

Ursodeoxycholic Acid Administration from the First Trimester in Case of a Severe Early-Onset Intrahepatic Cholestasis of Pregnancy

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Intrahepatic cholestasis of pregnancy is characterized by pruritus, raised maternal liver enzymes and bile acids. It usually presents in the third trimester and rarely before 25 weeks. Ursodeoxycholic acid is the most promising therapy to alleviate symptoms and prevent fetal risk. However, its administration has been restricted for the last trimester as its embryotoxic effect is undetermined. We report here a case of an extremely rare, severe obstetric cholestasis with early onset treated by ursodeoxycholic acid from the 9th week of pregnancy, the earliest ever reported in the literature. The treatment was well tolerated. At the 32nd week urgent caesarean section was performed due to intolerable symptoms, worsening laboratory results and signs of fetal distress. A healthy newborn was delivered. It is concluded that ursodeoxycholic acid in case of a severe early-onset intrahepatic cholestasis may be started in the early pregnancy to improve maternal condition and prevent fetal complications.

Keywords: intrahepatic cholestasis of pregnancy, first trimester, ursodeoxycholic acid

Abbreviations

CTG = cardiocography; ICP = intrahepatic cholestasis of pregnancy; UDCA = ursodeoxycholic acid

Intrahepatic cholestasis of pregnancy (ICP) usually presents in the third trimester and rarely before 25 weeks' gestation [1]. It is characterized by pruritus, mild jaundice [2], fat malabsorption and raised maternal liver enzymes and bile acids. The overall prevalence of the disease is estimated at 1/1000 to 1/10000 pregnancies [3]. Scandinavia (2%) and Chile (4%) have the highest prevalence [2, 4]. There is no uniform agreement on the criteria for diagnosing ICP. *Knox and Olans* [5] assert the role of elevated liver enzymes, whereas *Palma et al.* [6] emphasise that the most sensitive laboratory signs are the elevated total serum bile acids. *Rioseco et al.* suggest that the diagnosis can be made clinically based on altered laboratory results and typical symptoms [7].

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Although the prognosis for the pregnant woman is good, the condition has been associated with increased perinatal morbidity and mortality, such as preterm labour in 12% [7–9], fetal distress and intrauterine death in 7% [7, 10–12] and meconium staining of the amniotic fluid in up to 25% [7]. Interestingly, the severity of maternal symptoms does not seem to correlate with fetal prognosis.

Ursodeoxycholic acid (UDCA) is the most commonly used medication to alleviate maternal pruritus and improve fetal prognosis [13–14]. However, the use of UDCA has been restricted for the last trimester of pregnancy and data are missing about the first-trimester usage of UDCA in case of atypical early onset ICPs as it is not clear whether it has embryotoxic effect [15]. In case of a primary biliary cirrhosis UDCA was administered at the time of conception and was withdrawn at the time of diagnosis of pregnancy (5th week). 9 days later due to worsening symptoms UDCA was restarted and administered throughout the remainder of the pregnancy. No drug-related side effects were observed and a healthy newborn was delivered [16]. *Christensen et al.* reported a case of a primary sclerosing cholangitis where UDCA was administered throughout the first trimester, then withdrawn for a short time interval and restarted soon. No malformations were observed [17]. The earliest (16th week) administration of UDCA in case of a severe ICP was reported by *Cabrita et al.* [18].

We report here a case of an extremely rare, atypical, severe type of ICP with very early onset (6th week of pregnancy) treated by UDCA from the 9th week of pregnancy, the earliest ever reported in the literature.

Case Report

A 33-year-old Caucasian woman presented at our department at 9th week of gestation because of generalized pruritus which was worse on her palms and soles and excoriations from scratching started at 6th week of her second pregnancy. She had previously suffered from ICP in the last trimester of her first pregnancy which led to a meconium stained amniotic fluid and severe cerebral palsy. A previous use of an oral contraceptive resulted drug induced intrahepatic cholestasis necessitating immediate discontinuation of the drug.

Upon the first examination she presented dark urine, 10-fold increased transaminase levels, increased bilirubin and alkaline phosphatase levels and normal γ -glutamyl-transpeptidase level. Liver ultrasound scan was normal and screening for hepatitis B and C was negative. The patient had no history of gallstone disease and abdominal pain. No autoimmune disorders could be detected. Thyroid hormone levels were within the normal range.

After informed consent UDCA therapy was started with 250–250–500 mg daily doses. UDCA was administered without interruption throughout the entire pregnancy. Biochemical markers of cholestasis, such as serum transaminases, alkaline phosphatase, γ -glutamyl-transpeptidase and bilirubin levels were measured after overnight fasting every 2nd week and each time when the patient's symptoms requested it. The serum levels of biochemical markers during the pregnancy are presented in *Fig. 1*. On the 27th week of pregnancy due to worsening symptoms and increasing alkaline phosphatase and transaminase levels the initial UDCA dose was elevated to 250–500–500 mg daily dose.

During outpatient controls fetal well-being was monitored with Doppler velocimetry and cardiotocography (CTG) from the 30th week of pregnancy. No signs of fetal distress were seen

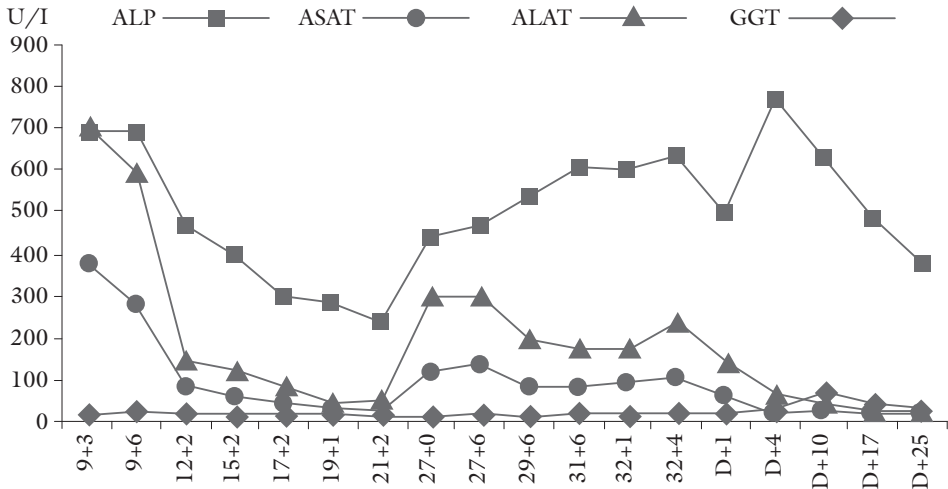


Fig. 1 Serum levels of liver enzymes according to different gestational weeks and days in the postpartum period (horizontal axis). (UDCA: ursodeoxycholic acid, ALP: alkaline phosphatase, ASAT: serum aspartate aminotransferase, ALAT: serum alanine aminotransferase, GGT: γ -glutamyl transpeptidase)

until the 32nd week of pregnancy, when the patient was admitted to the hospital due to worsened symptoms and signs of fetal distress seen on CTG.

Upon admission steroid prophylaxis (2 × 12 mg Dexamethasone) was given in anticipation of possible premature delivery. The UDCA administration was elevated to 3 × 500 mg daily dose and an additional 2x30mg daily dose of Phenobarbital was started. Daily CTG was performed for fetal monitoring. On week 32 day 4 in spite of the combined medical therapy the patient’s symptoms became unbearable, the liver enzymes slightly increased and the CTG showed signs of fetal distress. A decision was made to perform urgent caesarean section. The operation was uneventful and a live male infant, weighing 2200 g with Apgar scores of 8 and 9 at 1 and 5 minutes, respectively, was delivered.

The postnatal period was uneventful. The combined medical therapy was discontinued after delivery. The levels of liver enzymes were checked regularly. On discharge the patient was not complaining of pruritus and during outpatient controls 10 days after the delivery the transaminase levels, 25 days after the delivery the alkaline phosphatase level went down to normal range (Fig. 1).

Discussion

ICP usually occurs after the 30th week of pregnancy and rarely before. Here we describe a case of a woman in whom extremely high transaminase and alkaline phosphatase levels and pruritus appeared as early as the 6th week of the pregnancy. The patient experienced ICP in the last trimester of a previous pregnancy and had a history of contraceptive pill-induced intrahepatic cholestasis, which are both known risk factors for developing ICP in subsequent pregnancies [19–21].

Several reports have confirmed that UDCA is the most promising therapy in patients with ICP [15, 23]. A variety of other medications have been tried to alleviate maternal symptoms, but have not been shown to alter fetal prognosis. UDCA has been shown to restore the impaired bile acid transport across the trophoblast [13] and decrease the delivery of bile acids to the fetus [6, 14, 24]. Up to now, no adverse effects on the fetus of UDCA therapy has been reported. However, UDCA treatment is usually delayed until the third trimester minimizing the risk of the unknown teratogenicity. Treatment of pregnant rats with UDCA from the early pregnancy resulted in no dismorphogenic effects [26]. The use of UDCA in the first trimester in case of a primary sclerosing cholangitis caused no malformations in the newborn [17].

There is no guideline in the literature about the management of early-onset severe ICP cases and the safety and teratogenicity of UDCA is still undetermined. In our case, taking into account the extremely high levels of liver enzymes and the estimated poor fetal prognosis, UDCA treatment was started as early as the 9th week of pregnancy. After initiation of the UDCA therapy the serum transaminases decreased almost to normal levels and the symptoms improved. UDCA provided well tolerated and sustained medical treatment. The alkaline phosphatase activity decreased, but fluctuated above the normal range. The γ -glutamyl-transpeptidase activity was not modified during the pregnancy, in agreement with previous reports [15]. Serum bilirubin mostly in its conjugated form fluctuated between 55 $\mu\text{mol/l}$ and 12 $\mu\text{mol/l}$.

At the 27th week of pregnancy the symptoms worsened and the liver enzymes started to increase. The UDCA dosage was elevated causing a slight decrease in the transaminase levels and improvement of the maternal pruritus. However, the alkaline phosphatase levels were slightly increasing continuously. At the 32nd week of pregnancy the patient's symptoms escalated and the CTG showed signs of fetal distress. UDCA was elevated to the highest tolerable dose and an additional phenobarbital therapy was started. In spite of the combined medical treatment the maternal symptoms worsened and CTG showed signs of fetal distress. Considering the risk of increased fetal morbidity and mortality [7–11] a decision was made to perform urgent caesarean section.

UDCA and phenobarbital treatment was discontinued after delivery. The pruritus vanished and the transaminase and alkaline phosphatase levels decreased to baseline values within 5–10 and 25 days after the delivery, respectively.

No drug-related side effects were observed throughout the entire pregnancy and no signs of embryotoxicity could be detected.

Conclusions

ICP in atypical cases may occur very early in the first trimester and UDCA administration in these severe early-onset cases may be started in the early pregnancy in order to improve symptoms, decrease liver enzymes and prevent fetal complications.

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