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Plasmapheresis in management of severe cholestasis of pregnancy

Beata Polewiczowska, Nishant Gautam, Julie Wessels, Alison Brind

ABSTRACT

Introduction: Cholestasis of pregnancy usually presents with pruritus in the third trimester and it has good maternal prognosis. However, severe cholestasis can have a significant impact on the fetus leading to intrauterine death. Case Report: A 28-year-old female had severe cholestasis of pregnancy in first pregnancy, in second she developed pruritus and cholestatic liver function tests at 17 weeks gestation. Despite treatment with ursodeoxycholic acid and rifampicin, her liver function tests and bile acids increased significantly raising concerns about viability of pregnancy. Plasmapheresis, never previously used in the UK, was commenced with good response to treatment. Conclusion: In this report, we summarize the successful use of plasmapheresis to control bile acids and prolong pregnancy. Treatment with plasmapheresis should be considered for intrahepatic cholestasis of pregnancy (IPC) that is refractory to traditional therapies.

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INTRODUCTION

Cholestasis of pregnancy usually presents with pruritus in the third trimester with wide spectrum of severity. Ursodeoxycholic acid (UDCA) is the standard of care. Maternal prognosis is usually good and symptoms resolve soon after delivery, but severe cholestasis is associated with preterm labor and intrauterine death [1, 2]. Our patient had early onset with high bile salts and failed to respond to standard medical therapy. Plasmapheresis has been used to treat her as described previously in American studies, but never used in the UK.

CASE REPORT

The patient was first seen in the Hepatology clinic at 16 weeks gestation having developed pruritus and cholestatic liver function tests, ALP of 275 U/L, SGPT of 210 U/L and raised bile acids of 205 umol/L at 11th week gestation of her first pregnancy. By 16th week, she had dark urine, pale feces and extremely severe pruritus. She was

otherwise well and did not suffer from any other medical problems. Her BMI was 40. There was a family history of diabetes. A paternal aunt and sister had symptoms consistent with cholestasis of pregnancy in the past. Full liver screen bloods including anti-mitochondrial antibody and abdominal ultrasound were normal. Cholestasis of pregnancy was diagnosed and ursodeoxycholic acid, 15 mg/kg was commenced (UDCA). Despite UDCA liver functions worsened (Figure 1) suggestive of severe cholestasis of pregnancy. Ursodeoxycholic acid dose was increased to 1 g and shortly after increased to 2 g daily with addition of cholestyramine due to lack of response in her pruritus and worsening LFTs. Subsequently, rifampicin was added, 300 mg BD as her bile acid continued to rise. This initially led to a fall in bile acids and SGPT but then a rise and worsening pruritus was observed (Figure 2). At 32nd week cardiotocography (CTG) showed prolonged bradycardia prompting an emergency C-section. The baby was hypoxic at birth with poor Apgar scores of 0 at 1 minute, 5 at 5 minutes and 9 at 10 minutes. The baby spent 2 days on neonatal intensive care unit, 3 days on high dependency unit and 14 days on special care unit. However, the baby was resuscitated successfully and made a good recovery.

Following delivery, patient's pruritus resolved, however, LTFs remained elevated (Figure 3). Bile acid level was reduced to normal. A liver biopsy was therefore performed at eight month postpartum, this showed normal liver with mild sinusoidal dilatation compatible with resolved cholestasis of pregnancy (Figure 4). MRCP was performed a year later which showed a gallbladder stone, but no CBD stones. Portal vein and hepatic vein Doppler were done and revealed patent veins. Laparoscopic cholecystectomy was performed one year later. Although a severe variant of cholestasis of pregnancy with a biliary transporter mutation was thought likely. Concern was also raised with the patient regarding further pregnancies and high chance of recurrence of cholestasis of pregnancy.

Three years later the patient became pregnant again. At 17 weeks gestation, liver function tests worsened again, ALP 198 U/L, GGT 309 U/L, SGPT 106 U/L and bile salts 141 umol/L. She was commenced back on 15 mg/kg of UDCA with close monitoring by hepatologist and obstetrician. Bile acids level initially decreased with the use of medication. However, pruritus and biochemistry deteriorated. The dose of ursodeoxycholic acid was increased to 3 grams daily. Rifampicin was started at 300 mg, the maximum tolerate dose for the patient in this pregnancy. At 24th week bile acids, SGPT, INR, bilirubin raised concerns about viability of pregnancy. The patient was aware of possible treatment with plasmapheresis, but investigations suggested this had never been used in the UK. However, a joint decision was made to pursue this therapy.

Treatment

The patient received 11 plasma exchange sessions in total which proved to be very effective. The plasma exchange was four litres with replacement fluid of 4.5% human albumin and 7 ml of 10% calcium gluconate per 500 ml exchange. There was a significant improvement in bile salts level shortly after plasmapheresis was started. In fact, liver function tests had completely normalized and bile acids level has decreased to 9.6 umol/L and there was a good initial response (Figure 5), but by 31st week gestation patient experienced problems with her dialysis line. Antenatal scan showed fetus normal for dates and decision was made to proceed with elective C-section at 31 weeks gestation. The patient had already received steroid therapy at 27th week gestation. The baby was successfully delivered with Apgar scores of 4 at 1st minute, 7 at 5th minute and weight of 1960 grams and required no special care and the mother became asymptomatic.

Outcome and Follow-up

Six months following delivery, the patient reported loose and pale stools and intermittent right upper quadrant pain. Her blood tests showed worsened liver function tests with ALP of 190 U/L, GGT of 213 U/L, bilirubin of 5 umol/L and bile acids of 15.7 umol/L. She was therefore re-commenced on UDCA on a long-term basis due to strong suspicion that the cholestasis was not just present during pregnancy and there may be a defect in her bile acid transporters. She will remain under regular hepatology clinic follow-up.

DISCUSSION

ICP is a cholestatic disorder characterized by

1. Pruritus
2. Elevated serum SGPT (ALT)
3. Elevated fasting serum bile acid levels ≥11micmol/L
4. Spontaneous relief of signs and symptoms within four to six weeks after delivery
5. Absence of other diseases that can cause pruritus and jaundice [1, 2].

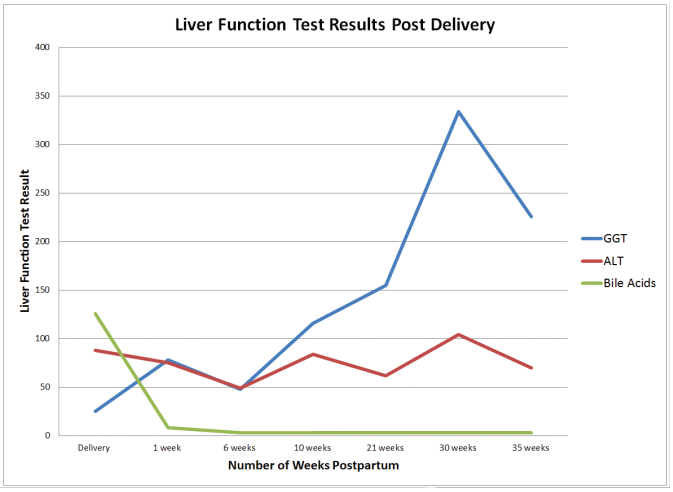

Figure 1: Liver function test results following delivery of the first baby.

The onset is in the second or third trimester of pregnancy. The prevalence of ICP is 0.4–2 % in Europe [2, 3].

Pruritus is the main symptom of ICP but most cases are mild and can be tolerated easily, however, few patients can develop very severe pruritus with significant effect on quality of life. Very rarely pruritus is refractory to standard medical treatment of ursodeoxycholic acid.

Maternal prognosis is good and symptoms resolve rapidly after delivery, accompanied by normalization of serum liver tests within six weeks, however, ICP affects fetal outcomes. ICP increases risk of preterm delivery. It can also increase the risk of asphyxia during delivery and can cause intrauterine death [3, 4].

The etiology of ICP is poorly understood. This is thought to be multifactorial, with genetic, hormonal and environmental factors playing important roles. During ICP, there is an increased flux of bile acids from the mother to the fetus, as indicated by elevated bile acid levels in amniotic fluid, cord blood and meconium .The central role of hormonal factors is supported by the higher ICP incidence in twin pregnancies and the observation that high-dose oral contraceptives and progesterone can trigger ICP. An increased ICP incidence in family members and ethnic differences point to genetic factors [5]. Mutations in genes coding for hepatocanalicular transporters have been identified (PFIC1 and PFIC2). Deficiency of ATP8B1 gene responsible for normal flow of bile over the membranes and its effects on instability and reduced function of transmembrane transport systems such as the bile salt export pump (BSEP) have also been studied [6].

The primary objective of pharmacologic treatment in ICP is to alleviate maternal symptoms and improve

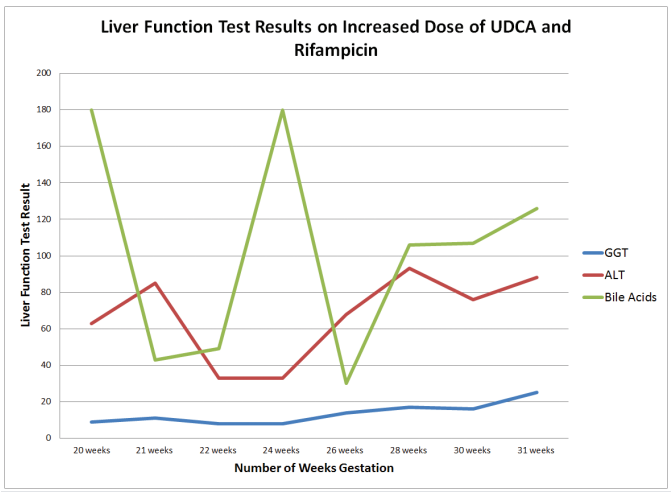

Figure 2: Liver function test results on 1-2 g UDCA and rifampicin treatment in first pregnancy.

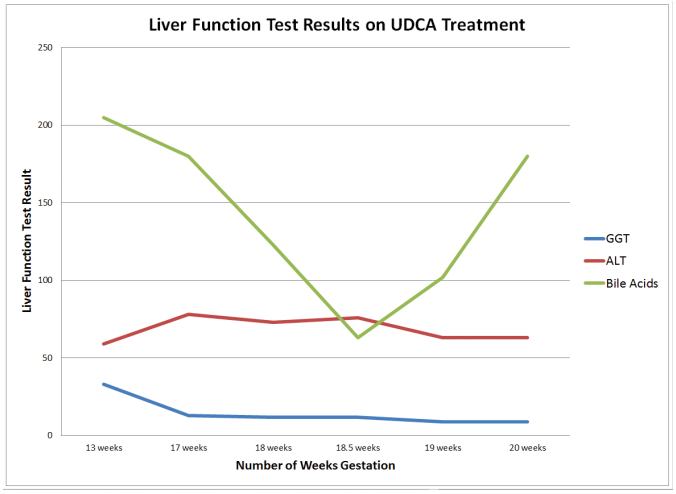

Figure 3: Liver function test results on 15 mg/kg UDCA treatment in first pregnancy.

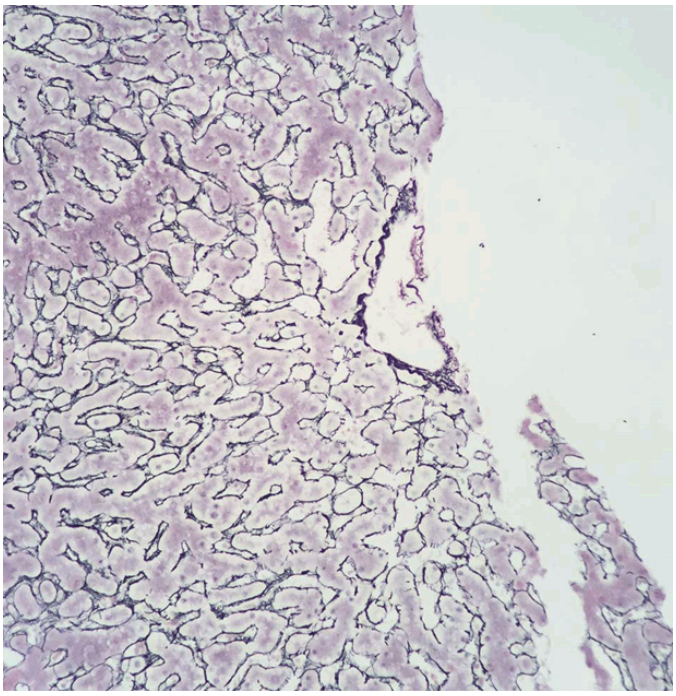

Figure 4: Reticulin Stain Image. Liver biopsy at eighth month postpartum showing resolution of severe cholestasis of pregnancy.

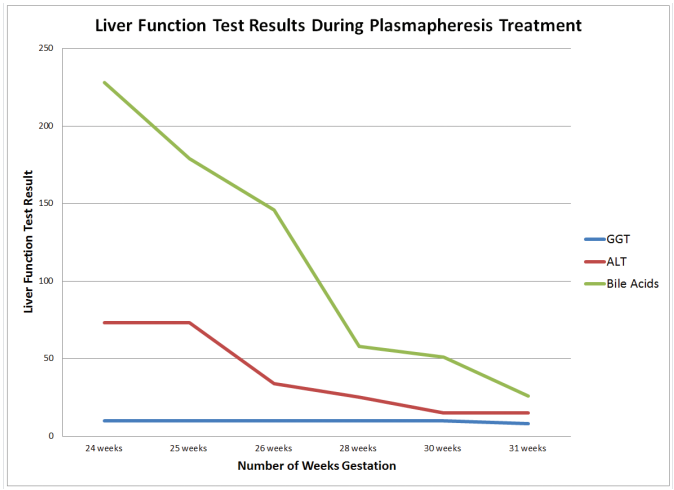

Figure 5: Liver function test results during plasmapheresis treatment in second pregnancy.

fetal outcome. Ursodeoxycholic acid (UDCA) remains the drug of choice for the treatment of ICP. UDCA at a daily dose ranging from 600–2000 mg is effective at reducing pruritus, decreasing the total serum bile acid levels, SGPT values, and bilirubin levels and allowing delivery closer to term improving fetal outcomes [7].

In patient refractory to medical therapy novel therapy like plasmapheresis, albumin dialysis (e.g., MARS), or plasma separation/anion absorption should be considered, however, there is paucity of data on use of these therapies.

Plasmapheresis is an extracorporeal procedure that can remove large molecular weight substances from the plasma. It is generally safe and well tolerated, and can be used safely in pregnant women, although rare complications of bleeding, infection, coagulation abnormalities and electrolyte disturbances may occur. The exact mechanism of how plasmapheresis decreases pruritus is unknown [8, 9].

Our patient was on maximal medical therapy which failed to alleviate her symptoms and biochemistry. Therefore, careful consideration with regards to plasmapheresis was made due to concerns about fetal outcome.

The role of plasmapheresis is thought to be transient and hence they may need repeated plasmapheresis. Our patient had repeated plasmapheresis. Duration was limited by concerns regarding central line and the fact that fetal condition was good at 31st week gestation.

There is a limited literature available for use of plasmapheresis in pregnancy. To our knowledge there are only three case reports on its use in pruritus associated with pregnancy. Of these, two have been with coexistent PBC and only one patient had plasmapheresis for isolated ICP (Table 1), [8, 9].

Table 1: Summary of Case Reports on Use of Plasmapheresis in Pruritus Associated with Pregnancy [8, 9].

Case	Study	Symptoms and Signs	Treatment Prior to Plasmapheresis	Stage of Pregnancy Treatment Commenced	Duration of Treatment	Outcome
1	UTAH, USA	Pruritus at 22 weeks Increased bile acids, 36.3 umol/L	Hydrocortisone Cholestyramine Diphenhydramine Zolpidem tartrate	32 weeks	Weekly for 4 weeks Each exchange was 1.3 plasma volume with 5% albumin as replacement fluid	Complete relief of symptoms 3-5 days post treatment Uncomplicated spontaneous vaginal delivery at 36.5 weeks
2	Toronto Canada	Severe Pruritus at 12 weeks Co-existing PBC ALT 137, AST 81, ALP 103, GGT 151, BILI 12	Cholestyramine Prior to pregnancy UDCA and Rifampicin	22 weeks	Twice a week for 2 weeks Each exchange was 1 plasma volume with 5% albumin as replacement fluid	Improvement after second plasma exchange Started on Rifampicin and ultraviolet B light therapy twice per week Delivered at 31 weeks following spontaneous rupture of membranes without complications
3	Toronto Canada	Significant pruritus at 12 weeks ALP 713, new diagnosis of PBC	Cholestyramine UDCA Rifampicin	31 weeks	Two consecutive days then every 10 days, total of 6 exchanges 1 plasma volume with 5% albumin	Uncomplicated delivery at 38 weeks

CONCLUSION

Plasmapheresis appears to be safe and can be used in refractory pruritus of intrahepatic cholestasis of pregnancy (IPC). More reporting of its use in pregnancy should be encouraged. The successful use of Plasmapheresis in our patient suggests that the procedure could be considered as a pregnancy-saving in pregnant women with severe cholestasis and intractable pruritus. Recognition of rare coexisting liver disease in patients with severe cholestasis of pregnancy is also important to exclude any underlying liver pathology. Furthermore, more studies should be conducted on molecular basis and markers of severity.

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Beata Polewiczowska – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Nishant Gautam – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Julie Wessels – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Alison Brind – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Guarantor
The corresponding author is the guarantor of submission.

Conflict of Interest
Authors declare no conflict of interest.

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