt intervention are critical to prevent maternal and fetal morbidity and mortality. These measures are best carried out as part of a multidisciplinary approach.

Conflict of Interest
The authors declare that they have no conflict of interest.

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Authors' Contributions
CCV (conceptualization); MVB (data curation); SS, MVB (formal analysis); CCV (funding acquisition); LD, DC, AMG (investigation); MBN (methodology); CCV, SS (project administration); AMG, MVB (resources); MBN, MVB (software); CCV (supervision and validation); CCV, SS (writing – original draft); MVB, CCV (writing – review and editing).

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Ethics Approval
The study was conducted by the Declaration of Helsinki and approved by the Ethics Committee of the University of Medicine and Pharmacy in Craiova (No. 175/14.09.2023).

Informed Consent
Informed consent was obtained from the subject involved in this study. The patient also gave written informed consent to publish this paper.

Data Availability
All data presented here are available from the authors upon reasonable request.

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