International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Indrani C et al. Int J Reprod Contracept Obstet Gynecol. 2025 Mar;14(3):979-980
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20250547

Case Report

A case of Dili-drug induced liver injury by norethisterone combined with mifepristone

Chaitanya Indrani, Anjali Antony*

Department of Obstetrics and Gynaecology, MVJ Medical College and Research Hospital, Hoskote, Bangalore, Karnataka, India

Received: 24 January 2025
Revised: 19 February 2025
Accepted: 20 February 2025

***Correspondence:**
Dr. Anjali Antony,
E-mail: anju2442@gmail.com

ABSTRACT

DILI related to female sex hormones like estrogen and progesterone generally occur with estrogen component. Progesterone related DILI are not commonly reported. We are reporting a case of DILI by norethisterone combined with mifepristone in a 37-year-old woman. Oral contraceptives have been shown to be associated with variety of liver injuries. Various manifestations include hepatitis, cholestatisis, hepatic adenoma, peliosis hepatitis, sinusoidal obstruction syndrome and increase in size of pre-existing hemangiomas. It is important to create awareness about norethisterone-induced liver injury among clinicians, especially gynaecologists and also use combination drugs after studying the mechanism of action, agonistic and antagonistic actions.

Keywords: Acute liver injury, Progesterone, Mifepristone

INTRODUCTION

A common progesterone prescribed in menstrual disorders is norethisterone. Since its metabolism occurs in the liver and also because of its smooth muscle relaxant property, it has shown to exhibit a variety of liver injury including hepatitis, cholestasis.etc.[1] DILI related to female sex hormones like estrogen and progesterone generally occur with estrogen component. Progesterone related DILI are not commonly reported.[2] We are reporting a case of DILI by norethisterone combined with mifepristone in a 37-year-old woman.

CASE REPORT

A 37-year-old para 2 living 2 with last child birth 12 years back presented to a gynaecologist with irregular cycle and heavy menstrual bleeding was diagnosed as AUB(O) in 2019 and underwent treatment modalities such as ovarian drilling, mirena insertion in 2022 for which she was non-compliant and was on OCPs for 3 years till 2024. She was then advised to stop OCPs and was started on Tab. Norethisterone 10 mg once daily along with Tab. Mifepristone 10 mg once daily for a period of 2 months. She was later diagnosed to have developed Type 2 Diabetes mellitus and hypertension and was started on medication. She was euthyroid.

Though her symptoms reduced she presented to us with icterus, hyperlipidaemia and deranged liver function tests. Her blood work up revealed raised transaminases (AST 147 IU/l, ALT 346 IU/l, ALP-124 IU/l, GGT-260 IU/l with raised direct bilirubin of 3.17 mg/dl) suggestive of hepatic cholestasis. Her total cholesterol-427 mg/dl out of which LDL was 319 mg/dl and triglycerides were 248 mg/dl.

She was asymptomatic despite raised transaminases >10 ULN (upper limit of normal). Her viral work up was negative for HBsAg, anti HCV, IgM anti HAV and IgM anti HEV. Her autoimmune work up was negative for anti-nuclear antibody, anti LKM, anti-mitochondrial antibody and smooth muscle antibody. Coagulation profile was

within normal limits. MRCP showed gall bladder sludge and MRI pelvis revealed small uterine fibroids with endometrial thickness of 6 mm and dilated pelvic veins suggestive of pelvic congestion syndrome.

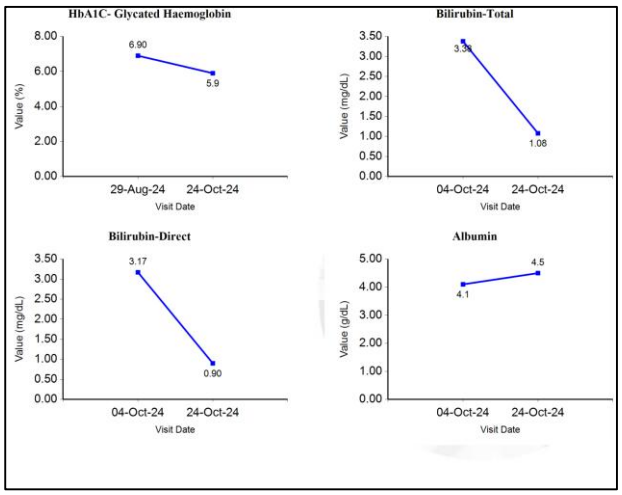

Figure 1: Liver function tests of the patient.

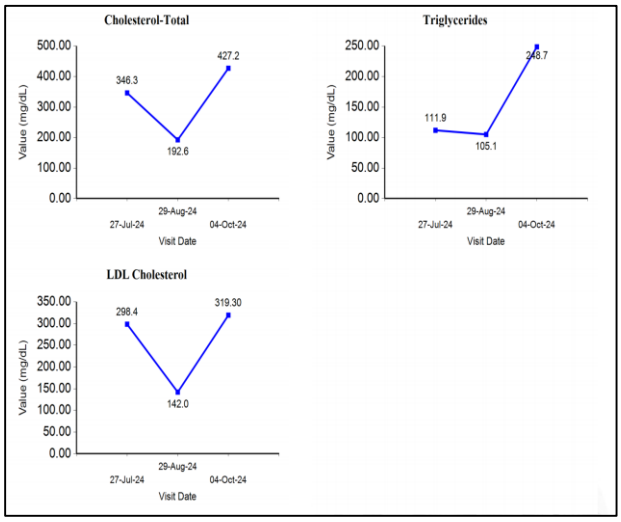

Figure 2: Lipid profile of the patient.

As the patient was concerned about her bleeding complaints, norethisterone was stopped and she was put on only Tab Mifespristone 25 mg once daily. Her transaminases (AST-38 U/l and ALT-58 U/l) and lipid profile showed improvement after discontinuation of Norethisterone. Bilirubin and cholesterol levels also improved in the subsequent visit. Figure 1 and 2. A diagnosis of drug induced liver injury (DILI) was kept. Her RUCAM score was +10, which was suggestive of highly probable DILI.

DISCUSSION

Oral contraceptives have been shown to be associated with variety of liver injuries. Various manifestations include hepatitis, cholestatisis, hepatic adenoma, peliosis hepatitis, sinusoidal obstruction syndrome and increase in size of pre-existing hemangiomas.[1] In our case patient was started on progesterone and mifepristone which is an antiprogestin. Norethisterone is metabolized in the liver via cytochrome P450 3A4 (CYP3A4), whereas mifepristone is a strong inhibitor of CYP3A4.

Mifepristone increased liver exposure to Norethisterone, resulting in the development of hepatic cholestasis that reversed after stoppage of norethisterone.[2] The RUCAM score +10 without the re-challenge point and was highly probable to be DILI. As the patient was advised to stop norethisterone, unintentional drug re-exposure criteria were not met.

CONCLUSION

Norethisterone-induced liver injury is a possibility and as in our case its effect was pronounced after the add on action of mifepristone. It should be a routine to do a liver function test both before and after initiating a female on this drug. It is important to create awareness about norethisterone-induced liver injury among clinicians, especially gynaecologists and also use combination drugs after studying the mechanism of action, agonistic and antagonistic actions.[2]

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Shah I, Putnam T, Daugherty E, Vyas N, Chuang KY. Mifepristone: an uncommon cause of drug-induced liver injury. Gastroenterology Res. 2019;12(3):181-4.
2. I Shah, T Putnam. Correction to: Mifepristone: An uncommon cause of drug induced liver injury. Gastroenterol Res. 2020;13(4):161-2.

Cite this article as: Indrani C, Antony A. A case of Dili-drug induced liver injury by norethisterone combined with mifepristone. Int J Reprod Contracept Obstet Gynecol 2025;14:979-80.