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(CASE REPORT)

Intrahepatic cholestasis of pregnancy: A case report

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Abstract

Intrahepatic cholestasis of pregnancy is the most common liver disease that occurs exclusively during pregnancy. Its development poses a potential risk to the mother, but especially to the fetus, and requires appropriate management and follow-up. The clinical presentation is characterized by pruritus and elevation of bile acid concentration, but there may be alterations in hepatic biochemical parameters, leading to a thorough differential diagnosis to rule out other liver diseases that may occur during pregnancy.

We present the case of a pregnant woman who presented with pruritus since the end of the first trimester with the finding of elevated bile acid concentration in the moderate range and in whom other possible causes of liver involvement were ruled out.

Keywords: Intrahepatic cholestasis of pregnancy; Liver diseases of pregnancy; Gestational pruritus; Bile acids; Pregnancy complications; Hepatocellular injury

1. Introduction

Pregnancy involves a number of adaptive physiological changes with increased neuroendocrine response resulting in increased hormonal exposure of tissues. Any alteration in the adaptive mechanisms can lead to the development of various diseases that increase the risk of maternal and fetal morbidity and mortality. Liver disease during pregnancy can be classified as disorders unique to pregnancy, acute liver disease occurring concurrently with pregnancy, or pre-existing chronic liver disease [1, 2]. Given that the physiologic changes of pregnancy may be like those observed in patients with pre-existing chronic liver disease. the evaluation of a pregnant woman with liver disease should include a thorough history, focusing on the history of liver disease, risk behaviors such as intravenous drug use and the presence of metabolic disorders, and inquiring about the course and possible complications of previous pregnancies. A complete physical examination should be performed to look for signs of chronic liver disease and to distinguish them from physiologic changes of pregnancy [2]. In addition, it should be noted that there is a physiologic increase in serum alkaline phosphatase concentration due to placental production, although there are no physiologic changes in serum bilirubin and aminotransferase concentrations. Liver diseases unique to pregnancy include hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, acute fatty liver of pregnancy, and the spectrum of pregnancy-associated hypertensive disorders (pre-eclampsia, eclampsia, and HELLP syndrome) [3]; intrahepatic cholestasis of pregnancy is the most common entity, with an incidence ranging from 0.7% to 10% [4].

Intrahepatic cholestasis of pregnancy is characterized by gestational pruritus associated with elevated bile acid levels (>10 µmol/L) [4], usually occurring in the third trimester when the pregnant woman's serum estrogen and progesterone levels are highest. However, it can also occur in the second trimester, although less frequently [2]. Risk factors associated with this condition include advanced maternal age, history of intrahepatic cholestasis in pregnancy,

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multiparity, metabolic syndrome, hepatitis C virus (HCV) infection, and family history of intrahepatic cholestasis in pregnancy. Persistent pruritus, predominantly on the palms and soles, worsening at night, is the most common reason for consultation in this condition [2, 5]. For symptomatic treatment, ursodeoxycholic acid (UDCA) is recommended, also because of the increased risk of fetal complications, and delivery before 37 weeks is recommended [5].

The following is the case of a pregnant woman in her second trimester presenting with pruritus and jaundice with markers of hepatocellular injury and elevated bile acids.

2. Case Presentation

A 31-year-old woman, 22.4 weeks pregnant by first trimester ultrasound, presents a clinical picture of 3 months evolution characterized by generalized pruritus with predominance in the hands and feet, without predominance of time, accompanied by altered liver biochemistry given by hyperbilirubinemia at the expense of direct fraction, elevation of transaminases more than 15 times the upper normal limit of reference, with predominance of ALT over AST with a ratio of 0. 6; and elevated alkaline phosphatase, but with an R factor of 8.5, indicating a hepatocellular pattern, without alteration of coagulation times. Imaging studies were performed, with a report of total abdominal ultrasound within normal limits and cholangioresonance without changes. Additional studies were requested to rule out infectious, immune, metabolic, and hepatic disorders of pregnancy. The results showed elevated bile acid levels (74.9 µmol/L), as well as negative viral serologies for hepatotropics, unaltered ferrokinetic profile, negative immune panel, normal levels of alpha-1 antitrypsin, the use of drugs or hepatotoxic herbal substances was excluded, so the diagnosis of intrahepatic cholestasis of pregnancy was made and treatment with UDCA was performed. The patient had a favorable evolution with a decrease in aminotransferase and bilirubin concentrations of more than 50% of the initial value, with subsequent discharge and strict outpatient follow-up by gastroenterology and perinatology due to fetal risk.

Table 1 Admission Paraclinics

Parameter	Result	Reference Values
Hemoglobin (g/dL)	9.3	12 - 14
Hematocrit (%)	27.8	35 - 43
Leukocytes (x10^3/uL)	10.12	5 - 10
Platelets (x10^3/uL)	317	150 - 450
Total Bilirubin (mg/dL)	2.67	0 - 0.9
Direct Bilirubin (mg/dL)	2.29	0 - 0.3
Alkaline Phosphatase (U/L)	255	35 - 105
Gamma Glutamyl Transferase (U/L)	22.0	5 - 36
ALT (U/L)	699.5	0 - 33
AST (U/L)	454.8	0 - 32
Bile Acids (µmol/L)	74.9	<10
Albumin (g/dL)	2.76	3.5 - 5.2
Creatinine (mg/dL)	0.56	0.51 - 0.95
Prothrombin Time (sec)	15.4	Control: 11.10
Partial thromboplastin time (sec)	30.2	Control: 27.8
INR	1.43	0.8 - 1.2
Ferritin (ng/mL)	128.8	13 - 150
Transferrin (%)	22.3	15 - 50
CRP (mg/dL)	0.11	<0.5
Lactic Acid (mmol/L)	2.05	0.5 - 2.2

3. Discussion

Intrahepatic cholestasis of pregnancy is the most common liver disease specific to pregnancy [6]. It is characterized by pruritus, elevated serum ALT and bile acid levels in a pregnant woman in whom other causes of hepatic dysfunction or pruritus have been excluded and who has normalization of liver biochemical tests after delivery [1]. The American Association for the Study of Liver Diseases (AASLD) does not require altered aminotransferases to diagnose this condition and only considers the presence of pruritus and bile acid levels above 10 μmol/L [3]. The South Australian Maternal and Neonatal Community of Practice states that although bile acid levels > 10 μmol/L are suggestive of this disease, there is no diagnostic doubt if these levels are above 15 μmol/L [7].

This disease usually occurs in the second half of pregnancy, especially at the end of the second and throughout the third trimester. However, some cases have been described in the first trimester of pregnancy [6]. In the presented case, the onset of the patient's symptoms occurred at the end of the first trimester and the beginning of the second trimester of pregnancy, making it an interesting case.

Pruritus is the characteristic clinical manifestation of the disease, but it is not specific to this entity and can be common in people with both acute and chronic cholestatic liver disease. The severity of pruritus in cholestatic liver disease can be assessed using scoring scales such as the 12-item Pruritus Severity Scale (12-PSS). This scale classifies pruritus into three categories: mild, moderate, and severe. The scoring ranges are as follows: mild pruritus is classified with scores from 3 to 6, moderate with scores from 7 to 11, and severe with scores from 12 to 22 [8].

At the serum level, there is an increase in bile acid concentration above 10 μmol/L, but the risk increases with levels above 40 μmol/L, where the prevalence of preterm labor and fetal distress increases. Considering the concentration of bile acids, the disease can be classified as mild if it is between 10 and 40 μmol/L, moderate from 40 to 100 μmol/L, and severe above 100 μmol/L [4]. Bile acids are synthesized in the liver as a product of cholesterol metabolism and facilitate cholesterol excretion and intestinal absorption of dietary fats and fat-soluble vitamins [9]. Their involvement in disease can be explained by their function as detergents that, when accumulated in hepatocytes, induce an inflammatory response in the hepatocyte with damage to the cell membrane and release of aminotransferases, bilirubin, alkaline phosphatase and γ-glutamyl transpeptidases (GGT) into the blood [6].

Affected pregnant women present with varying degrees of aminotransferase elevation; hyperbilirubinemia may occur in up to 30% of cases and is usually mild [4]. Although the severity of the disease is based on the serum level of bile acids, a significant increase in the concentration of aminotransferases indicates extensive hepatocyte injury, and liver function is also closely associated with fetal condition, regardless of the level of serum bile acids [10]. Elevated bile acids and altered liver biochemistry may continue to increase as pregnancy progresses and usually resolve within 3 months postpartum; however, if persistent, investigations should be performed to exclude underlying liver disease [1]. The case patient has a moderate degree of disease severity considering the serum level of bile acids and had severely elevated aminotransferases, suggesting a large degree of hepatocyte involvement.

Intrahepatic cholestasis of pregnancy usually resolves rapidly and spontaneously after the end of pregnancy; however, there is a risk of recurrence in subsequent pregnancies, which may have a more severe course. Early diagnosis and treatment are important to reduce the risk of fetal complications, especially the risk of unexpected intrauterine death [6]. Zhan et al, conducted a systematic review to evaluate the relationship between intrahepatic cholestasis of pregnancy and fetal cardiac function and concluded that there is an impairment of global fetal ventricular function and alteration of the fetal cardiac conduction system in pregnant women with intrahepatic cholestasis of pregnancy. In addition, women with severe intrahepatic cholestasis of pregnancy have an increased risk of fetal death, especially if they have bile acid levels above 100 μmol/L [11].

Treatment is based on the use of ursodeoxycholic acid, a natural hydrophilic bile acid that reduces the cholesterol saturation index of the bile and suppresses intestinal cholesterol absorption. It also has anti-inflammatory and antioxidant properties that contribute to the regulation of immune balance and apoptosis. The combined use of UDCA with hepatoprotective agents for the treatment of intrahepatic cholestasis of pregnancy is described in practice, but there is no consensus on the use of these hepatoprotective agents in the disease [10].

Table 2 Differential Diagnoses of Cholestasis

Differential Diagnosis	**Laboratories**
Viral Hepatitis (A, B, C, E, EBV, CMV, Herpes)	Viral serologies: Hepatitis A IgM: 0.33 (Non-reactive, Ref: <1.0). Hepatitis B Anti-core IgM: 0.07 (Non-reactive, Ref: <1.0) Hepatitis C Antibody: 0.04 (Non-reactive, Ref: <0.9) EBV IgM: 1.73 (Positive, Ref: >1.0) CMV IgG: 8.39 (Reactive, Ref: >1.0) Herpes IgM: 2.09 (Reactive, Ref: >1.0)
Autoimmune hepatitis	Antibodies: ANA: Negative Anti-smooth muscle: 5.74 (Negative, Ref: <20.0) Anti-mitochondrial: 18.69 (Negative, Ref: <20.0)
HELLP syndrome	LDH: 524 U/L (Upper Normal Limit) - Platelets: 317,000 (Normal, Ref: 150,000 - 450,000) AST/ALT <1 (No HELLP pattern)
Acute fatty liver of pregnancy	No hypoglycemia or coagulopathy was recorded duringthe stay.
Drug-induced cholestasis	- Negative history of hepatotoxic drug use
Cholelithiasis and choledocholithiasis	Abdominal ultrasound and cholangioresonance: - No evidence of lithiasis or bile duct dilatation.
Primary sclerosing cholangitis	Cholangioresonance: - No alterations in intrahepatic and extrahepatic biliary tract.
Primary biliary cirrhosis	Specific antibodies: - Anti-mitochondrial: 18.69 (Negative, Ref: <20.0).
Metabolic disorders (alpha-1 antitrypsin deficiency, Wilson's disease)	Alpha-1 antitrypsin: 103.6 mg/dL (Normal, Ref: 90 - 200) Ceruloplasmin: 47.7 mg/dL (Normal, Ref: 15 - 60)

4. Conclusion

A variety of liver diseases may occur during pregnancy, classified as gestational liver disease, acute disease occurring concurrently with pregnancy, or pre-existing chronic liver disease. Careful clinical and biochemical evaluation is essential to establish the diagnosis. Intrahepatic cholestasis of pregnancy is the most common liver disease specific to pregnancy in which bile acid levels play a critical role. Diagnostic confirmation allows symptomatic treatment with ursodeoxycholic acid to improve symptoms and reduce the risk of fetal complications. It is important to understand the clinical, pathophysiologic, and therapeutic characteristics of the disease and to implement a multidisciplinary approach to reduce the risk of complications and to consider the possibility of recurrence in future pregnancies.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of informed consent

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

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