Early Onset of Intrahepatic Cholestasis of Pregnancy: a Case Report

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Case Report

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Abstract

Intrahepatic cholestasis of pregnancy is a disorder, characterized by pruritus and elevated liver function tests. Associated with a high incidence of adverse perinatal outcomes, intrahepatic cholestasis of pregnancy (ICP) requires thorough attention in clinical practice. In addition, there is a high rate of stillbirth in cases of ICP. Women with ICP should be informed of the inability to predict stillbirth. Multi-disciplinary cooperation is critical for managing the condition and ensuring better pregnancy outcomes.

Introduction

Intrahepatic cholestasis of pregnancy (ICP), also known as cholestasis gravidarum, is a liver disorder characterized by pruritus. Pruritus is the most evident clinical symptom that cannot be explained by other causes. Elevated liver function tests (LFTs) and/or elevated serum bile acids (BA) in patients with ICP are characteristic as well [1].

The prevalence of cholestasis gravidarum varies greatly depending on geographical region, with an estimated 0.5–1% of the global population affected [2]. At the same time, a higher incidence of ICP is exhibited in twin pregnancies (2.1%) and pregnancies conceived by IVF (2.7%) [3]. Hepatitis C virus seropositivity has been identified as a risk factor for ICP, and it may be linked to an earlier onset of the pathology [4]. Some cases of early onset ICP are described in the literature, but most commonly the disorder develops in the third trimester of pregnancy [5].

Liver function tests, including BA, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are essential for assessing the functional state of the liver. According to the literature, in the majority of ICP cases liver function tests are scientifically high [2, 6]. The assessment of serum BA levels is considered the definitive biochemical marker for the diagnosis of ICP, as it is used for monitoring the patients' state [7]. Based on serum BA levels, ICP can be classified into mild (BA 10 – 39 $\mu\text{mol/L}$), moderate (BA 40 – 99 $\mu\text{mol/L}$) and severe (BA $\geq$ 100 $\mu\text{mol/L}$) conditions [8]. In the literature, there is a discrepancy regarding the onset of ICP and whether elevated serum BA or clinical symptoms appear first. In some studies, most patients were first diagnosed with elevated BA prior to exhibiting clinical symptoms or other changes in LFTs [9]. Nevertheless, other studies have described cases of ICP with initially normal BA and LFTs, but with the presence of clinical symptoms suggestive of the condition, which were followed by the onset of biochemical changes over 4-5 weeks later [10].

Case Report

Patient T, a 31-year-old woman with a dichorionic diamniotic twin pregnancy at 22⁺⁰ weeks' gestation, was admitted to the hospital complaining of pruritus on her palms, legs, and abdomen, which became worse at night, thus causing insomnia. As a result of the symptoms that began one week ago and their increasing intensity, patient T called for a consultation. In the outpatient department, LFTs were conducted with the following results: ALT – 643 U/L (reference range: 0 – 33 U/L), AST – 425 U/L

(reference range: 0 – 32 U/L), alkaline phosphatase (AP) – 131 U/L (reference range: 100 – 240 U/L), and total bilirubin – 9,34 µmol/L (reference range: 0 – 21 µmol/L). Based on clinical symptoms and elevated LFTs, the patient was diagnosed with ICP. At this point, patient T was admitted to the hospital.

Anamnesis revealed that the patient had 2 previous extrauterine pregnancies, in the left fallopian tube in 2012 and in the right in 2014, thus resulting in tubectomy and the recommendation of in vitro fertilization (IVF). The patient's somatic and hereditary anamnesis were uncomplicated. The assessed hepatitis markers, hepatitis B surface antigens and hepatitis C antibodies, were negative. Patient T was administered progesterone (according to IVF protocol), which is thought to have a possible role in the onset of ICP [11]. Despite discontinuing the administration of progesterone following the diagnosis of ICP, the patient did not experience any improvements in exhibited clinical symptoms.

Physical examination upon hospital admission did not reveal any signs of rash or other dermatological problems in the patient. Patient T was asked to rate the intensity of her pruritus upon first contact and again following hospital admission, thus revealing an increase in pruritus intensity from 5 to 10 points, based on the visual analogue scale provided. The assessment of LFTs reflected the following: BA – 125.7 µmol/L, ALT – 789.7 U/L, AST – 505.2 U/L, total bilirubin – 8.1 µmol/L, AP – 120 U/L, and γ-glutamyl transferase (GGT) – 18 U/L (reference range: 6 – 42 U/L). Consequently, patient T was diagnosed with severe ICP. At 22⁺² weeks gestation, a drastic increase in ALT and AST levels was observed, with ALT levels reaching 1121.5 U/L and AST levels reaching 657.9 U/L, respectively (Fig. 1).

Considering the patient's gestational age, it was decided to initiate symptomatic treatment and to monitor the pregnancy and the patient's status. Clinical management was carried out according to international recommendations. During hospital admission, patient T was prescribed *ursodeoxycholic acid* (UDCA) 750 mg/day, divided into twice-daily dosing. In light of worsening clinical symptoms and further elevated LFTs, the UDCA dose was increased to 900 mg/day, divided into three daily doses. In addition, the patient was recommended to administer *enteroadsorbent polymethylsiloxane polyhydrate* and use topical emollients, such as menthol 1% in aqueous cream, which can provide relief from pruritus without systemic effects [12]. At the same time, as a complementary treatment, patient T was recommended to administer *S-adenosyl-L-methionine* (SAM) 500mg in aqueous solution intravenously and antihistamine medication.

In the current pregnancy, an interdisciplinary management of the patient was undertaken, with the involvement of a gynecologist, gastroenterologist, and hepatologist during the perinatal period. Patient was admitted to the hospital three times throughout the course of pregnancy, thus requiring careful monitoring. Patient T was diagnosed with calculous chronic cholecystitis, biliary sludge, and a bladder polyp. The patient was recommended to have LFTs assessed weekly. However, during weeks 26–31 of pregnancy, the patient did not come in for a consultation, hence there is a lack of data on LFT levels for this period.

An elective caesarean section was planned to be performed after the patient's gestational age reached 37 weeks. However, a spontaneous premature rupture of membranes occurred at 32⁺⁶ weeks' gestation., followed by the onset of uterine contractions. Therefore, an emergency caesarean section was performed taking into account the twin pregnancy and the patient's complicated anamnesis. Patient T gave birth to a male fetus weighing 2158 g and a female fetus weighing 1369 g. The newborns had Apgar scores 7/8 and 6/7 points, respectively. Quantitative blood loss was estimated at 600 mL.

Patient T was admitted to the intensive care unit following delivery, where she spent 4 days requiring treatment for electrolyte imbalances, hypoalbuminemia and anemia. Patient T was then transferred to the postpartum unit. LFTs were reassessed 3 days after delivery; ALT and AST levels were 16.1 U/L and 21.0 U/L, respectively.

The neonates were admitted to the neonatal intensive care unit (NICU), where they spent eight days. In both newborns, diagnoses of congenital pneumonia and neonatal jaundice were established. In addition, the male newborn was diagnosed with necrotizing enterocolitis.

Patient T was discharged from the hospital on the eighth day after delivery. Her newborn babies required prolonged hospital care and were discharged from the hospital 30 days after birth.

Discussions

Considering ICP's impact on the pregnant women's health and the various perinatal outcomes associated with the disorder, assessment of BA levels is extremely important for ICP patients. A study conducted by *Glantz A. et al.* showed an increased rate of adverse perinatal outcomes in pregnant women with serum BA levels of >40 µmol/L [13]. These conclusions were later confirmed by other researchers [14]. The same study reported a 1-2% increase in the risk of spontaneous premature birth, fetal asphyxia, and the presence of meconium in the amniotic fluid with each subsequent 1 µmol/L increase in maternal serum BA levels [15].

A recent study suggests that women with ICP in whom BA values were > 40 µmol/L gave birth on average 2 weeks earlier than pregnant women in the control group [16]. According to recent data, in approximately 20% of cases of cholestasis gravidarum, the BA level will exceed 40 µmol/L, signifying a severe form of ICP [17]. In a recent meta-analysis of published studies, perinatal outcomes in pregnant women with ICP were assessed. Extremely high serum BA levels (> 100 µmol/L) were found to significantly increase the risk of fetal intrauterine death [18]. There is data in the literature suggesting that in pregnancies complicated by ICP, elevated levels of total bilirubin are observed in approximately 10% of cases, although their values rarely exceed 85.5 µmol/L [15, 19]. At the same time, other authors consider that total bilirubin values increase in 25% of ICP cases, often constituting the only laboratory symptom [20]. Serum GGT levels are expected to decrease during an uncomplicated pregnancy, while AP activity may increase in late pregnancy due to placental isoenzyme production and increased bone isoenzyme levels. Simultaneous elevation of GGT and AP indicates liver pathology, being markers of bile duct alteration

[21]. Moreover, it is known that ALT levels can increase by 2-10 times in ICP, compared to AST [9]. In the postpartum period it is recommended to assess LFTs not sooner than 10 days after delivery, provided that in normal pregnancy, LFTs may increase in the first 10 days of the puerperium. [1].

A study conducted by *Browers et al.* showed that treatment with natural progestins in patients with imminent preterm birth can cause cholestasis gravidarum, which was diagnosed in 11 out of 12 women included in the study [11]. These conclusion have been confirmed by other researchers [22].

The first-line pharmacological treatment in the management of ICP is UDCA, which improves LFTs and relieves maternal symptoms in the majority of cases [6]. UDCA is used to improve excretion of pruritogenic substances, such as progesterone sulfates [2]. A number of other pharmacological drugs, such as SAM, rifampicin, and cholestyramine, among others, can be used in the management of ICP. However, there is conflicting medical evidence about the effectiveness of the aforementioned drugs in relieving pruritus and improving LFTs. Therefore, the Cochrane review concluded that there is insufficient evidence of the drugs' effectiveness in the management of cholestasis gravidarum [23]. Nevertheless, some authors consider that in women treated with UDCA failing to exhibit improvements in LFTs and clinical symptoms, the other drugs could be recommended as a second-line treatment [24].

According to the different ICP guidelines, most management strategies recommend delivery between 37 and 38 weeks' gestation; however, obstetric anamnesis, laboratory test data and gestational age should be considered. A study conducted in the United Kingdom revealed stillbirth rate of 7% among women with ICP. Intrauterine death of the fetus in the case of ICP has occurred at various gestational ages. On average, intrauterine fetal demise in patients with ICP takes place within 38 weeks' gestation for singleton pregnancies. In the case of multiple pregnancies, the intrauterine fetal death rate before 37 weeks' gestation was 22% [19]. Hence, women with ICP should be informed about the inability to predict stillbirth [1].

In most cases, the maternal prognosis of ICP is benign. However, some authors suggest an increased risk of cholangitis, chronic hepatitis, fibrosis, and liver cirrhosis among women with an anamnesis of ICP, compared to women whose pregnancy was uncomplicated [19]. Reports in the literature suggest that there are currently no methods for ICP prophylaxis [25].

Conclusions

ICP is a severe condition due to its maternal and fetal impact, requiring active management. Women should be informed about the risks and possible complications of cholestasis gravidarum, such as the inability to predict stillbirth, the high rate of premature birth and respiratory distress that may be exhibited in newborns. Furthermore, despite the fact that ICP usually begins in the third trimester of pregnancy, an early onset of cholestasis gravidarum is often related to a severe form of the condition. At the same time, women with ICP require careful monitoring of their pregnancy considering numerous readmissions to the hospital. Management of the condition requires cooperation between obstetricians, gastroenterologists, hepatologists, and other specialists as needed, in order to better ensure the best possible outcomes.

Declarations

Ethics

Written informed consent was obtained from the patient.

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Competing interests

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Figures

Figure 1

ALT and AST levels (U/L) in patient T by weeks of gestation