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Intrahepatic cholestasis of pregnancy resistant to both therapeutic plasma exchange and albumin dialysis

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SUMMARY

Intrahepatic cholestasis in pregnancy (ICP) represents, depending on its severity, a serious risk for the fetus. Those cases with unusually high bile acid levels may be resistant to pharmaceutical treatment and can be treated with plasma exchange or albumin dialysis. However, the success rate of these therapeutic options and the factors influencing therapeutic response are unknown. Furthermore, if these options fail to improve ICP and serum bile acid levels are very high (>200 µm/L), there are no clear recommendations when delivery should be planned. Here, we report a patient with severe ICP resistant to both therapeutic plasma exchange and albumin dialysis. Caesarean section was performed at 32 weeks of gestation followed by rapid remission of ICP.

BACKGROUND

Intrahepatic cholestasis of pregnancy (ICP) is characterised by the presence of pruritus and abnormal liver function tests (including elevated bile acids) in the absence of other pathologies.[1 2] Even though pruritus represents the cardinal feature of ICP, jaundice seemed to be the more central symptom in the early literature. This condition was named 'idiopathic jaundice of pregnancy' by Eppinger,[3] or 'recurrent jaundice of pregnancy' by Svaborg.[4] However, according to more recent studies, jaundice is present in approximately 15%–20% of women with ICP.[5 6] Hence, jaundice seems to indicate severe disease while pruritus may often be the first symptom preceding the diagnosis of ICP.[1] High levels of serum bile acids and bilirubin are associated with poor neonatal outcome, including stillbirth, asphyxial events and spontaneous preterm birth.[7 8] Thus, severe ICP may not only cause symptoms in the woman, which are resistant to pharmaceutical treatment, but also represent a serious risk for the fetus. However, it is not clear how long a pregnancy complicated by severe ICP with very high bile acid levels (>200 µm/L) can be prolonged and when delivery should be pursued.

Therapeutic plasma exchange is a relatively new approach in cases of severe ICP both to treat pruritus, decrease bile acids and consequently improve fetal outcome. In some case studies, therapeutic plasma exchange has shown good effects while other investigators reported no improvement by this therapy.[9–12] To this day, the rate of successful plasma exchange or the factors influencing it are unknown.

The advanced organ support (ADVOS) is an extracorporal liver support procedure based on albumin dialysis, which aims to eliminate albumin-bound toxins such as bile acids.[13] However, there is no literature that reports this approach in pregnant women with ICP.

CASE PRESENTATION

We present a G3P0 with newly appeared jaundice at 20 weeks of gestation. Fever, vomiting, abdominal pain or influenza like symptoms were not present. Her urine was dark, her stools were light and she did not report about pruritus. She had a history of Crohn's disease for which she has been taking azathioprine and mesalazine for the previous 4 years. She did not take steroid and did not have surgery for that condition in the past. Other medical conditions (eg, preexisting liver dysfunction) were absent and the pregnancy was conceived without assisted reproductive technology. She underwent amniocentesis due to hydramnios, which showed a normal karyotype. Virological examination was negative for herpes simplex virus, Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, SARS-CoV-2 and hepatitis A, B, C and E. Ultrasound found no evidence of obstruction of the bilary ducts and the fetus showed normal growth and normal umbilical artery Doppler. Serum sFlt-1 and Placental Growth Factor (PlGF) were normal and proteinuria or hypertension was absent. Laboratory studies at 20 weeks of gestation returned as follows: alanine aminotransferase (ALAT) 49 U/L (reference value: 10–34 U/L), bile acids 249 µm/L (reference

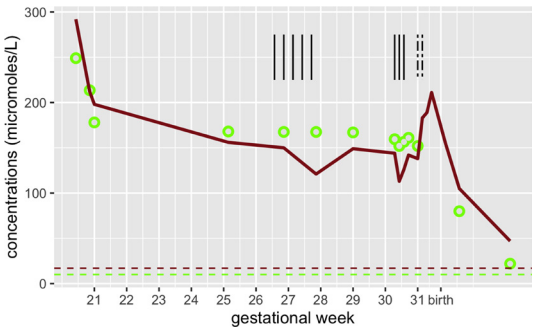

Figure 1 Biochemical parameters during pregnancy and postpartum. Total bilirubin (solid line) and bile acids (circles) show a pronounced elevation compared with the upper reference limit (horizontal dashed line) without significant response to plasma exchange (vertical solid lines) or albumin dialysis (vertical dashed line).

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Table 1 Clinical features and outcomes of reported ICP cases with very high bile acids (>200 µm/L)

Reference	Peak contentration of bile acids (µm/L)	Therapeutic plasma exchange	Gestational week at delivery	Mode of delivery	CTG changes	Apgar scores*	Days in the NICU
Keitel *et al*[15]	202	No	35th	Spontaneous delivery	N/A	8^{1}-8^{5}-9^{10}	None
Steele[27]	205	No	33rd	Emergency caesarean section	Prolonged bradycardia	0^{1}–5^{5}–9^{10}	3 weeks
Favre *et al*[23]	223	No	31st	Caesarean section	None	Intrauterine fetal demise	
Johnston *et al*[26]	217	No	31st	Caesarean section (PPROM, akute Chorioamnionitis)	N/A	N/A	N/A
Polewiczowska *et al*[11]	205	No	32nd	Emergency caesarean section	Prolonged bradycardia	5^{5}–9^{10}	2 weeks
	230	Yes	31st	Planned caesarean section	None	4^{1}–7^{5}	None
Hubschmann *et al*[29]	243	No	32nd	Planned caesarean section	None	8^{1}–2^{5}–9^{10}	None
Ovadia *et al*[10]	360	Yes	35th	Planned caesarean section	None	7^{1}–8^{5}	>24 hour
	290	Yes	32nd	Emergency caesarean section	N/A	4^{1}–7^{5}	>24 hour
	440	Yes	32nd	Emergency caesarean section	Non-reassuring fetal heart rate	6^{1}–7^{5}	>24 hour
Wongjarupong *et al*[30]	462	No	35th	Induction of labour	N/A	N/A	None

N/A indicates that the information is not available.
*Superscript number indicates minutes at which Apgar scores were calculated.
CTG, cardiotocography; ICP, intrahepatic cholestasis in pregnancy; NICU, neonatal intensive care unit; PPROM, preterm premature rupture of the membranes.

value: 0–10 µm/L), total bilirubin 292 µm/L (reference value: 0–17 µm/L). Indirect bilirubin, gamma-glutamyl transferase and prothrombin time were normal. Albumin (25 g/L) and total protein (46 g/L) were decreased.

TREATMENT

Therapy with ursodeoxycholic acid was initiated (1 g/day until delivery) without sufficient effect, as both serum bile acids and total bilirubin remained high. At 26 weeks of gestation, therapeutic plasma exchange was begun. A total of eight cycles of plasma exchange and two cycles of albumin dialysis (ADVOS) were performed without improvement of either bilirubin or bile acids (figure 1). Additionally, rising levels of transaminases (ALAT-peak: 148 U/L) and gamma glutamyltransferase (peak: 97 U/L) were observed and, thus, the decision was made to deliver the baby by caesarean section at 32 weeks of gestation after antenatal corticosteroids. Both surgery and the neonatal course were uneventful.

OUTCOME AND FOLLOW-UP

The patient showed a rapid improvement of bilirubin and bile acid levels and was discharged 4 days after the operation. The genetic analysis from blood samples did not detect any gene variants associated with severe cholestatic hepatopathy. However, the patient was homozygous for a bile salt export pump variant (V444A), which is associated with low expression of the encoded export pump and, thus, may have contributed to the severity of this clinical course.[14 15]

DISCUSSION

ICP may be resistant to medical treatment in a significant proportion of women.[16] Especially cases with severe ICP may only respond to plasma exchange, which has been first reported by Warren and colleagues.[12] Since then, there have been various attempts to use this therapy in cases resistant to pharmaceutical treatment with encouraging results.[10 11] However, Covach and colleagues first reported a case of ICP resistant even to repeated plasma exchange.[9] Similarly, our patient also showed a lack of improvement with plasma exchange and albumin dialysis, thus raising the question of how effective this therapy truly is. Interestingly, both the case of Covach *et al* and our case showed some sort of pre-existing liver disease. The patient of the former case report had active hepatitis C, which has been associated with an increased severity of ICP.[17] The woman in our case report had Crohn's disease, which may have negative effects on liver function.[18] Hence, diseases afflicting the liver may limit the effect of plasma exchange in ICP. A very recent study also found that women treated with azathioprine who developed ICP often experienced a significant improvement if this medication was discontinued.[19] Consequently, the azathioprine taken by our patient may have negatively influenced the effect of therapeutic plasma exchange and albumin dialysis. However, more research is required to determine the predictive factors for successful plasma exchange, as this treatment is both costly and invasive.

Interestingly, our patient did not suffer from pruritus, which is regarded as the most characteristic symptom and a prerequisite for the diagnosis of ICP.[8 20] However, the Royal College of Obstetricians and Gynaecologists (RCOG) guideline states that otherwise unexplained elevation of bile acids or other abnormal liver parameters may be sufficient even without pruritus for the diagnosis of ICP.[2] It is, therefore, difficult to estimate the proportion of patients presenting with ICP without itch, as the definition of this condition is not universally agreed on and changed over the decades. When ICP was mainly defined by the presence of jaundice, several cases without pruritus have in fact been reported. Eliakim *et al* reported five cases of 'recurrent jaundice of pregnancy' of which one did not have any pruritus.[21] Svanborg and Ohlsson found that pruritus was absent in 5 out of their 22 cases.[4] Additionally, the constellation of very high bile acids and bilirubin without pruritus may not be unusual, as these parameters do not correlate well with each other.[22 23] Progesterone sulfates and autotaxin activity may play a more important

role in the pathogenesis of pruritus in ICP.[24 25] Notably, the total bilirubin levels measured in this case are unusually high for ICP since concentrations reported by other authors (table 1) were not higher than 106 μm/L.[26]

It is not clear when fetuses subjected to such severe ICP should be delivered. A meta-analysis by Ovadia and colleagues showed that the risk of stillbirth was best predicted by total bile acids and bilirubin. Especially bile acids higher than 100 μm/L were associated with increased risk of stillbirth.[7] Interestingly, case reports describing ICP with very high bile acids levels (over 200 μm/L) often describe non-reassuring fetal heart rate patterns around the 32nd week of gestation leading to emergency caesarean section.[10 11 27] Also, intrauterine fetal demise has been reported around this gestational week if bile acids were very high.[23] These observations could be due to a vasoconstrictive effect of bile acids on placental veins,[28] consequently causing fetal compromise. Hence, in pregnant women afflicted by ICP with very high bile acids and resistant to treatment, it seems prudent to plan delivery at 32 weeks of gestation, as emergency caesarean section and poor neonatal outcome (low Apgar, need of neonatal intensive care) have been reported by various authors (table 1).

However, further research is needed to determine when babies subjected to such high bile acids should be delivered and which factors influence the success of plasma exchange in severe ICP.

Learning points

- Intrahepatic cholestasis of pregnancy with very high bile acid levels and jaundice is rare.
- Therapeutic plasma exchange and/or albumin dialysis may not always be effective in patients with intrahepatic cholestasis of pregnancy and very high bile acid levels.
- There is a significant risk to the fetus with very high bile acid levels (over 200 µm/L) and early delivery should be considered. Most cases reported in the literature have been delivered between 31 and 33 weeks of gestation.

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Case reports provide a valuable learning resource for the scientific community and can indicate areas of interest for future research. They should not be used in isolation to guide treatment choices or public health policy.

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