CASE REPORT

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Non-alcoholic steatohepatitis in pregnancy: a case report



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Abstract

Background Dyslipidemia and non-alcoholic fatty liver disease are well-known diseases and are part of a very broad spectrum evolving toward non-alcoholic steatohepatitis (NASH). This entity has not been described in pregnant women and could have obstetrical repercussions.

Case presentation A 26-year-old woman with 28 + 5 weeks of pregnancy presented with preterm labor. At admission, a significant hepatic cytolysis was detected (AST/ALT 265/485 U/L—GGT/alkaline phosphatase 60/164 U/L). She had normal blood pressure and negative 24-h proteinuria. She did not have intrahepatic cholestasis of pregnancy (bile acid at 7) and also no organic hepatic etiology (negative serologies and imaging). This cytolysis worsened until a more detailed history revealed a potential etiology: a diet very rich in sugars and fatty acids corresponding to a NASH syndrome. Dietary rebalancing improved the cytolysis. Complications such as intrahepatic cholestasis of pregnancy and preterm birth favored by significant dyslipidemia could not be avoided.

Conclusions It is important to consider the lipid profile of our patients. This will allow for a more personalized follow-up given the possible obstetrical repercussions that can arise from this pathology. It should also be considered in the differential diagnosis of liver test alterations during pregnancy. A healthy diet seems to help control the disease.

Keywords NASH, Pregnancy, Obesity, Dyslipidemia, Diet

Background

Dyslipidemia and non-alcoholic fatty liver disease (NAFLD) are well-known diseases and are part of a very broad spectrum evolving toward non-alcoholic steatohepatitis (NASH). This entity has not been described in pregnant women and could have obstetrical repercussions (Sarkar et al. 2020; Hershman et al. 2019; Koralegedara et al. 2022; Jamaly et al. 2022).

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Case presentation

A 26-year-old woman presented at 28+5 weeks of pregnancy in the emergency room of the Marie Curie Hospital for uterine contractions. This was her first pregnancy, and she had no complications up to this admission. The patient had no medical or surgical history and was not taking any chronic medication apart from pregnancy vitamins. She was a smoker with no other addictions. Uterine contractions have been present since the previous day with no other associated complaints. There was no antepartum haemorrage or discharge that could correspond to amniotic fluid. There were no urinary or digestive complaints. She had normal blood pressure and no fever.

On clinical examination, uterine contractions were felt, but no elective pain was evident on abdominal palpation, costovertebral angles were negative, and there was no edema of the lower limbs.



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We performed a routine cardiotocogram. This showed good fetal vitality with irregular uterine contractions. In view of the uterine activity that was well documented on monitoring, an endovaginal ultrasound was performed and showed a shortened cervix of 20 mm without a funnel. The vaginal examination showed a shortened but closed cervix.

In the presence of the following elements, uterine activity, and a shortened cervix, we considered this patient at risk of preterm delivery. The various complementary examinations for the development were carried out according to the CRGOLFB protocol (GGGOLFB 2017).

A pulmonary maturation was recommended associated with a tocolysis by nifedipine. Vaginal smears and urine culture were negative. The blood test revealed hepatic cytolysis associated with cholestasis (Table 1: AST/ALT 265/485 U/L—GGT/alkaline phosphatase 60/164 U/L) without any alteration of the coagulation or inflammatory syndrome.

In view of this significant alteration in liver tests, vast etiological research was launched. Proteinuria was negative at 154 mg/24 h (<0.3 g/24 h), and she had normal blood pressure. Biologically, the patient did not had hemolytic anemia, hypoplaketosis, or renal failure, only the significant liver cytolysis persisted. Although

Table 1 Table of the different biological assays

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 12	Day 20	Reference value
AST	265	698	749	777	669	531	467	265	251	5–34
ALT	485	1169	1410	1549	1452	1179	1069	779	564	< 55
GGT	60	56	60	68	68	58	57	49		9–36
Alkaline phosphatase	164	167	167	182	187	168	200	230		40-150
Total bilirubin		0.67	0.64	0.65	0.73	0.65	0.65	0.67		< 0.5
Bile salts	7							9	52	< 10
Haptoglobin		0.96								0.65-2.5
Anti-EBV IgG antibodies		37.5								< 20
Anti-EBV IgM antibodies		<10								<20
Anti-CMV IgG antibodies		154.3								<6
Anti-CMV IgM antibodies		-								< 0.85
lgG anti-toxoplasmosis antibodies		-								
lgM anti-toxoplasmosis antibodies		-								
Anti-rubella IgG antibodies		27								<5
Anti-rubella IgM antibodies		-								
Anti-HIV antibodies		-								
Anti-HAV IgG antibodies		-								
Anti-HAV IgM antibodies		-								
HBs antigen		-								
Antibodies anti-HBs		>1000								< 10
Antibodies anti-HCV		-								
Antibodies anti-Parvo B19		-								
PCR HEV		-								
Anti-nuclear CA				-						
Antibodies anti-mitochondria				-						
Antibodies anti-smooth muscle				-						
Antibodies anti-LKM				-						
Anti-neutrophil cytoplasmic antibodies				-						
Rheumatoid factor				< 20						< 30
Total cholesterol					358					130-190
Triglycerids					300					<150
HDL					42					40-160
LDL 265					256					< 100

proteinuria is no longer an absolute criterion, the biological data and mainly the absence of hypertension allow us to reasonably exclude pre-eclampsia/HELLP syndrome (Gestational Hypertension and Pre-eclampsia 2020; Helewa et al. 1997). Bile salt came back negative ($7 < 20 \mu$ mol/L) as well. An infectious and immunological work-up was also undertaken and found to be negative (Table 1: EBV/CMV immune//Toxoplasmosis not immune//Hepatitis negative including Hepatitis E//Parvovirus B19 immune//No autoantibodies).

During hospitalization, cytolysis worsened (Table 1 and Fig. 1), and in the face of this phenomenon, an imaging investigation was recommended to exclude an organic pathology that went unnoticed. In the first instance, abdominal ultrasound did not reveal any signs of lithiasis and did not reveal any focal lesions. In the second stage, an abdominal MRI was performed and did not reveal any etiology. Faced with this situation, which was at the very least questionable, a complementary history was taken to highlight an element of the patient's lifestyle that could explain the clinical situation. During the interrogation, the patient mentioned that she only consumed sweetened drinks such as soda and energy drinks without ever drinking mineral water. She consumed more than 2 L of soda per day. On the other hand, there was no excessive consumption of alcohol, either during or before her pregnancy. In terms of diet, she revealed that she ate mainly very fatty foods such as French fries, pizzas, and since the beginning of her pregnancy a lot of sweets. It should be noted that the patient had a completely normal BMI. This excessive consumption of junk food was stopped at the time of her hospitalization, and a slight decrease in liver tests was noted at the end of her stay, without, however, becoming normal.

From a fetal perspective, maturation was achieved, and daily monitoring never showed any abnormalities in fetal

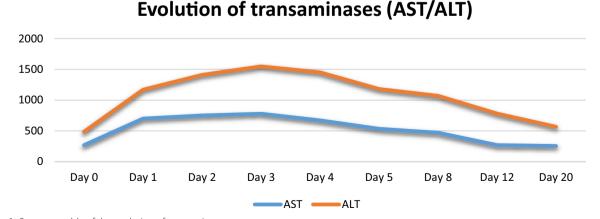
heart rate. An obstetric ultrasound was performed on admission and was completely normal with growth at the 17th percentile for age.

Thanks to the new elements of the history and in the absence of evidence from complementary examinations, the most likely diagnosis of non-alcoholic steatohepatitis was retained in agreement with the hospital's gastroenterology team. In the absence of previous lipid profile values, it is, therefore, more of a diagnosis of exclusion, which will require further assessment in the post-partum period.

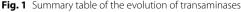
The patient was, therefore, discharged after 5 days in hospital. A treatment-based mainly on hygienic and dietary measures was recommended. It is based on the avoidance of all consumptions of sugary drinks and fatty foods, as well as any medication that is metabolized by the liver.

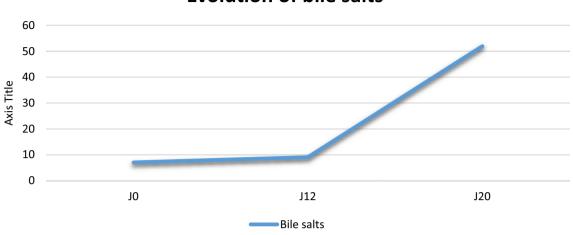
A suitable follow-up with blood tests and monitoring was instituted. Dyslipidemia was detected (Table 1) but was difficult to interpret given the context of pregnancy and the absence of previous values. Despite this, these values are entirely consistent with the diagnosis. The liver tests were still improving (Fig. 1). A bile salt test was carried out 1 week after discharge to check for possible gestational cholestasis and was negative. After 3 weeks, following the appearance of mild pruritus on the hands and feet, a new blood test was performed with a bile acid analysis. As the analysis was not performed in our laboratory, the results took a long time to obtain (>1 week) and were positive (52 μ mol/L) (Fig. 2).

Even before the results of the bile acid were available, 2 days after the blood test, the patient presented in spontaneous labor at 31 + 1SA. A magnesium sulfate infusion was started, and the delivery took place vaginally without any complications. The baby had a pH of 7.35 with an Apgar score of 9/10/10 for a weight of 1750 g, which is









Evolution of bile salts

Fig. 2 Summary table of the evolution of bile salts

approximately the 50th percentile for age (Massoud et al. 2014). He was admitted to the neonatology department where he was managed. It should be noted that during the 1st hours of life, the newborn presented hypoglycemia and premature jaundice. The rest of his hospitalization was unremarkable.

Conclusions

Obesity and overweight, defined as a body mass index > 30 and > 25, respectively, are major public health problems. In 2016, more than 1.9 billion adults aged 18 and over were overweight. Of these, over 650 million were obese (World Health Organization (WHO) https:// www.who.int/news-room/fact-sheets/detail/obesity-andoverweight). The main cause of obesity is an imbalance in energy balance. On the one hand, excessive consumption of energy-rich foods, and on the other, very lowenergy expenditure characterized by physical inactivity (World Health Organization (WHO) https://www.who. int/news-room/fact-sheets/detail/obesity-and-overw eight). In 60–70% of cases, these obese patients will have dyslipidemia (Feingold et al. 2000). As a result, the proportion of pregnant patients who are overweight or obese is increasing significantly. For example, the rate is rising from 34.7 to 41.2% in Wallonia and from 32.7 to 39.4% in Brussels (2010 to 2019) (Centre d'Epidémiologie Périnatale asbl 2019). This is a statistic that is true in a large majority of other countries such as the USA (Driscoll and Gregory 2020) or the UK (Denison et al. 2019). During pregnancy, obesity can have enormous implications and will increase the morbidity and mortality of patients. It will increase the risk of obstetric pathologies such as gestational hypertension, pre-eclampsia, gestational diabetes, and preterm birth (Poston et al. 2011; Hamsir et al. 2022; Radesky et al. 2007; Gete et al. 2020).

Dyslipidemia is a major public health problem because of its high prevalence (40-50% of the population), and because most patients are asymptomatic (Haslam et al. 2020; Green 2003; Descamps et al. 2012). We know its impact on cardiovascular disease, but we know very little about the influence it can have on pregnancy. The lipid profile of patients may influence the obstetrical outcome (Jin et al. 2016; Jiang et al. 2017; Page and Girling 2011; Martineau et al. 2015; Sarkar et al. 2020; Hershman et al. 2019; Koralegedara et al. 2022; Jamaly et al. 2022). NAFLD is defined as an accumulation of fat in the liver without any other proven cause such as alcohol, medication, etc. It is the hepatic expression of the metabolic syndrome. It is well known in older women but is not well known in pregnant women (Sarkar et al. 2020; Hershman et al. 2019). Given the impact of multiple genetic and environmental factors in NAFLD, much remains to be learned about the mechanisms leading to the disease (Hershman et al. 2019). However, it may be found more often in the future given our dietary habits (Haslam et al. 2020), and it is more frequently included in the differential diagnosis of alterations in liver tests during pregnancy (Page and Girling 2011). The overlapping features of the metabolic syndrome make it difficult in retrospective studies to distinguish the contribution of each metabolic risk factor to NAFLD in pregnancy. Prospective studies are needed to elucidate the association between NAFLD and pregnancy-specific features such as GDM and the actual impact of NAFLD on pregnancy outcomes (Hershman et al. 2019). Dyslipidemia is a common (40-50%) and asymptomatic condition with many implications both at the cardiovascular level (Descamps et al.

2012) and in pregnancy (Jin et al. 2016; Jiang et al. 2017; Page and Girling 2011; Martineau et al. 2015; Sarkar et al. 2020; Hershman et al. 2019; Koralegedara et al. 2022; Jamaly et al. 2022). Our diet is an important risk factor as shown in this clinical case. Excessive consumption of sugary drinks such as SODA has a very strong impact on the lipid profile with an increase in triglycerides and LDL and a decrease in HDL (Haslam et al. 2020). This imbalance caused by eating habits will favor the development of dyslipidemia characterized by LDL > 160 mg/dl, HDL < 50 mg/dl in women, triglyceride > 175 mg/dl, and cholesterol > 190 mg/dl (Haslam et al. 2020). It is true that pregnancy modifies lipid parameters from the 12th weeks of amenorrhea and induces a physiological hyperlipidemia (Jin et al. 2016). However, the patient did not change her lifestyle during pregnancy, which suggests that gestation could only exacerbate this pathology (Page and Girling 2011). Because of this increase in fatty acids in the bloodstream, the entity known as NAFLD develops, defined by the accumulation of fat in the liver in the absence of major alcohol consumption and other pathologies (drugs, lipodystrophy, Wilson's disease, parenteral nutrition, and viral hepatitis). It is necessary to exclude all secondary causes before confirming the diagnosis (Sharma and Arora 2019). This accounts for 20-30% of liver disease. There is a wide clinical spectrum within this pathology, ranging from simple steatosis to steatohepatitis, which is characterized by steatosis complicated by inflammation with or without fibrosis, and which can progress to non-alcoholic cirrhosis and hepatocarcinoma (Green 2003; Descamps et al. 2012; Jin et al. 2016; Jiang et al. 2017; Page and Girling 2011; Martineau et al. 2015; Sarkar et al. 2020; Hershman et al. 2019; Koralegedara et al. 2022; Jamaly et al. 2022; Mousa et al. 2018; Sharma and Arora 2019). This is the hepatic side of the metabolic syndrome. Most often, it is asymptomatic and will lead to an incidental diagnosis on biology or imaging. Altered liver tests and a pathological lipid profile are the biological features, while hyperechogenicity of the liver will be demonstrated on ultrasound. However, to certify the diagnosis of NASH, histology or possibly a fibro scan is mainly required to judge the degree of liver fibrosis (Sharma and Arora 2019). It is true that our patient does not present the typical profile of a person with a complete metabolic syndrome, but because of her excessive consumption of soda, she presents an important criterion, which is dyslipidemia despite her normal BMI. The association of metabolic syndrome and NAFLD/NASH is not universal. Not all patients with metabolic syndrome have NASH. This is a misleading factor as our patient with a normal BMI could lead to the neglect of this hypothesis. Pregnancy probably allowed the disease to be exacerbated because it develops preferentially in a context of insulin resistance, a situation found especially during pregnancy (Page and Girling 2011; Martineau et al. 2015; Sarkar et al. 2020; Hershman et al. 2019). It is also difficult to confirm this with certainty in the absence of a previous lipid profile and without knowing the precise mechanism linking NAFLD to obstetrical repercussions.

In the face of such an alteration of the liver tests during pregnancy, it is advisable first to exclude a more common gravidic pathology such as pre-eclampsia/HELLP or intrahepatic cholestasis of pregnancy without forgetting the acute fatty liver of pregnancy (Page and Girling 2011; Martineau et al. 2015; Sarkar et al. 2020; Hershman et al. 2019; Koralegedara et al. 2022; Jamaly et al. 2022; Mousa et al. 2018; Sharma and Arora 2019; Ko and Yoshida 2006). The various examinations carried out, and the clinical course made it possible to exclude these pregnancy-related pathologies. In addition, imaging techniques and serological assays have also made it possible to exclude an organic, infectious, or even autoimmune etiology. The exclusion of all these pathologies and the thorough history of the patient allow us to retain NAFLD/NASH as the most probable diagnosis and will have to be assessed post-partum to allow an adequate follow-up given the evolution of this clinical entity.

The other important consideration in dyslipidemia is the possibility of obstetric repercussions. There is an increased risk of gestational diabetes (33%), pre-eclampsia (25%), gestational cholestasis, and macrosomia (Jin et al. 2016; Jiang et al. 2017; Page and Girling 2011; Martineau et al. 2015; Sarkar et al. 2020; Hershman et al. 2019; Koralegedara et al. 2022; Jamaly et al. 2022; Mousa et al. 2018) (Table 2).

This dyslipidemia had no impact on the carbohydrate tolerance of our patient who did not develop gestational diabetes. However, she did develop intrahepatic cholestasis during her NAFLD/NASH, which was more than likely favored by her pathological lipid profile which already had an impact on her liver. Cholestasis has been shown to be associated with carbohydrate intolerance and dyslipidemia (Martineau et al. 2438). Some studies have shown

Table 2	Obstetrica	l impact of	dyslipic	demia
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	Triglycerides		
	OR (CI)	P value	
Gestational diabete	1.37 (1.18–1.58)	0.000	
Pre-eclampsia	1.50 (1.16–1.93)	0.002	
Pregnancy cholestasis	1.28 (1.09–1.51)	0.002	
Premature delivery	1.61 (1.11–2.34)	0.001	
Fetal growth restriction	0.63 (0.40-0.99)	0.046	
Macrosomia	1.19 (1.02–1.39)	0.024	

an association between preterm birth and dyslipidemia (Jiang et al. 2017; Page and Girling 2011; Martineau et al. 2015; Sarkar et al. 2020; Hershman et al. 2019; Koralegedara et al. 2022; Jamaly et al. 2022). Although the mechanism is still unclear, high lipid levels play an important role in supporting pregnancy, lipids also seem to have a negative role. Indeed, hyperlipidemia is responsible for oxidative stress as well as inflammation with deleterious effects on the pregnancy in progress. It is, therefore, this inflammatory state that could be responsible for these premature deliveries (Martineau et al. 2015), but the many factors involved require prospective studies to identify a precise mechanism linking NAFLD and its obstetric implications (Hershman et al. 2019).

In our patient's case, she gave birth prematurely, which seems to be in line with the literature. Despite the dietary efforts made and the slight improvement in her biological tests, it is possible that these efforts were not sufficient. As the situation was already well advanced at the time of diagnosis, treatment would only have pushed back the deadline. The situation should be assessed in the postpartum period to assess the impact of the diet on her lipid profile and to determine the outcome of any future pregnancy.

The child presented hypoglycemia and premature jaundice which could be attributed to the secondary development of gestational cholestasis.

Currently, no treatment has been approved by the FDA or EMA. The cornerstone of treatment is lifestyle modification that combines both a balanced diet and physical activity. Indeed, a weight loss of more than 10% will lead to a clinical and biological cure of NASH in 90% of patients. From a medicinal point of view, various molecules have been used (e.g., metformin, ursodeoxycholic acid, statins, etc.) without showing any real added value. From a dietary point of view, it is recommended to adapt a Mediterranean-type diet and avoid processed foods and drinks rich in added fructose as much as possible (Eslam et al. 2020; Semmler et al. 2021; Lanthier 2020) (Table 3).

During pregnancy, the dietary recommendations are quite equivalent. It is advisable to eat in moderation all foods that may contain hidden fats (pastries, ready meals, fried foods, etc.) but also added sugars and sweeteners. It is advisable to eat fruit and vegetables as well as legumes, which can help reduce meat consumption. It is obvious that advice on prevention of possible toxoplasmosis or listeria infection should be followed (Office de la naissance et de l'enfance https://www.one.be/public/broch ures/brochuredetail/brochure/grossesse-et-allaitementque-manger/) (Table 4).

In conclusion, it would be interesting to know the lipid profile of pre-conceptional patients. A rapid dietary history and analysis of the patient's clinical profile could **Table 3** Dietary recommendations in NASH (Eslam et al. 2020;

 Semmler et al. 2021; Lanthier 2020)

Type of diet Weight loss	Low calorie (minus 500–1000 kcal/day) 7 à 10%
Macronutrient composition	No evidence of effectiveness of a par- ticular diet but in practice: Low carbohydrate component Low-fat content Mediterranean diet Rich in fruits and vegetables, who- legrains and legumes Rich in olive oil Rich in fish Less red and processed meat Less refined cereals and potatoes Less sugary drinks
Fructose	Avoidance of drinks with added fructose
Physical exercise	Aerobic and resistance training

Table 4 Dietary recommendations during pregnancy (Office de la naissance et de l'enfance https://www.one.be/public/broch ures/brochuredetail/brochure/grossesse-et-allaitement-quemanger/)

Fruit and vegetables	400 g/day
5	5 ,
Starches	3 times a day, wholegrain cereals are preferred
Dairy products	3–4 times a day to meet the estimated calcium requirement of 950 mg/day
Meat/poultry/fish/eggs	Especially lean meats Favor fish twice a week You do not have to eat them every day and legumes can be an excellent alternative Eggs are rich in omega 3 and therefore beneficial
Fats	In moderation and preferably uncooked Olive or rapeseed oil, or even salt-free butter, are to be preferred

initially be used to filter out patients at risk of dyslipidemia and in whom NAFLD or even NASH decompensation is possible. This could lead to closer follow-up, given the likely obstetrical repercussions, which merit further study. It should also be considered in the differential diagnosis of alterations in liver tests after exclusion of gravidic and non-gravidic pathologies. A balanced diet before and during pregnancy could help to control the disease and its possible complications.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CMV	Cytomegalovirus
CRGOLFB	Collège Royal des Gynécologues Obstétriciens de la Langue Fran- çaise de Belgique

EBV	Epstein–Barr virus
EMA	European Medicines Agency
FDA	Food and Drug Administration
GGT	Gamma-glutamyl transferase
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
HELLP	Hemolysis, elevated liver enzymes, and low platelets
MRI	Magnetic resonance imaging
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis

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Author contributions

JC managed the patient, analysed the data, and wrote the article. CL helped to write the article and provided his expert opinion on obstetrics. MB helped to write the article and made corrections based on his experience and his various publications. CR, head of department at the Marie Curie Hospital, contributed to the care of the patient and the writing of the article. All authors have read and approved the manuscript

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Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare that they have no competing interest.

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