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CASE REPORT

Rifampicin as an Adjunct to Ursodeoxycholic Acid for Treating Severe Refractory Intrahepatic Cholestasis of Pregnancy in a Patient with Elevated Bilirubin

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Introduction

Ursodeoxycholic acid (UDCA) is the mainstay of treatment in intrahepatic cholestasis of pregnancy (ICP), which improves pruritus and normalizes bile acids in most cases. Other adjuvants used are topical emollients and anti-histaminics for symptomatic relief [1]. A case with severe ICP, not controlled on UDCA alone, and managed successfully by adding rifampicin,is being reported.

Case Report

A 28-year-old, G7P0 + 3+3 + 1 presented at 12 weeks' gestation with previous three preterm deliveries and also history of jaundice in all pregnancies. Micronized-progesterone was started, and history-indicated cerclage applied at 15 weeks.

Patient developed itching with jaundice at 17^{+6} weeks. Liver function tests (LFT) revealed: bilirubin 6.6 mg/dL (conjugated 6.1 mg/dL), alkaline-phosphatase (ALP) 735 IU/L and aspartate/alanine aminotransferase (AST/ALT) 22/37 IU/L. Viral markers (IgM hepatitis A virus antibody, IgM hepatitis E virus antibody, IgM hepatitis B core antibody and anti-hepatitis C virus antibody) autoimmune markers (antimitochondrial, anti-smooth muscle, antinuclear and anti-liver kidney microsomal type-1 antibodies) were negative; liver parenchyma was normal on ultrasound with no intrahepatic biliary dilatation or gallbladder disease, thus excluding liver disease. A provisional diagnosis of ICP was made, which was confirmed as serum bile acids (SBA) levels were 198 µmol/L (Normal range < 10 µmol/L).

Oral UDCA 300 mg thrice-daily was started along with anti-histaminics and local emollients, and weekly LFTs were done. Despite UDCA therapy, bilirubin continued to rise and reached 14 mg/dL (conjugated 12.6 mg/dL) at 22 weeks. Progesterone was stopped, and UDCA was increased to 450 mg thrice-daily. Since there was no improvement (bilirubin remained 13.6 mg/dL), oral rifampicin 300 mg daily was added at 24 weeks, which led to slow decline in bilirubin (Fig. 1); however, pruritus decreased only by 50%. Repeat SBA 4 weeks after UDCA and rifampicin was still high (133 µmol/L) though transaminases were normal, ALP was 677 IU/L, and bilirubin continued to fall. Anticipating early delivery, antenatal corticosteroids were administered at 28 weeks. Patient went into spontaneous preterm labour at 31^{+6} weeks and delivered a 1.54 kg, male baby with 9/9 Apgar and meconium stained liquor. UDCA–rifampicin were

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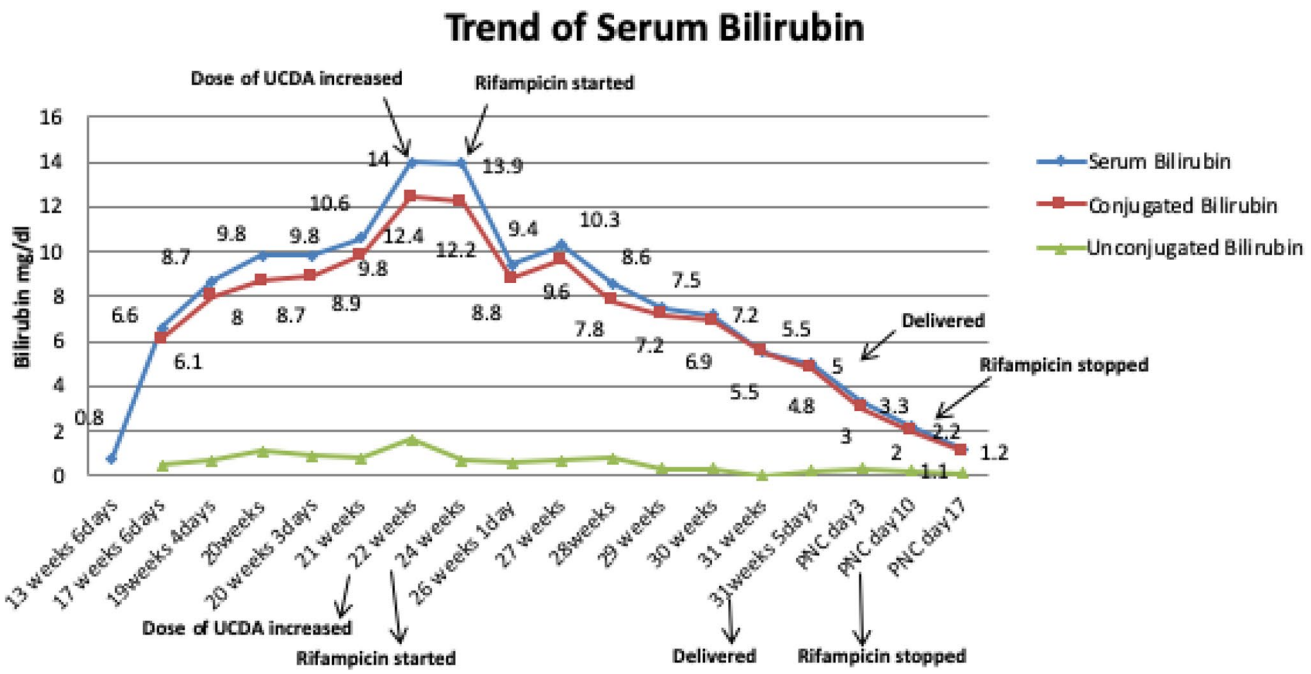

Fig. 1 Effect of UDCA, Rifampicin and delivery on serum bilirubin levels

stopped on 10th postpartum day when bilirubin decreased to 2.2 mg/dL and pruritus resolved.

Discussion

Intrahepatic cholestasis of pregnancy (ICP) is characterized by unexplained pruritus, raised bile acids and/or abnormal liver function tests (LFTs). Though without severe adverse effects on the mother, ICP is associated with significant perinatal morbidity and unexplained stillbirths [2]. Diagnosis of ICP is made at SBA levels of > 10 µmol/L, levels > 40 µmol/L strongly correlate with poor neonatal outcome [2]. Raised serum bilirubin is seen in up to 10% patients, causing cholestatic jaundice with conjugated hyperbilirubinemia. Though Ursodeoxycholic acid (UDCA) is the mainstay of treatment, many cases may not respond to it. In such cases, rifampicin may be added to UDCA because of the synergistic effect on bile acid clearance.

UDCA displaces hydrophobic toxic bile acids, enhances their excretion and reduces hepatic damage. Rifampicin is a hepatic enzyme-inducer which enhances bile acid detoxification and hepatic efflux of SBA and improves pruritus. Hence,UDCA–rifampicin act complementarily in refractory ICP [3]. Role of adding rifampicin to UDCA in ICP is reported in a retrospective study [4] and a recent case report [5]. In this study of 28 women with severe ICP, no case had significant hyperbilirubinemia. Rifampicin in the dose varying from 300 to 1200 mg was used as an adjunct to UDCA where bile acids remained high despite maximal UDCA dose; resulting in at least 50% reduction in SBA in 38% women with mean age at delivery being 34^{+4} weeks with no adverse event effect of treatment and no stillbirth [4].

Present case had history of jaundice in all pregnancies, early development of severe ICP (bile acids > 100 µmol/L) at 17 weeks in the current pregnancy, conjugated hyperbilirubinemia reaching 14 mg/dL, no response to higher UDCA dose but improved with combining rifampicin. We monitored the patient with weekly LFT to assess for any deterioration in liver enzymes. Safety of rifampicin in pregnant women with deranged LFTs is unclear,and its use should be considered on case to case basis.

Conclusion

Adding rifampicin to UDCA enhances bile acid excretion and is an option for severe refractory ICP.

Author Contributions All authors contributed in the patient management and follow-up. Additionally, VK was responsible for manuscript writing. SN was responsible for the acquisition of clinical data, and figure design, obtaining informed consent. VK, SN, S and NB were responsible for manuscript editing.

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Compliance with Ethical Standards

Conflict of interest None of the authors have any potential conflict of interest.

Ethical Statement Informed consent was obtained from the patient for presenting her data for publication.

Human Participants and/or Animals All parts of Declaration of Helsinki have been applied.

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