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Case Series

Intrahepatic cholestasis of pregnancy- case series done in a tertiary care hospital

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ABSTRACT

Intrahepatic cholestasis of pregnancy (ICP) also known as obstetric cholestasis is a liver disorder of pregnancy which is characterised by maternal pruritus usually in the third trimester, raised serum bile acids and increased incidence of adverse fetal outcomes and usually complete resolution of symptoms post-delivery. The etiology of ICP is complex and multifactorial as is the mechanism by which fetal complications occur which is yet not completely understood. The introduction of ursodeoxycholic acid in the management of ICP has provided significant improvement in maternal symptoms as well as fetal outcome. We present a case series of 5 cases of obstetric cholestasis which presented in our tertiary care hospital which could possibly help and guide obstetricians in the future who are dealing with dilemma in diagnosis and management of this condition.

Keywords: Cholestasis, Pregnancy, Pruritis, Bile acids, Ursodeoxycholic acid

INTRODUCTION

Liver disorders in pregnancy is one of the least studied topics in the field of obstetrics which presents as a dilemma to the treating obstetrician as approximately 3% of pregnancies are complicated by liver disease.[1] Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disorder related to pregnancy and its incidence is 0.2-2% of pregnancies.[2,3]

ICP was originally described by Ahlfield in 1883 as recurrent jaundice which resolved after delivery.[4] It is a cholestatic disorder characterised by: pruritis onset in 2nd or 3rd trimester of pregnancy, elevated serum aminotransferases and bile acid levels, and spontaneous relief of signs and symptoms within 2-3 weeks after delivery.[5]

It has a rather complex etiology including interactions between genetic, endocrine and environmental factors.[5] Usually maternal outcomes are favourable however it may be with associated with fetal and neonatal morbidity including preterm delivery, meconium-stained amniotic fluid and sudden intrauterine fetal demise.[5]

In this case series we are presenting 5 cases of intrahepatic cholestasis which presented in our tertiary care hospital and discussing their course and outcome.

CASE SERIES

Case 1

A 33-year-old G2P1 at 32 weeks of gestation with previous lower segment caesarean section (LSCS) presented at our emergency ward with abdominal pain, vomiting and severe pruritis, her blood work up showed serum bilirubin to be raised to 2.3 (with a direct bilirubin of 1.8), SGOT/SGPT:226/324, bile acids-24 micromol/l, viral markers were negative, ultrasound abdomen did not show any abnormality, all other investigations were within normal limits.

She was started on tablet UDCA 300mg twice a day, gradually patient showed symptomatic improvement as well as marked improvement in liver function tests. Weekly monitoring for maternal and fetal wellbeing was done. At 37 weeks of gestation serum (se) bilirubin was 1.1 and SGOT/PT came down to 54/56. The patient went into labour at 38 weeks and emergency LSCS was done (in view of previous LSCS not willing for VBAC) delivering a healthy 2.8 kg baby girl.

Post operatively patient did not have any complications LFTS were normalised and postnatal follow up showed mother and baby in good health.

Case 2

A 30-year-old Primigravida presented at 26 weeks of gestation with intrauterine fetal demise. The patient was a booked case at a government hospital. She gave history of pruritis since 2 weeks and decreased fetal movements since 1 day, she did not have any symptoms suggestive of severe preeclampsia. There was history of taking oral contraceptives for 1 year in the past.

Her vitals were stable (BP was 110/70 mm Hg), blood work up showed Se bil: 2.8 (direct-2.2), ALP-384, SGOT/PT- 280/250, bile acids-46 micromol/l, sugars and coagulation profile were normal, Anomalies scan-did not show any gross anomalies. Ultrasound abdomen was normal as were the other investigations.

Labour was induced with misoprostol and she delivered a 1.1 kg male stillbirth. Liver functions improved dramatically post-delivery and she was started on tablet UDCA 300 mg BD. Postnatal follow up after 15 days showed mother in good health.

Case 3

A 38-year-old G2P1 presented at 32 weeks of gestation with severe pruritis and loss of sleep since one week, she had history of ICP in previous pregnancy. She did not have any other comorbidities.

Her evaluation showed serum bilirubin: 1.8 (direct 1.2), OT/PT-300/360, bile acids-42 micromol/l. Viral markers and ultrasound abdomen was normal. All other routine investigations were normal.

She was admitted for safe confinement and started on tab UDCA 150 mg bd, symptomatically and clinically she showed an improvement and labour was induced at 37 weeks with cerviprime gel however in view of non-reassuring fetal heart rate and meconium-stained amniotic fluid she was taken up for LSCS. She delivered a 2.5 kg female baby who was kept in NICU for observation for 2 days.

Postoperative course was uneventful, she had complete resolution of symptoms post-delivery and postnatal follow up showed both mother and baby having good health.

Case 4

A 26-year-old G3P2 presented at 33 weeks of gestation with pruritis and loss of appetite since 2 weeks. She had no other significant past or family history.

Her investigations revealed bile acids: 11.8 micromol/l, bilirubin 1.2 (direct 0.8), SGOT/SGPT- 163/277, coagulation profile was normal and ultrasound abdomen did not show any abnormality. All other routine investigations were normal.

Patient was admitted for safe confinement and was started on T. UDCA 300 mg BD, however at 34 weeks of gestation she went into preterm labour and LSCS was done in view of breech presentation wherein she delivered a 2.1 kg baby boy. She had atonic PPH intraoperatively which was managed with uterotonics, B-Lynch compression sutures and bilateral uterine artery ligation. She was given 2 units of packed red blood cells thereafter following which postoperative course was uneventful. Baby had an NICU stay for 1 week after which he was doing fine, at postnatal follow up both mother and baby were doing fine.

Case 5

A 35-year-old primigravida presented at 34 weeks of gestation with itching and nausea.

She was also a known case of preeclampsia and GDM which were under control with anti-hypertensive and oral hypoglycaemic agents.

Investigation profile showed SGOT/SGPT-240/280, se bilirubin-1.3 (direct 0.8), bile acids 20.1 micromol/l, viral markers were negative and ultrasound abdomen showed fatty liver. Rest of the investigations were within normal limits.

In view of raised bile acids, a diagnosis of obstetric cholestasis was made and the patient was started on tab UDCA 300 mg BD, patient showed symptomatic improvement as well as normalisation of liver enzyme gradually. Labour was induced at 37 weeks with cerviprime gel and she delivered a 2.8 healthy female baby vaginally. At post-delivery follow up both mother and baby were doing fine with complete resolution of symptoms in mother.

Table 1: Relative risk of abnormal Doppler indices with adverse perinatal outcome.

Age (yrs)	Parity	Symptoms at present action	Se bil (mg/ dl)	Bile acids (micro mol/l)	OT/ PT (units /l)	Treatment given	Maternal complica -tions	Mode of delivery	Delive- red at (weeks)	Neonate details and complic- ations
Case 1										
33	G2P1	Abd pain vomiting pruritis at 32 weeks	2.3 d-1.8	24	226/ 324	UDCA 300 mg bd vit K	nil	LSCS (prev LSCS)	38	2.8 kg female
Case 2										
30	Primi	Pruritis dec fetal movts at 26 weeks h/o OCP intake	2.8 d-2.2	46	280/ 250	UDCA 300 mg bd vit. K	IUFD	Vaginal delivery	26	1.1 kg male stillbirth
Case 3										
38	G2P1	Pruritis loss of sleep at 32 weeks h/o ICP in prev preg	1.8 d-1.2	42	300/ 360	UDCA 150 mg bd vit. K	Meconium stained amniotic fluid (MSAF)	LSCS (MSAF)	37	2.5 kg female in NICU (for observa- tion)
Case 4										
26	G3P2	Pruritis loss of sleep at 33 weeks	1.2 d-0.8	11.8	163/ 277	UDCA 300 mg bd vit. K	Preterm labour PPH	LSCS (breech)	34	2.1 kg male premat- urity
Case 5										
35	Primi	Pruritis nausea at 34 weeks	1.3 d-0.8	20.1	240/ 250	UDCA 300 mg bd vit. K	Preeclam psia GDM	FTND	37	2.8 kg female

DISCUSSION

The incidence of ICP varies with geographical location and ethnicity.[6] It is most commonly seen in South America in Chile where overall incidence is 10%, with higher rates seen in women of Araucarias Indian descent.[7] All 5 of our patients were of Indian origin.

The etiology of ICP is complex and multifactorial, evidence suggests that there may be a genetic predisposition to the disease.[8] Several studies provide evidence that reproductive hormones particularly estrogen may play a crucial role in the etiology of ICP.[9] ICP usually occurs in the last trimester when estrogen levels usually reach their peak[9].It has also been associated with twin and triplet pregnancies which usually have higher estrogen levels than singleton gestations, oral contraceptive use among women with personal or family history of ICP could result in clinical features of ICP particularly when higher dose of estrogen preparations were used.[10] One of our patient gave history of taking oral contraceptive pills for 6 months prior to conception. Bacq et al observed that administration of natural progestins to women with threatened preterm labour resulted in ICP in 11 of the 12 women, this finding was further confirmed by 2 subsequent studies.[11-13] The seasonal variation ,the incomplete recurrence in subsequent pregnancies as well as the decrease in prevalence of ICP in high incidence regions in association with improved nutritional supply suggests that exogenous factors such as nutritional factors like selenium deficiency may contribute to ICP.[14]

Pruritis is the primary clinical symptom of ICP, it may be mild and tolerable for some patients while for others it may be severe and disabling. It may considerably impair the patients' quality of life causing sleep deprivation, psychological suffering and even suicidal thoughts in some.[15] Pruritis is most severe in the evening, with a

predilection for palms and soles and is not associated with any specific skin lesions.[16] It usually presents in the third trimester after 30 weeks of gestation, but in rare cases may develop at 6-10 weeks.[17] All of our patients presented with symptoms in the third trimester of pregnancy. All of our patients had pruritis and one of them had severe pruritis which impaired sleep.

Mild jaundice with moderately elevated serum levels of conjugated bilirubin occurs in 10-15% of cases.[16] Jaundice typically develops 1-4 weeks after the onset of pruritis but occasionally can be the initial symptom.[17,18] Subclinical steatorrhea may be seen along with fat malabsorption which may lead to vitamin K deficiency resulting in a prolonged prothrombin time and postpartum haemorrhage.[19] Abdominal pain, malaise and other constitutional symptoms are uncommon.[20] One of our patient presented with nausea, vomiting and abdominal pain.

Serum bile acid measurement is now considered to be the most suitable biochemical marker with cholic acid or the ratio of cholic acid: chenodeoxycholic acid being proposed as the most sensitive indicator for early diagnosis of the condition.[21] Bile acid levels may increase 10-100 times above the normal range and higher fetal complication rates were observed with maternal fasting bile acid levels exceeding 40 micromol/l.[22] Intra uterine fetal demise and meconium stained amniotic fluid was observed in two patients with bile acid levels being more than 40 micromol/l.

Serum aminotransferases are also elevated 2-10 fold above normal in 20-60% of patients with pruritus, and may even exceed 1000 u/l in exceptional cases.[22] Serum levels of alkaline phosphatase may rise upto 7-10 times above normal, but are difficult to interpret due to the elevation of the placental isoenzyme.[10] One study has shown that ICP is associated with impaired glucose tolerance, although there was no difference in fasting glucose levels between cases and controls, but the 2 hours post prandial and oral glucose tolerance tests were higher in ICP.[23] In association with impaired coagulability one study reported prolonged prothrombin time in 20% of patients.[24] All of our patients had raised serum bilirubin with raised values of direct bilirubin, they also had raised serum aminotransferases(more than thrice the normal value). In addition, all of them had raised serum bile acids and two of them had bile acids more than 40 micromol/l.

Maternal prognosis is good and symptoms usually resolve rapidly post-delivery accompanied by normalisation of liver function tests.[25] Persistent abnormalities should prompt reconsideration of other underlying chronic liver diseases like primary biliary cirrhosis, primary schlerosing cholangitis or chronic hepatitis C which may all be associated with development of pruritis during late pregnancy.[15] All of our patients had complete resolution of symptoms post-delivery. ICP can reccur during subsequent pregnancies in 45-70% with varying severity of recurrent episodes. One of our patients had history of ICP in previous pregnancy.

ICP increases the risk of preterm delivery (upto 19-60%), meconium staining of amniotic fluid, fetal bradycardia (upto 14%), fetal distress (upto 22-41%) and fetal loss (upto 0.4-4.1%), particularly when associated with fasting serum bile acids >40 micromol/l.[26,27] One patient presented with an unexplained still birth, one patient went into preterm labour, one patient had meconium-stained amniotic fluid. The pathogenesis of the fetal complications is still poorly understood, although a role for bile acids has been suggested.[28] Bile acids were shown to induce contraction of the chorionic veins of the placenta and myometrial sensitivity of healthy women to oxytocin was increased after incubation with cholic acid.[28] In a prospective study of ICP in patients with bile acids >40 micromol/l the frequency of meconium passage was 44% compared to 22% in a group with only mild ICP.[27]

The primary objective of pharmacological treatment in ICP is to alleviate maternal symptoms and improve fetal outcome. Presently the hydrophilic bile acid UDCA is the most effective treatment for ICP. In an open randomised parallel group study, 84 symptomatic patients with ICP were randomised to UDCA 8-10 mg/kg/day for 14 days, relief of pruritis was significantly more pronounced in the UDCA group and serum alanine and aspartate levels along with endogenous bile acid levels were more effectively lowered after UDCA therapy, it was also noted that delivery was closer to term in patients treated with UDC.[29] UDCA is well tolerated by pregnant women and no adverse effects in mothers or newborns were observed.[30] All of our patients were started on UDCA 300 mg BD and showed symptomatic improvement with the same.

Another treatment modality which has been proposed is dexamethasone, it inhibits placental estrogen synthesis by reducing secretion of precursor dehydroepiandrosterone sulphate from the fetal adrenals. An early observational study of 10 affected women from Finland suggested a beneficial effect with reduced serum estriol and estradiol levels and symptomatic improvement in all cases, however, this was not reported by subsequent studies.[31] In addition to the conflicting reports of efficacy there are concerns over safety, dexamethasone has been widely used to promote fetal lung maturity and is reported to be safe in this context ,however since it crosses the placenta easily repeated high doses may be associated with low birth weight and abnormal neuronal development.[32] Another drug which is used is rifampicin , a recent study investigating the role of rifampicin has shown that it enhances bile acid detoxification an effect that is complimentary to the upregulation of bile acid export that is induced by UDCA, suggesting that the 2 drugs used in combination may be more effective than monotherapy.[33] ICP is associated with a risk of malabsorption of fat soluble vitamins due to the reduced enterohepatic circulation of bile acids and subsequent reduction in uptake in the terminal ileum, therefore many clinicians opt

to treat women with oral vitamin K to guard against the theoretical risk of postpartum haemorrhage, however there are no studies to support or refute this practice. All of our patients were given vitamin K prophylactically to prevent postpartum, haemorrhage, one of our patients had postpartum haemorrhage which was managed with B-Lynch compression sutures.

Since conventional antepartum testing does not reliably predict fetal mortality, there are several reports of normal CTG and/or normal fetal movements in the hours preceeding fetal loss, thus the general consensus is that these forms of fetal surveillance do not prevent IUFD, however they may provide some reassurance to the patients and their treating obstetricians.[34] In view of the same induction of labour at 38 weeks of gestation has been observed to reduce fetal risk and delivery has been recommended at 37-38th week of gestation in ICP, in severe cases (prior to the advent of therapy with UDCA) delivery has even been initiated at 36 weeks of gestation.[35,36] We delivered three of our patients by 37-38 weeks and one patient went into preterm labour at 34 weeks. 1 patient delivered a still born, whereas the rest of the babies did not have any sequelae in the neonatal period. All patients had complete recovery post-delivery without any residual disease.

CONCLUSION

ICP is a relatively common cause of hepatic dysfunction in pregnancy, it causes maternal pruritis with impaired liver function and raised serum bile acids. The maternal cholestasis is transient with complete resolution in the postpartum period however a few cases may be at an increased risk of hepatobiliary disorders later in life. It has also been associated with adverse fetal outcome (meconium-stained amniotic fluid, fetal asphyxia and spontaneous preterm delivery, spontaneous IUFD) when there is a marked elevation in serum bile acids, however with a wide variety of strategies in the active management of ICP fetal outcomes have markedly improved.

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