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Severe Neonatal and Obstetric Outcomes in Recurrent Early Intrahepatic Cholestasis of Pregnancy in a Patient with Pre-Existing Myasthenia Gravis: A Case Report of Two Consecutive Pregnancies

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ABSTRACT

Intrauterine fetal demise (IUFD) is a recognized risk in intrahepatic cholestasis of pregnancy (ICP), particularly when bile acids exceed 40 µmol/l.

Therefore, many obstetric societies recommend considering induction of labor at or before term, depending on bile acid levels. The Danish guidelines recommend induction of labor after gestational week 34+0 if bile acids exceed 100 µmol/l.

This report details a case of a woman experiencing recurrent early ICP, characterized by initially elevated bile acid levels, leading to IUFD at 33+6 weeks of gestation in her first pregnancy and a preterm subacute delivery at 32+1 weeks of gestation in her second pregnancy. Comprehensive medical evaluations during and after the first pregnancy identified no underlying hepatic disorders. Despite an initial decline in bile acid levels following treatment in both pregnancies, pruritic symptoms intensified and bile acid levels began to rise again at beginning of the third trimester. This case suggests that an early onset of ICP, characterized by increasing bile acids despite treatment and reduced fetal movements, may warrant consideration for preterm delivery even before 34 weeks of gestation; however, the decision to deliver is complex.

Keywords: Intrahepatic Cholestasis of Pregnancy, Intrauterine Fetal Demise

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INTRODUCTION

Pruritus in pregnancy can affect up to 20% of pregnant women (1), but should prompt consideration of intrahepatic cholestasis of pregnancy (ICP) with the diagnosis being made through elevated bile acids on serologic analyses. Given the increased risk of intrauterine fetal demise (IUFD) associated with significantly elevated bile acid levels, determining the optimal timing for preterm delivery remains a complex and nuanced clinical decision (2).

Bile acids are a constituent of the bile salts in bile and facilitate digestion of dietary lipids and vitamins by encapsulation. Bile acids are mostly absorbed again in the ileum but 200-600 mg are lost through the feces and replaced by a daily cholesteroloxidation in the liver (3).

Ursodeoxycholaic acid is another bile acid often used as a symptomatic treatment for ICP, but small amounts are normally produced by bacteria in the human gut. It works by counteracting membrane disruptive effects of bile salts and by reducing the re-uptake in the gut (4). Treatment does not improve fetal or neonatal outcomes (5). Studies have demonstrated, that ursodeoxycholaic acid reduces pruritus and improves liver function in patients with ICP (6).

Pruritus is frequently attributed to elevated estrogen levels, which are associated with ICP. ICP typically manifests in the latter half of pregnancy when serum estrogen concentrations peak. This correlation explains the increased risk of ICP in twin pregnancies, where estrogen levels are notably higher (7). Additionally, non-pregnant women using estrogen-progestin contraceptives are at increased risk of developing cholestasis. The occurrence of ICP has also been documented in early pregnancy following ovarian hyperstimulation (8,9). Furthermore, the resolution of ICP postpartum is consistent with the cessation of placental estrogen production, underscoring the placenta's role as a major source of estrogen production.

In Denmark the incidence of ICP is about 1.5% (10,11), but has been reported as high as 27.6% (12). The incidence is higher in winter (11) and low vitamin D status increases the risk of ICP (13).

Animal studies have shown that bile acids affect the fetal heart and placenta which may be the cause of sudden IUFD (14,15). Surveillance with cardiotocography and fetal ultrasound may theoretically reduce perinatal mortality, but evidence is lacking.

ICP with bile acid levels exceeding 100 µmol/l are associated with a 30-fold increased risk of IUFD compared to those with bile acid levels below 40 µmol/l (6). However, there is limited evidence as to the optimal timing for induction of labor. Danish guidelines recommend considering induction of labor after 34 weeks of gestation for patients with bile acid levels above 100 µmol/l (10).

CASE REPORT

A 24-year-old nullipara woman, at gestational week 11+5, presented to her general practitioner with complaints of pruritus in her hands and feet, accompanied by light-colored stools and dark urine. Her medical history revealed a prior episode of facial nerve palsy, which spontaneously resolved five years before pregnancy. Imaging studies, including a computed tomography scan (CT) and a magnetic resonance scan (MRI) scan of the cerebrum, demonstrated cavum vergae and bilateral maxillary sinus retention cysts. Additionally, four years prior to conception, she was diagnosed with seropositive generalized myasthenia gravis in Hungary, and remained asymptomatic during pregnancy without adverse effects from Imurel and Mestinon treatment, which was continued throughout the pregnancy.

Laboratory investigations revealed elevated bile acids (>150 µmol/L), LDH 220 U/L, and normal levels of alanine-aminotransferase (ALT), amylase, bilirubin, and gamma-glutamyltransferase. Initial

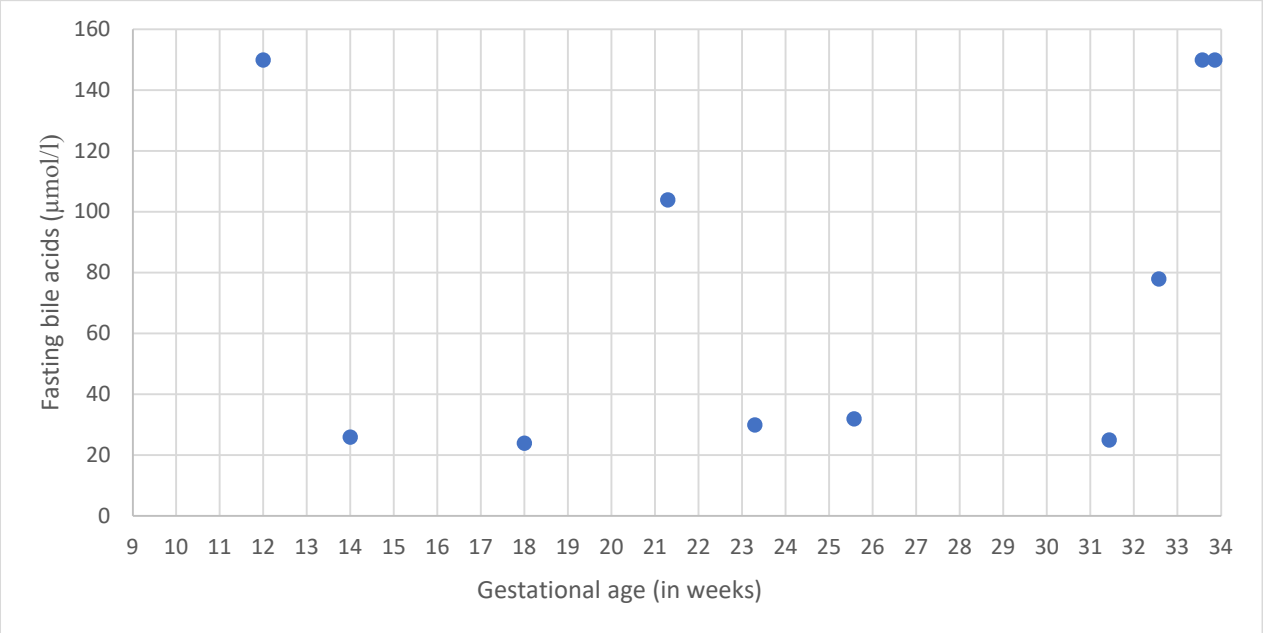

Figure 1: Fasting bile acids in the first pregnancy, in regards to the gestational week.

treatment with Prednisolone and Cetirizin proved ineffective for the described symptoms and was discontinued after one week. Subsequently, she was referred to Kolding Hospital in Denmark, where further testing at gestational age 12+0 confirmed markedly elevated fasting bile salts (>150 µmol/L) and now modest elevations in liver enzymes (conjugated bilirubin 20, bilirubin 27, lactate dehydrogenase 220. ALT and amylase levels normal).

Ursodeoxycholic acid was initiated at a dosage of 250 mg three times daily, later at gestational week 14+4 increased to 500 mg three times daily due to persistent pruritus. Levels of fasting bile acids was 26.

Despite this intervention, a subsequent rise in bile acid levels, ALAT and alkaline phosphatase at gestational week 21+2 was observed, fasting bile acid levels throughout the pregnancy are visualized in figure 1. The hepatology department was asked for a consult at gestational week 22+2 which prompted a switch to Questran at 4 g daily, resulting in temporary improvement in liver function parameters.

However, by gestational week 32+4, fasting bile salt levels began to rise again, reaching >150 µmol/L by gestational week 33+4. In accordance with Danish national guidelines, induction of labor was scheduled at Odense University Hospital at gestational age 34+0. Routine cardiotocography monitoring at the local obstetric department was scheduled for gestational ages 33+4 and 33+6, respectively. At the appointment at gestational age 33+4, the patient mentioned a decrease in fetal movement, although a subsequent cardiotocography appeared normal. At the scheduled appointment at gestational week 33+6 the patient again mentioned having noticed a decrease in fetal movement, prompting an ultrasound scan which confirmed IUFD.

Subsequently, the patient delivered a stillborn boy weighing 2675 grams (+12.8%) without apparent malformations. Throughout the pregnancy, ultrasound scans were unremarkable; she had a normal nuchal translucency ultrasound in gestational week 13+0 and low risk of genetic disorders, a normal fetal anomaly scan in week 19+2, and subsequently normal fetal biometry ultrasound scans in weeks 24+4, 29+0 and 33+0.

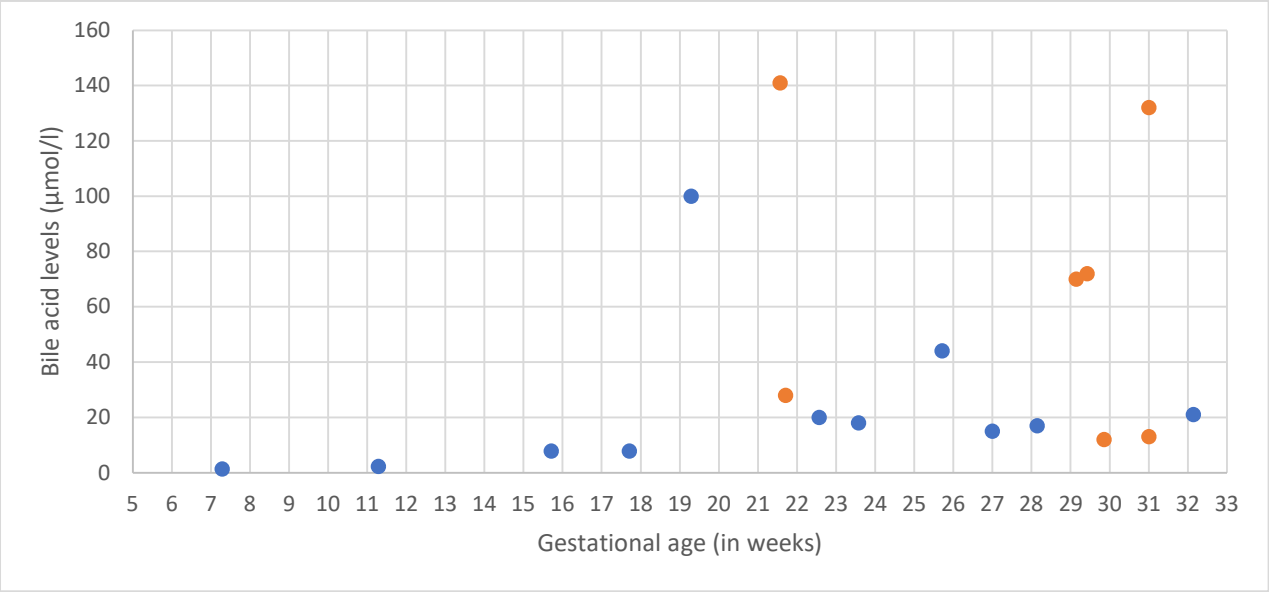

Figure 2: Fasting (blue) and non-fasting bile acids (orange) in the second pregnancy, in regards to the gestational week. Since the spring of 2022, Danish obstetric guidelines have shifted from recommending fasting to non-fasting bile acid measurements, and these changes were implemented during the patient's second pregnancy.

Second pregnancy

Approximately eight months after her first pregnancy, the patient was referred from her general practitioner for an early fetal ultrasound at gestational week 10+2. Between her pregnancies, the patient experienced complete normalization of the liver function tests.

A magnetic resonance cholangiopancreatography (MRCP) scan, liver biopsy, and ultrasound revealed normal findings. Extensive hepatologic, immunologic, and genetic testing revealed no abnormalities except for heterozygosity for UGT1A, which is associated with Gilbert's syndrome in its homozygous form.

At gestational week 12+1, a nuchal translucency scan was normal. The hepatology department recommended periodic blood tests for bile acids and liver enzymes every four weeks throughout the pregnancy. At gestational week 17+5, ursodeoxycholic acid tablets 250 mg three times daily was prescribed, with fasting bile acids measuring 9.8 µmol/L due to pruritus.

By gestational week 19+2, fasting bile acids had risen to 100 µmol/L. Three days later, the dosage of ursodeoxycholic acid was increased to 500 mg three times daily, and rifampicin 300 mg once daily and Questran 4 grams three times daily were added. A routine ultrasound for fetal anomalies at gestational week 19+6 was normal.

At gestational week 21+4, the patient's pruritus had slightly improved, and a normal ultrasound including amniotic fluid and flows of the umbilical artery and middle cerebral artery was performed. However, non-fasting bile acids were measured at 141 µmol/L. The next day, non-fasting bile acids were down to 28. By gestational week 22+4, fasting bile acids had decreased to 20 µmol/L and were 18 µmol/L a week later at 23+4. Bile acids were monitored at 1-2 week intervals for the remainder of the pregnancy, as shown in Figure 2.

At gestational week 29+1, the bile acid level increased again to 70 µmol/L and the patient was prescribed antenatal corticosteroids for accelerating fetal lung maturation (diprofos 14 mg once a day for two days) due to clinicians assessing the

patient of having an increased risk of preterm delivery. Two days later a new blood sample was drawn, and the bile acid level was stationary at 72 µmol/L. Until gestational week 31+0 the bile acid level stayed below 20. At gestational week 31+0 two blood samples were taken the same day with only a few hour interval and non-fasting bile acids were measured at 132 and 13, respectively. It has not been possible to clarify by assessing the medical charts why the test was taken twice. The management plan henceforth included daily cardiotocographies from gestational week 32+0 and induction of labor was scheduled at gestational week 33+0.

However, at gestational week 32+1, the cardiotocography was classified as pathological, showing reduced variability (<5 bpm), tachycardia (baseline at 155 bpm), and absence of accelerations. The patient had not felt fetal movements for 24 hours. Fetal ultrasound indicated brain sparing and no visible fetal movements. Despite normalized fasting bile acids at 21 µmol/L, a decision was made for a subacute cesarean delivery. A healthy preterm boy was delivered with an Apgar score of 10 at 5 minutes. The child developed hypertension and was diagnosed with renal vein thrombosis and necrosis of a testicle at three days post partum. The subsequent neonatal period progressed without complications and the family was discharged from the Neonatal ward after 25 days.

DISCUSSION

This case report presents two pregnancies complicated by recurrent ICP in a woman with myasthenia gravis. The first pregnancy culminated in IUFD at gestational week 33+6, and the second resulted in a subacute cesarean section at week 32+1, yielding a live-born male infant. Both pregnancies were marked by increasing bile acid levels despite therapeutic interventions, coupled with the patient's reports of reduced fetal movements, ultimately necessitating expedited delivery. Between pregnancies, extensive examinations did not reveal any underlying hepatic disorders.

To our knowledge, this is the first documented case of ICP occurring in a patient with myasthenia gravis. A related case has been reported where a woman with myasthenia gravis developed primary biliary cirrhosis three months postpartum (16). The primary treatment for myasthenia gravis, pyridostigmine, is a cholinesterase inhibitor not associated with hepatic dysfunction (17). Therefore, it is unlikely that myasthenia gravis contributed to the development of ICP in this patient.

Severe ICP presenting in early pregnancy is exceptionally rare, with only a few cases documented. Delivery prior to 34 weeks was reported in 3 out of 7 cases in one series (18). In a retrospective series of 21 pregnancies complicated by ICP and IUFD, the average gestational age at IUFD was 33+6 weeks, with a range from 29 to 41 weeks (19).

Since the spring of 2022, Danish obstetric guidelines have shifted from recommending fasting to non-fasting bile acid measurements, enhancing the detection of severe ICP (6). This change explains the differences in bile acid monitoring between the patient's first and second pregnancies. During the second pregnancy, both fasting and non-fasting bile acids were measured, revealing significant fluctuations within days. For clinical decision-making, the higher bile acid levels should be considered.

Daily CTGs were ordered from gestational week 32+0 due to increasing bile acid levels, but to our knowledge this strategy has limited evidence in detecting signs of fetal deterioration in cases of ICP. However, in this case, it may have played a role. A daily CTG is also a convenient way of keeping an eye on the patient and giving them an easier opportunity to communicate to a clinician if there are changes in the fetal movements.

Elevated bile acid levels exceeding 100 µmol/L, particularly when accompanied by reduced fetal

movements, should prompt immediate obstetrical evaluation and consideration of preterm delivery. However, delivering before 34 weeks introduces the additional complexity of balancing the risks associated with prematurity against the risk of IUFD, which remains rare before 37 weeks gestation (10,20).

CONCLUSION

In conclusion, this case underscores the necessity of vigilant monitoring and proactive management in pregnancies complicated by early-onset ICP, especially in patients with comorbid conditions. Early detection and timely intervention are critical to optimizing maternal and fetal outcomes in such high-risk scenarios.

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