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Recurrent Acute Fatty Liver of Pregnancy: About A Case and A Review of the Literature

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Abstract:

Acute hepatic steatosis of pregnancy (SHAG) is a specific but rare liver disease, which can usually complicate the third trimester of pregnancy. It is potentially fatal for the mother and the fetus. To our knowledge, only 8 cases of recurrence - of the order of 10% - have been published, and we are reporting one new case. The first episode presented by our 23-year-old patient was suspected in the presence of cutaneous-mucous jaundice with vomiting occurring in pregnancy of 35 weeks, hyperleucytosis, abnormal liver tests, as well as hypoglycemia were biological elements supporting the diagnostic harness. However, the imagery could not provide clear confirmation. The outcome was favorable after delayed extraction by the upper route for pulmonary maturation.

Three years later, she presented to the obstetric emergency room after 36 weeks + 6 days, with a clinical-biological picture almost similar to that of the first episode, and the pregnancy was terminated by caesarean section for suspected recurrence. The evolution has been favorable for the mother and her children. The importance of communication on the risk of recurrence, and clinical and biological monitoring, in particular in the third trimester of subsequent pregnancy, are imperative in order to improve the prognosis of this pathology

Summary

Acute fatty liver of pregnancy (AFLP) is a specific but rare hepatopathy that can usually complicate the third trimester of pregnancy. It is potentially fatal for the mother and the fetus. To our knowledge, only 8 cases of recurrence -about 10%- have been published, and we report a new case. The first episode presented by our 23-year-old patient was suspected in front of a cutaneous-mucosal jaundice with vomiting occurring on pregnancy of 35 SA. Hyperleucytosis, abnormalities of the hepatic balance, as well as a hypoglycemia were biological elements supporting the diagnostic beam. On the other hand, imaging could not bring a clear confirmation. The evolution was favorable after deferred extraction by caesarean section for pulmonary maturation. Three years later, she presented to the obstetrical emergency room at 36 weeks and six days of amenorrhea, with a clinical and biological picture almost similar to that of the first episode, and the pregnancy was interrupted by caesarean section for suspicion of recurrence. The evolution was favorable for the mother and her childrens. The interest of the communication on the risk of recurrence, the clinical and biological monitoring in particular in the third trimester of the subsequent pregnancy are imperative, in order to improve the prognosis of this pathology.

Introduction

Acute fatty liver disease was once considered extremely rare. However, with increased awareness, improved prenatal care and screening, diagnosis is made early, and less obvious cases are recognized. Currently, the prevalence of SHAG is estimated at 1 to 3 cases per 10,000 deliveries **[**1,2**]**.

SHAG is a condition whose clinical and laboratory symptoms are well known **[**3,4**]**. Liver puncture biopsy (PBH) is the gold standard diagnostic test since the definition of SHAG is histological **[**5**]**. However, this invasive examination, the morbidity of which although low is not negligible, occupies a limited place

when SHAG is suspected. A range of arguments to lead to an early diagnosis, without resorting to an invasive procedure, improves the maternal-fetal prognosis **[**6**]**.

SHAG is a rare pathology whose incidence varies according to studies from 1 / 1,000 to 1 / 20,000 deliveries **[**8-9**]**, and may be responsible for acute hepatocellular failure. The prognosis has been considerably improved in recent years with early fetal extraction **[**5**]**. The cause of the accumulation of lipids during this micro-vacuolar steatosis is currently not fully understood. SHAG has been shown to be associated with an inherited deficiency of the LCHAD (Long-chain 3 hydroxy-COA dehydrogenase) enzyme in the mitochondrial beta-oxidation cycle of fatty acids. It is indeed an autosomal recessive inherited defect.

Few cases of recurrence have been published, the first was reported in 1990 by Barton et al. **[**10**]**, then seven other cases were published subsequently **[**11-12**]**. We report a new case of relapsing SHAG.

Observation

A 23-year-old woman, primigest, admitted to maternity in 2017 after 35 weeks of amenorrhea, for onset of increasing jaundice which appeared two weeks before her admission. The patient did not report any particular history, did not take any long-term medication and did not consume alcohol. The pregnancy was progressing normally. On the day of her admission, the patient complained of vomiting, nausea, with abdominal pain. The clinical examination objectified: a generalized cutaneous-mucous jaundice of cholestatic appearance without associated pruritus, a normal blood pressure at 120/60 mmhg, with negative proteinuria, the gyneco-obstetrical examination found: a bishop at 0 and BCFs perceived.

The obstetric ultrasound found an active pregnancy, and an estimated fetal weight was 2100g. The results of the laboratory tests were as follows: hemoglobin at 11.5 g / dl, platelets at 312,000 elements / mm3, white blood cells at 17,400 elements / mm3, prothrombin (PT) level at 53%, prolonged activated cephalin (TCA), aspartate aminotransferase (ASAT) 494 IU / L (10 times normal), alanine aminotransferase (ALAT) 123 IU / L (3 times normal), gamma glutamyl transferase (γGT) at 26 IU / L, total bilirubin at 162 µmol / L, with conjugated bilirubin at 111 µmol / L, serum creatinine at 6.5 mg / L, urea at 0.18 g / L, blood glucose at fasting at 0.48g / L, and lactate dehydrogenases (LDH) at 722 IU / L.

The abdominal ultrasound did not show any sign that argued for a fatty liver, namely diffuse hepatic hyperechogenicity. Likewise, there was no ultrasound evidence of intraperitoneal effusion, and the intra- and extrahepatic bile ducts were undilated.

Due to the strong suspicion of SHAG, delivery was performed by cesarean section after an injection of β-methasone to promote lung maturation of the fetus. It was extracted a living child, male, APGAR 10/10, with a birth weight of 2200 g, whose evolution was favorable. After childbirth, the symptoms disappeared and the laboratory tests gradually normalized. Hepatitis A, B, C, and HIV serologies were negative.

The Patient is said to have been released from the hospital after her improvement. She would have been informed about the risks of recurrence in the event of a subsequent pregnancy.

The Patient was lost to follow-up. Three years later, in 2020, she presented to the maternity emergency room after 36 weeks + 6 days, with recent generalized jaundice with a few episodes of vomiting and pain in the right hypochondrium.

The patient reported a normal course of the pregnancy, and specified that the psychomotor development of her first child was without abnormality. She was hospitalized urgently. The clinical examination on admission found generalized cutaneous-mucous jaundice of the retentional type without pruritus, normal blood pressure, no proteinuria, with the gyneco-obstetrical examination perceived BCF and a bishop at 0.

The obstetric ultrasound showed an active pregnancy, and an estimate of the fetal weight at 2600g, with normal dopplers.

The results of the laboratory tests were as follows: hemoglobin at 14 g / dl, platelets at 272,000 elements / mm3, white blood cells at 15,000 elements / mm3, prothrombin (PT) level at 70%, activated partial thromboplastin time (TCA) normal, aspartate aminotransferase (ASAT) at 218 IU / L (6 times normal), alanine aminotransferase (ALAT) at 425 IU / L (9 times normal), total bilirubin at 120 µmol / L predominantly conjugated at 73 µmol / L, serum creatinine 6 mg / L, urea at 0.11 g / L, fasting blood glucose at 0.6 g / L and LDH at 560 IU / L. Liver B and C serologies were negative.

A liver ultrasound did not show any evidence for a fatty liver. There was no intraperitoneal effusion, and the intra- and extrahepatic bile ducts were undilated.

In front of the table above a suspicion of recurrent SHAG had led to a cesarean section emergency, giving birth to a female child, APGAR 10/10, birth weight 2700g.

The condition of the mother and her newborn remained stable, and the course was marked by clinical and biological improvement in the patient who was declared discharged on the ninth day postpartum.

The patient was again informed of the risks of recurrence for a future pregnancy.

Discussion

Acute hepatic steatosis of pregnancy (SHAG) is a relatively rare disease occurring most often during the third trimester of pregnancy and the diagnosis of which must be easily suspected in the face of clinical and laboratory manifestations which are well known **[**12**]**. The gold standard for diagnosing SHAG is liver histology. Notwithstanding the hepatic puncture biopsy (PBH) is an invasive examination and the morbidity and mortality of this examination is not zero. In addition, with advanced SHAG disorders, coagulation disorders appear and increase the risk of complications. In case of diagnostic doubt pre or postpartum, a liver biopsy should be discussed. If coagulation disorders exist, PBH should be performed by the trans-jugular route. And the sample must be associated with a fixative that does not dissolve fat and will be studied after Oil Red O staining **[**13**]**. Centrilobular micro-vacuolar steatosis is observed. The hepatocyte nuclei keep their central position. A few foci of hepatocyte necrosis are possible but remain limited, without massive necrosis. An electron microscope study may be useful in cases of minimal steatosis. It will also show mitochondrial abnormalities. These lesions disappear very quickly after childbirth and do not progress to cirrhosis **[**13**]**.

The main clinical manifestations are nausea and / or vomiting, abdominal pain, jaundice, and polyuropolydipsic syndrome without hyperglycemia. The main laboratory abnormalities are hepatocellular failure, acute cytolysis, hypoglycemia, hyperbilirubinemia, hyperammonemia, thrombocytopenia, hyperuricaemia and renal failure **[**14**]**.

The antithrombic activity (antithrombin III) is often severely collapsed in cases of acute hepatic steatosis of pregnancy, and can be very interesting to distinguish a HELLP syndrome from a SHAG - quite frequent association -, whose delicate differentiation, sometimes impossible even with histology data which can be diverse and difficult to interpret. This does not prevent the biological results from taking time, and should in no case delay treatment **[**14**]**.

Incorporation of the antithrombin activity assay may be a further aid in the diagnosis of SHAG **[**14**]**. Although jaundice is by no means a pathognomonic clinical sign, it remains the most frequently found reason for consultation. Indeed the latter inaugurates the so-called icteric phase of SHAG which is a diagnostic and therapeutic emergency. The etiological approach will then be made by deduction, by eliminating jaundice of drug origin (Methyl-dopa, Erythromycin, Chlorpromazine, etc.), jaundice of infectious origin (viral hepatitis A - B - C). Biliary obstacles (hepatic colic with jaundice, and hepato-biliary ultrasound will correct the diagnosis). Pregnancy intrahepatic cholestasis (predominance of pruritus in the foreground followed by jaundice, confirmation is by elevation of the bile salt level). As for the HELLP syndrome in a context of preeclampsia, the main differential diagnosis, the similarity of the clinical and biological picture, and the frequent association found in 50% of cases with SHAG, sometimes

makes it difficult to distinguish between these different entities, nevertheless the management therapy follows the same objectives.

In our observation and for both episodes, the diagnosis of SHAG was strongly suspected in the face of the clinical and biological signs described in the literature, while imaging did not provide any confirmatory elements, unlike in the case reported by BACQ et Al, who reported a case of recurrent SHAG, where the Imaging revealed a heterogeneous liver parenchyma, with hyperechoic plaques **[**15**]**.

In our case, the indication for a liver biopsy could be discussed to confirm the diagnosis, however the transient disturbance of the blood crase report that appeared in the immediate postpartum period contraindicated this additional examination.

Liver biopsy is rarely performed during pregnancy given the risks of the procedure. Its indication is particularly controversial because it is not necessary for the management, it could even delay it if the diagnosis is strongly suspected. In addition, it carries an increased risk of bleeding increased by liver failure and associated coagulopathy **[**16**]**.

The fatty liver on abdominal ultrasound takes on a diffuse hyperechoic appearance, which may be associated with perihepatic ascites. However, a similar appearance can be observed with fibrosis, and also with granulomatosis. The sensitivity of the ultrasound depends mainly on the intensity of the steatosis, and diagnostic performance is also reduced by morbid obesity. Ultrasound is frequently normal and should not exclude the diagnosis in this case, rather it remains a means of screening **[**17**]**.

Currently, it would also be discussed to perform magnetic resonance imaging (MRI). However, the value of MRI in confirming steatosis in women suspected of SHAG has not been validated **[**18**]**. Indeed, SHAG is a typically microvacuolar steatosis, a form of steatosis rarer than macrovacuolar steatosis. Steatosis is mainly made up of free fatty acids, unlike other steatosis, in particular nutritional, made up of triglycerides. It is therefore not certain that MRI performs as well in SHAG as in other forms of steatosis.

It is imperative to discuss the diagnosis and to confirm it quickly. However, and in the face of the non-specificity of certain signs and in the absence of an alternative diagnosis, the diagnosis can be retained in front of criteria, called “Swansea criteria”. These are 14 elements, clinical, biological, radiological and histological, of which at least 6 are necessary to strongly suggest the diagnosis of SHAG **[**14**]**:

• Vomiting.

• Abdominal pain.

• Polyuria-polydipsia.

• Encephalopathy.

- Coagulopathy.
- Hyperbilirubinemia (total bilirubin> 14 mg / L).
- Hypoglycemia (blood glucose <0.72 g / l).
- Hyperuricemia (uric acid> 57 mg / l).
- Hyperleukocytosis (leukocytes> 11,000 elements / mm3).
- Renal failure (serum creatinine> 17 mg / l).
- Elevation of transaminases (GOT> 42 IU / L).
- Hyperammonemia (ammoniaemia> 47 µmol / L)
- Ascites or shiny liver on ultrasound.
- Microvacuolar steatosis on liver biopsy.

To the best of our knowledge, we report the ninth case of recurrence of SHAG.

Identical to our observation, the two episodes of recurrence of SHAG occurred during the first two pregnancies, except for the first case of recurrence reported in 1990 **[**10**]**. This is consistent with the existence of a predisposing genetic factor in women with SHAG. Indeed, it is related to a deficit of beta-oxidation of acids fatty, linked to a decrease in the activity of the LCHAD enzyme (Long-chain 3 hydroxy-COA dehydrogenase), this due to mutations in the gene encoding the LCHAD enzyme in women with SHAG and their children **[**12 -19-20**]**. In practice, it is therefore currently recommended to test for this mutation in women with SHAG and their children, and possibly in their partner **[**12, 21,22**]**.

Conclusion

SHAG is a condition that can recur. If a new pregnancy is desired, the patient must be clearly informed of this risk of recurrence and of the need for clinical and laboratory monitoring throughout the pregnancy, in particular during the third trimester.

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