Journal of Carcinogenesis
Covering Genesis to Therapeutics
Journal of Carcinogenesis, ISSN: 1477-3163
2025; Vol 24: Issue 10s, https://carcinogenesis.com/

Significance Of Pre-Pregnancy Acne Fulminans As A Marker Of Dyslipedmia And Nash With Its Association Of Aflp

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ABSTRACT

Most frequent cause of acute liver failure in pregnancy is AFLP also known as acute fatty metamorphosis/acute yellow atrophy. Though it is known to be associated with autosomal recessive mitochondrial fatty acid oxidation abnormalities, a correlation has also been found with AFLP as a continuum of dyslipidemia and NASH, which is the most common hepatic manifestation of PCOS. Here 15 cases of pregnancy with AFLP were studied, where preconceptionally 13 patients had PCOS and out of which 9 patients had acne fulminans, dyslipidemia and NASH. Moreover, in pregnancies with h/o acne fulminans, dyslipidemia and NASH, AFLP progressed at rapid rate with earlier onset and landed in decompensated liver failure compared with sporadic cases. As pregnancy progresses, insulin resistance increases, levels of lipoprotein particles and lipids are in atherogenic range which allows for proper nutrients for fetus. Though cases of AFLP are known to occur due to LCHAD deficiency, these changes in lipid metabolism, insulin resistance in a setting of pre-pregnancy dyslipidemia & NASH can lead to acute fatty metamorphosis, thus culminating in acute fatty liver of pregnancy. There by concluding pre-pregnancy acne fulminans as a manifestation of dyslipidemia &NASH helps in identifying pregnant women at risk of AFLP..

Keywords: PCOS (polycystic ovarian syndrome), NAFLD (Non-alcoholic fatty liver of pregnancy), NASH (Non-alcoholic steatohepatitis) dyslipidemia, lipoproteins

How to Cite: Dr Sripathi Anusha, Dr Renu Sahani, Dr Shobha , Dr.Divya Daniel , Dr.Deepthi , Dr.Monica Poreddy (2025) Significance Of Pre-Pregnancy Acne Fulminans As A Marker Of Dyslipedmia And Nash With Its Association Of Aflp, *Journal of Carcinogenesis*, *Vol.24, No.10s*, 87-92

1. INTRODUCTION

The most frequent cause of acute liver failure during pregnancy is acute fatty liver also called acute fatty metamorphosis or acute yellow atrophy. It is characterized by accumulation of microvesicular fat that literally “crowds out” normal

hepatocytic function. Grossly, the liver is small, soft, yellow,

and greasy. In its worst form, the incidence approximates 1 in 5,000 -20000. Although the underlying cause remains unclear, many cases of AFLP are associated with recessively inherited mitochondrial abnormalities of fatty acid oxidation. Several mutations for the mitochondrial trifunctional protein enzyme complex that catalyzes the last oxidative steps in the pathway are implicated. The most common are the G1528C and E474Q missense mutations of the gene on chromosome 2 that codes for long-chain-3-hydroxyacyl-CoA dehydrogenase.

Mutations for medium-chain acyl-CoA dehydrogenase (MCAD) and for carnitine palmitoyltransferase 1 (CPT1) deficiency are others. It is hypothesized because the mutation is recessive, under normal physiological conditions the mother does not have abnormal fatty acid oxidation. However, when both parents are heterozygous for this abnormality and the fetus acquires both of these mutations, the fetus will be unable to oxidize long-chain fatty acids. The unmetabolized free fatty acids return via the placenta to the mother's circulation, which strains maternal hepatic activity and overwhelms any diminished maternal hepatic enzyme activity, resulting in the symptoms of AFLP.[1]

Normal pregnancy is a state of insulin resistance and high triglyceride levels. These change if already in a setting of preexisting PCOS complicated with dyslipidemia and NASH, can lead to further lipid deposition causing hepatotoxicity and acute liver failure. So apart from fatty oxidation defects, pre-pregnant PCOS with NASH and dyslipidemia can be potential risk factor for AFLP.[2]

2. CASE STUDY:

Incidence groups:

Out of 15 pregnant AFLP cases- 10 in the age group of 20 -25,7 in the age group of 25-30,3 in the age group of 30-35. 13 are nulliparous pregnancies while 2 are multiparous. 11 are singleton pregnancies while 4 are multiparous. (Table 1)

Pre-pregnancy metabolic profile:

Patients have BMI >25 and 13 patients had history of PCOS, 9 patients with acne fulminans ,10 patients with dyslipidemia, USG showing mild fatty liver in 7 patients.

Pregnancy complications:

8 patients with PCOD developed gestational diabetes, 5 patients developed gestational hypertension.

Course of AFLP:

The age of onset of AFLP is 32 weeks in dyslipidemic patient while rest developed at 36weeks GA. 5 out of 15 AFLP cases landed in decompensated liver failure, all of which have dyslipidemia. Median time of recovery is 2 weeks in dyslipidemic patients while rest of pregnant females recovered in 1 week.

Incidence group	No of patients
AGE	
20-25 25-30	10 7
PARITY	
Nulliparous Multiparous Singleton pregnancy Multiple pregnancy	13 2 11 4
PREPREGNANCY METABOLIC PROFILE	

Incidence group	No of patients
BMI >25 h/o PCOS acne fulminans Dyslipidemia USG showing fatty liver	11 13 9 10 7
PREGNANCY COMPLICATIONS	
GDM G, HTN	8 5
AFLP COURSE	
GA of onset 32 weeks 36 weeks Decompensated liver failure Rate of recovery	10 patients with dyslipidemia 5 patients in rest 5 patients with dyslipidemia 2 weeks

Table 1. Incidence among groups

3. DISCUSSION

Etiopathogenesis and clinical course:

The AFLP is a rare obstetric emergency with features of acute liver dysfunction/failure during pregnancy, which poses a high-risk of morbidity and mortality for both the mother and foetus. However, global outcomes have improved due to early diagnosis and prompt delivery of the foetus. The condition was first described by Sheehan in 1940 and its incidence ranges from on in 5,000 to 20,000 pregnancies.[3]

The pathogenesis of AFLP is not well understood. LCHAD deficiency, a recessively inherited metabolic defect, is considered the most important factor in foetal development. Non-metabolized fatty acids from the fetal circulation re-enter the maternal circulation through the placenta and accumulate in hepatocytes, leading to lipotoxicity.[2] It has been observed that mothers with fatty liver of pregnancy often have children with LCHAD deficiency and Reye-like syndrome.[2,3] Some identified high-risk factors for AFLP include primigravida, male foetus, previous history of AFLP, and multiple gestation.[4]

Fatty liver of pregnancy presents with a spectrum of clinical severity. Symptoms may include persistent nausea/vomiting, malaise, anorexia, and progressive jaundice. Many patients also exhibit signs and symptoms overlapping with severe preeclampsia, such as hypertension, proteinuria, low platelet count (HELLP syndrome), and edema. Laboratory parameters typically show hyperbilirubinaemia, elevated liver transaminases, hypoglycaemia, leukocytosis, increased creatinine levels, and prolonged clotting times.[4,6] Profound activation of endothelial cells with capillary leakage can lead to hemodynamic instability, acute kidney injury, ascites, and pulmonary oedema. Decreased uteroplacental flow can also jeopardize foetal well-being.

Pre-pregnancy NASH and lipid metabolism in pregnancy leading to AFLP

PCOD, one of the most common endocrinopathy in early reproductive age, is characterized by chronic anovulation, hyper androgens in polycystic ovaries. They are apparent any young age might disappear with ageing; however metabolic disturbances persist and deteriorate with aging. Most of endocrine and metabolic characteristics of women with PCOS, including elevated androgens, insulin resistance, dyslipidemia and elevated low grade inflammation levels are thought to contribute to presence and progression of NAFLD/NASH. In addition, oral contraceptives, antiandrogens and insulin sensitizers used in PCOS can adversely affect liver function.[7]

Mechanisms linking nonalcoholic fatty liver disease to polycystic ovary syndrome. Obesity and insulin resistance, features highly prevalent in polycystic ovary syndrome (PCOS) patients and hyperandrogenism, a predominant characteristic of PCOS, as contributing factors to the development of nonalcoholic fatty liver disease (NAFLD). Hyperandrogenism may exert direct effects on the liver and indirect effects by modulating insulin sensitivity and favoring visceral adiposity. Insulin resistance/hyperinsulinemia contributes to hyperandrogenism by affecting the production, the clearance and bioavailability of ovarian androgens.[8](Figure 1)

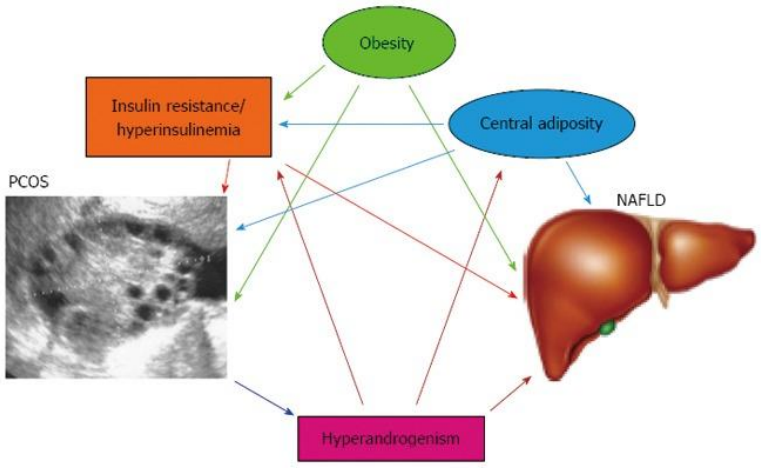

Figure 1. PCOS and its interrelation

Lipid metabolism in pregnancy

In the first trimester, there is a discernible decrease in levels during the first 6 weeks of pregnancy. As pregnancy progresses, there is a noticeable increase by the third month or at the end of the first trimester. There is a steady increase throughout pregnancy. By the third trimester or near the end of pregnancy (term), levels peak. Levels of lipoprotein particles and lipids, particularly in the later part of pregnancy, are in the atherogenic range when compared to non-pregnant levels in women of comparable ages without medical conditions. After delivery, lipid and lipoprotein levels rapidly return to normal. The changes in lipid metabolism throughout pregnancy allow for proper nutrients for the fetus and the normal, steady increase throughout pregnancy is associated with increased insulin resistance in the mother. Regardless of dietary differences in cholesterol, by late pregnancy, plasma cholesterol levels are approximately 50% higher than routinely seen pre-pregnancy while triglyceride levels are increased 2-3 times. These changes can be viewed as important for the enhanced availability of substrates for the fetus.[9,10] (Table 2, 3)

Since pregnancy is a atherogenic state preexisting PCOS complicated with dyslipidemia and NASH, can lead to further lipid deposition causing hepatotoxicity and acute liver failure, making it as a risk factor for AFLP apart from LCHAD deficiency.[11,12]

Table 2. Lipid metabolism in pregnancy

Estrogen increase	Inhibits Hepatic Lipase
	Stimulates VLDL production
	Stimulates lipogenesis in the liver
Human Placental Lactogen increase	Induces insulin resistance
	Increases lipolysis
Insulin Resistance	Decreases LPL activity

	Increases lipolysis
	Increase CETP
	Stimulates lipogenesis in the liver

Triglycerides	2.7-fold increase
Total Cholesterol	43% increase
LDL Cholesterol	36% increase
HDL Cholesterol	25% increase
Lipoprotein (a)	190%*
Apolipoprotein B	56% increase
Apolipoprotein AI	32% increase

Table 3. Lipid level rise in pregnancy

Preconceptional management:

PCOS patients, particularly with acne fulminans as clinical manifestation of Hyperandrogenism & dyslipidemia, with features of the metabolic syndrome, should be submitted to screening for NAFLD comprising assessment of serum aminotransferase levels and of hepatic steatosis by abdominal ultrasound. Lifestyle modifications including diet, weight loss and exercise are the most appropriate initial therapeutic interventions for PCOS patients with NAFLD.[12,13] When pharmacologic therapy is considered, metformin may be used, although currently there is no medical therapy of proven benefit for NAFLD.[11]

4. CONCLUSION

Though it is understood that AFLP occurs due to LCHAD deficiency, strong association is found with AFLP and NASH. Since pregnancy is an atherogenic state, changes in lipid metabolism, insulin resistance in a setting of pre-pregnancy dyslipidemia & NASH can lead to acute fatty metamorphosis, thus culminating in acute fatty liver of pregnancy, showing that AFLP can occur as a continuum of NAFLD/NASH. So, patients with acne fumninans can have underlying hyperandrogenism, dyslipidemia and should be screened for NASH.

Life style modifications and weight reduction can reverse these steatohepatic changes thus decreasing the risk of AFLP in future pregnancy. Thereby concluding pre-pregnancy acne fulminans as a manifestation of dyslipidemia &NASH helps in identifying pregnant women at risk of AFLP.

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