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(RESEARCH ARTICLE)

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Acute fatty liver of pregnancy About 20 cases

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Abstract

Our retrospective study concerned acute hepatic steatosis in pregnancy: diagnostic problems, severity and therapeutic perspectives in the Moroccan context.

It concerns a series of 20 cases of SHAG collected in the department of gynecology-obstetrics and maternal resuscitation of the CHU MOHAMED VI in Marrakech over a 5-year period from January 2017 to December 2021.

We included in this sample women admitted during pregnancy or post partum for management of SHAG.

In our series, the frequency of SHAG was 1 case per 4340 deliveries.

The age of the patients ranged from 18 to 45 years, with an average of 28 years and an average gestational age of 32 days and 3 weeks. Thus the majority of patients were multiparous and multigestational with a frequency of 55%.

Clinically: polyuria-polydipsia syndrome was present in 20% of patients, nausea-vomiting in 70% and epigastralgia in 60%.

Biologically: Hypoglycaemia present in 60%, hyperleukocytosis in 85%, creatinine level above 12mg/l in 70%, hyperuricaemia in 75%, hepatic cytolysis in 90%, hyper bilirubinaemia in 95% with conjugated predominance, prolonged PT in 50% and hyperammonia in 10%.

Concerning complications, acute fulminant liver failure was observed in 30% of our patients, it is the most serious and fatal complication.

The therapeutic management of SHAG requires, in addition to uterine evacuation associated with adequate medical and surgical resuscitation.

Keywords: Hepatic steatosis; Pregnancy; Balance; Obstetrics; Thrombocytopenia

1. Introduction

Acute hepatic steatosis in pregnancy or Sheehan's disease is a rare but serious complication of pregnancy [1,2].

Its clinical presentation can be typical but is sometimes confusing. Although its diagnosis is increasingly common, its incidence is still underestimated as moderate and/or atypical cases still escape diagnosis [3,4].

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Sheehan's disease is a condition that should not be ignored, even if the clinical signs are not specific, which can lead to misdiagnosis, because early and rapid management considerably improves the fetal and maternal prognosis.

Our aim is to describe the clinical and biological characteristics, to detail the therapeutic management and to identify the elements of poor maternal prognosis of SHAG in our region.

2. Patients and methods

Our study is a retrospective series of 20 observations of cases of acute gravidic hepatic steatosis collected in the department of gynecology-obstetrics and maternal resuscitation of the CHU MOHAMED VI in Marrakech.

The study was conducted over a period of 5 years, from January 2017 to December 2021.

We included in this sample the women admitted pregnant or postpartum to the gynecology-obstetrics and maternal intensive care unit for the management of acute gravidic hepatic steatosis.

For each patient, an evaluation form was drawn up. We used the following to fill in these forms: hospital records, delivery room registers, maternity unit registers and operating theatre reports.

The data collected was entered and analysed using Word 2007 and Excel 2013.

The records and data collected in our study were kept confidential.

2.1. Epidemiology

Over a period of 5 years, from January 2017 to December 2021, 86,808 patients gave birth in the gynaecological-obstetrics department of the CHU Mohammed VI, Twenty patients among them presented with SHAG, i.e. a frequency of 1 case for 4340 deliveries.

The age of the patients varied between 18 and 45 years, with an average age of 28 years. The age group between 21 and 25 years was the most dominant with a rate of 30%.

2.2. Clinical data

The study of the reason for consultation showed that 60% of parturients consulted for mucocutaneous jaundice, 10% had digestive signs, especially epigastralgia. 10% of the patients were referred for consciousness disorders. All our patients were seen at an advanced stage of Acute Gravidic Liver Steatosis.

We found that the majority of patients were multigestate with a frequency of 55%, compared to 45% who were primigravida. Of the 20 patients interviewed, 4 presented with a gynaeco-obstetrical history, i.e. 20% of cases, including 10% with a history of fetal death in utero, 5% with a history of retro placental haematoma and 5% with a history of post partum haemorrhage. Of the 20 patients interviewed, 18 had a vaginal delivery and 2 had a caesarean section. The average gestational age in our series was 32 days with extremes ranging from 21 days to 40 days. The gestational age range between 36 and 40 days was the most dominant with a rate of 30%.

Of the 20 patients, 70% had a GCS score of 15/15, while 6 patients or 30% had neurological problems, either since admission or during their hospitalisation. Of note, two of the 6 patients were admitted in a coma state with a GCS score < 8/15 following haemorrhagic shock.

Of the 20 patients, 55% had normal blood pressure and 35% had hypertension. 2 patients or 10% were admitted in haemorrhagic shock with SAP<90mmhg. Tachycardia was found in 9 patients or 45%, while 55% had normal heart rate. Polypnoea was found in 5 patients or 25%, while 75% had normal respiratory rate. Edema was found in 65% of patients. Proteinuria was found in 6 patients (30%). Among the 20 patients, icterus was found in 17 patients (85%). Oligo-anuria (diuresis<1000 ml/24h) was found in 7 patients or 35%, while polyuria (diuresis > 3000 ml/24h) was found in 4 patients. Eight patients (40%) had neurosensory signs such as headache, hearing and/or visual disorders, while 2 patients (10%) had sharp osteotendinous reflexes on clinical examination.

2.3. Biological data

2.3.1. Blood count

All patients underwent a blood form count with the exploration of haemoglobin, leucocytes and platelets. The mean serum haemoglobin level was 8.5 g/dl with extremes ranging from 3.2 to 12.9 g/dl.

Haemoglobin testing diagnosed anaemia (Hb<12 g/dl) in 18 patients or 90% of cases, of which 4 patients or 20% had Hb<7g/dl.

The mean platelet count was 114,000 elements/mm^3 with extremes ranging from 12,000 to 376,000 g/dl. Thrombocytopenia was observed in 15 patients, i.e. 75% of cases, of which 15% were severe.

The average white blood cell count was 22,305 cells/mm^3 with extremes ranging from 2,700 to 37,900 cells/mm^3. 17 patients (85%) had hyperleukocytosis and 2 patients (10%) had leukopenia.

2.3.2. Haemostasis test

The prothrombin time and activated partial thromboplastin time were performed in all patients.

The mean value of the PT was 48.82% with extremes ranging from 21.7% to 93%.

Ten patients, i.e. 50%, had an elevated PT (<70%) and 55% had an elevated APTT.

2.3.3. Blood glucose

Twelve patients or 60% had a blood glucose level <0.7 g/l, compared to only one known diabetic patient who presented with hyperglycemia

2.3.4. Renal function

Blood urea measurement showed that 9 patients (45%) had a blood urea level above 0.5g/l. The mean value of blood urea was 0.61 g/l with extremes ranging from 0.21 to 1.27 g/l

Creatinine measurement is a good means of monitoring renal function and allows the diagnosis of renal failure when its value exceeds 12mg/l. In our series, 14 patients (70%) had a creatinine level above 12mg/l on admission. The mean creatinine value was 22.26 mg/l with extremes ranging from 4.3 to 45 mg/l.

Uricemia is a very important diagnostic test. The mean value in our series was 85.75 mg/l with extremes ranging from 36 to 167 mg/l. Hyperuricemia (greater than 60mg/l) was found in 15 patients, 75%.

2.3.5. Blood ionogram (Natremia, Kalemia)

The analysis of the blood ionogram was carried out in all the patients and made it possible to objectify: An average natremia of 132.8 mmol/l with extremes ranging from 124 to 142 mmol/l. Moderate hyponatremia (120-125 mmol/l) in one patient, i.e. 5%. Mild hyponatremia (125- 135 mmol/l) in 10 patients, i.e. 50%.

A mean kalaemia of 4.55 mmol/l with extremes ranging from 2.4 to 6.6 mmol/l. Severe hyperkalaemia (K+>6.5 mmol/L) in 5%. Moderate hyperkalaemia (6 < K+ < 6.5 mmol/L) in one patient (5%). Mild hyperkalaemia (5 < K+ < 6 mmol/L) in 3 patients or 15%. Hypokalaemia at 2.5 mmol/L in only one patient, i.e. 5%.

2.3.6. Liver function

Transaminase tests were carried out in all patients and showed a mean ASAT value of around 292 IU/L with extremes ranging from 32 to 1500 IU/L. The mean ALT value was 232 IU/L with a range of 22 to 910 IU/L. Hepatic cytolysis (transaminases greater than 3 times normal) was observed in 90% of patients.

Total and conjugated bilirubin levels were measured in all patients and showed an average total bilirubin level of 150µmol/l with extremes ranging from 13 to 384 µmol/l. Nineteen patients (95%) showed hyperbilirubinemia with conjugated predominance.

2.3.7. Other biological tests

Hepatitis B and C serologies were requested in 8 patients (40%) to eliminate possible differential diagnoses, mainly acute viral hepatitis. They were found to be negative.

CRP was elevated in all patients, the mean CRP value was 87.25 mg/l, with extremes ranging from 16 to 310 mg/l.

Ammonia is an important test in the diagnosis of SHAG.

Only two patients had an ammonia level above 50 µmol/l.

2.3.8. Radiological data

In this series, abdominal ultrasound was performed in all patients (100%). It revealed ascites in 7 patients (35%), of whom 4 patients (20%) had a hyperechoic liver.

Other abnormalities were observed: Two patients had presented with minimal ureterohydronephrosis. One patient presented with nephromegaly. Seven patients presented with hepatomegaly.

2.4. Pathological data

Liver biopsy was not performed.

2.5. Therapeutic management

The management is both medical and obstetrical. All our patients benefited from the following resuscitation measures after their admission to the intensive care unit: All our patients benefited from the following resuscitation measures after admission to the intensive care unit: Rest in the left lateral decubitus position, monitoring, pulse oximetry, taking two peripheral venous lines with vascular filling. Correction of hypoglycaemia, Placement of a gastric and urinary probe. Establishment of a monitoring sheet.

All patients who had an indication to terminate the pregnancy between 28 and 34 weeks' gestation received corticosteroid therapy for fetal lung maturity according to the following protocol Betamethasone: 2 doses of 12 mg 24 hours apart.

Two patients were sedated, intubated and ventilated. On the other hand, 18 patients, i.e. 90%, benefited from analgesia with non-opioid analgesics,

Treatment of convulsions: In the case of severe forms (complications) magnesium sulphate was administered in 3 patients (15%).

The administration of an antihypertensive in case of hypertension was necessary either as monotherapy in 25% of cases or as bitherapy (10%). The different antihypertensive drugs used were : Alpha-methyldopa, nicardipine and nefidipine,

In view of the oligo-anuria that was observed in 13 patients, an indication for the administration of diuretics (furosemide) +/- vascular filling was given, and haemodialysis was indicated in 3 patients (15%). Six patients (30%) benefited from plasma exchange during their hospitalization in the maternal intensive care unit. The average number of sessions was 3 per patient with extremes ranging from 1 to 5.

In our study, 12 of the patients, i.e. 60%, gave birth by vaginal delivery, while caesarean section was indicated in 40% of cases.

2.6. Course and complications

Six patients developed hepatocellular failure during the natural course of the disease, which allowed us to distinguish two groups:

2.6.1. First group

Treated by uterine evacuation associated with symptomatic treatment.

Second group with hepatocellular insufficiency: Treated, in addition to uterine evacuation associated with symptomatic treatment, by plasma exchange.

Maternal mortality was around 6 patients or 30%. The number of newborns who died was 14 (66%).

In our study, 19 cases of patients presented at least one complication, i.e. 95% of all patients.

The complications were as follows: Acute renal failure in 14 patients or 70%. Acute hepatocellular failure in 6 patients or 30%, of which 25% had hepatic encephalopathy (5 patients). Retroplacental haematoma in 2 patients (10%). Haemorrhagic complications in 13 patients (65%). Acute lung oedema in 2 patients, i.e. 10%. Convulsions in 3 cases, i.e. 15% of patients. Pancreatic involvement in 2 patients (10%). Ascites in 7 patients (35%). DIC in 7 patients or 35%.

Among the 21 births, 7 newborns had a favourable outcome, i.e. 33%. Fourteen cases presented at least one complication (67%), distributed as follows Fetal death in utero or neonatal death in 57% of cases. Acute fetal distress in 5%. Prematurity in 5%.

3. Discussion

Acute gravidic hepatic steatosis or Sheehan's disease is an exceptional but serious complication of pregnancy [1,2]. Although its diagnosis is increasingly common, its incidence remains underestimated [3, 4, 10]. Before 1980, its incidence was estimated at 1/106 deliveries [11]. This incidence is gradually increasing and varies from one country to another [10]. Indeed, in India, according to a study carried out between 1999 and 2000, the incidence was estimated at 1/3069 deliveries [12], whereas it was estimated at 1/900 deliveries [13] according to a British study carried out during the same period.

Hepatic steatosis is mainly due to triglyceride accumulation. In acute gravidic steatosis, it seems to be more a question of an accumulation of free fatty acids, which may be due to an anomaly in the activation of free fatty acids into acetyl coenzyme A, or else to a reduction in the transformation of free fatty acids into triglycerides [14]. This accumulation of free fatty acids is thought to be the cause of hepatocellular failure and ultrastructural changes in the mitochondria [14,15].

SHAG is more common in twin and triplet pregnancies [19]. This risk is attributed to the increased maternal production of free fatty acids, the decreased oxidation of free fatty acids and the very high production of fatty acid metabolites by both or all three fetuses.

SHAG is generally more common in primiparous women [20]. However, it can occur after several normal pregnancies in up to 50% of cases [5]. Our study agrees with this finding, as we found that SHAG was more common in multiparous patients.

Recurrence of SHAG exists but is rare: the incidence of recurrence is very low at around 10-20% [1, 11, 21-23]. Indeed, SHAG is classically described as a non-recurrent disease [1,23]. This is based on the publication of many cases of normal pregnancies following HGAHS [21,23]. However, recurrent SHAG has been exceptionally reported [24,25].

SHAG usually occurs during the third trimester of pregnancy [2]. Indeed, this complication is usually observed between 32 and 38 weeks of amenorrhoea [5, 10,24] with a mean term of 34.5-36 SA [1,20]. However, it can occur in the second trimester of pregnancy as well as early postpartum [22, 26, 27]. In our study all patients reached the third trimester of gestation

Clinically, SHAG is characterised by two phases: a pre-ictal phase and an icteric phase. The pre-ictal phase lasts for an average of ten days with extremes reported from 1 to 29 days [23, 24, 28]. According to Mantz [29], the clinical signs marking this phase may be trivial and non-specific, but their grouping is suggestive. They are most often digestive symptoms and more rarely general symptoms [20, 23, 24]. The association with polyuropolydipsia is suggestive of the diagnosis [30]. In our study this syndrome was absent. Digestive signs are the most frequent clinical signs [24]. This is confirmed by our study.

SHAG may begin with a flu-like syndrome, associated with anorexia in 21% of cases [1, 11, 28, 29]. Pregnancy-induced hypertension may be associated with SHAG in 20-50% of cases [1,24]. Signs of pre-eclampsia are present in 40-50% of cases [2].

The icteric phase is the state phase of the disease. It is characterised by the appearance of mucocutaneous jaundice with an increase in the initial symptomatology. Neurological signs or pruritus may be associated [2, 20, 31].

The appearance of jaundice in a woman with SHAG is an alarming sign. It is a retention-type jaundice that usually precedes delivery by 1 to 20 days, but it can also occur intra- or postpartum in 14% of cases [18].

During this phase, disturbances of consciousness are present in 31% of cases [24]. They vary in intensity from drowsiness, agitation and confusional syndrome to full-blown hepatic coma reflecting the severity of liver failure [24,30]. In our study the development of coma was correlated with a poor prognosis.

Biologically, in normal pregnancy, serum transaminase activity remains within normal limits (20-40 IU/l) [17]. In SHAG, transaminases are elevated with an average of ten times normal [1, 2, 11, 28, 17]. Our study confirms this finding, as the mean levels of AST and ALT were ten and five times normal respectively. Similarly, during normal pregnancy also, bilirubinemia remains within the normal range (5-17 µmol/l) exclusively in free form. In early SHAG, bilirubinemia is normal, then as the disease progresses, a predominantly conjugated hyperbilirubinemia develops and rarely exceeds 170 µmol/l [29, 16,9].

Hypoglycaemia is characteristic of SHAG. It reflects the severity of the liver damage. It is due to the decrease in hepatic glycogenolysis secondary to the depletion of hepatocytes in glycogen [1, 11,8]. This hypoglycaemia is early, constant and severe since it can aggravate or be responsible for coma. Its occurrence is therefore a criterion of disease severity.

When SHAG is diagnosed early, PT and coagulation factors (I, II, V, VII, XI and X) are normal. However, disseminated intravascular coagulation (DIC) with consumption of coagulation factors may be present in the early phase [2,5]. This DIC supports the diagnosis of SHAG [1, 18, 7].

The physiological value of white blood cells in normal pregnancy is less than 15,000 cells/mm3 [22,28]. During HGAHS, the blood count shows a predominantly neutrophilic hyperleukocytosis (>15,000 cells/mm3) in the absence of any infectious syndrome in 88% of cases. This hyperleukocytosis, although poorly explained, is characteristic of SHAG [4, 20, 28].

Acute renal failure is a frequent complication. It occurs in 50-80% of patients with acute liver failure [7,6]. It may be functional or organic and is in itself a poor prognostic element [7]. Like liver failure, renal failure contributes to the slowing of drug metabolism and elimination. It therefore favours the development of encephalopathy. Our study confirms these data. Indeed, urea levels were significantly higher in patients who died ($p < 0.01$).

The therapeutic management of SHAG requires a multidisciplinary team. Indeed, the management of HGAHS includes obstetrical treatment (urgent evacuation of the pregnancy to promote recovery of liver function) and adequate resuscitation [22,27]. Pregnancy is the only aetiological factor in GAS [11,20]. Therefore, uterine evacuation is the only curative treatment for this disease [20,24,27,6].

4. Conclusion

HGAHS remains a serious disease despite the development of resuscitation methods. It is a pathology that should be considered in the presence of any digestive symptomatology and/or disturbance of the liver balance in any pregnant woman. Its treatment is multidisciplinary. Early uterine evacuation is currently the only effective curative treatment. Better information for women on the symptoms and seriousness of this disease should certainly improve the prognosis of this disease.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interests.

Statement of ethical approval

The authors appropriate statement of ethical approval.

Statement of informed consent

Informed consent was obtained from all individual participants included in the study.

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