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Correction

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Correction to: Mifepristone: An Uncommon Cause of Drug-Induced Liver Injury

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This is to correct the published article, Gastroenterology Research, 2019;12(3):181-184. DOI: 10.14740/gr1188.

After the publication of our initial article [1], we were made aware by the patient's treating endocrinologist that the patient was also on ethinyl estradiol and norethindrone (Loestrin), an oral contraceptive. The patient failed to provide us with this information when she was admitted. We were also given access to more detailed information regarding the patient's mifepristone dosing history (Fig. 1). These are essential data to be included in our case report as two potential mechanisms could be used to explain the patient's development of jaundice while taking mifepristone.

Drug-induced intrahepatic cholestasis has long been observed in patients on oral contraceptives and during the latter stages of pregnancy [2]. In hepatocytes, the bile salt export pump constitutes the predominant bile salt efflux system and mediates the cellular excretion of conjugated bile salts into the bile canaliculus [3]. *In vitro*, inhibition of the bile salt export pump by exogenous estrogen has been proposed as the pathophysiological mechanism behind estrogen-exposure-inducing inhibition of bile acid secretion and transportation [4]. This mechanism is consistent with the liver biopsy findings of this patient, demonstrating intrahepatic cholestasis.

Loestrin is metabolized in the liver via cytochrome P450 3A4 (CYP3A4), whereas mifepristone is a strong inhibitor of CYP3A4. We postulate that the gradual escalation of mifepristone increased liver exposure to Loestrin, resulting in the development of hepatic cholestasis that reversed upon discontinuation of both drugs. Although it could be questioned why Loestrin and mifepristone were prescribed concurrently, the patient's endocrinologist deemed it essential as Loestrin provided estrogen replacement and contraception that is required for women of reproductive age while taking mifepristone.

An alternative mechanism that could have caused the patients symptoms could be mifepristone-induced direct cholestatic liver injury similar to that caused by anabolic steroids because mifepristone has a classic 17-carbon steroid ring structure typical of steroids [5]. Funke et al [6] reported a similar case of a patient with Cushing's syndrome on increasing doses of mifepristone up to 900 mg once daily, who then developed a cholestatic liver injury. This patient, in contrast to our patient, was not on any other medications known to induce cholestatic injury. Upon cessation of mifepristone, the patient's hyperbilirubinemia and elevated alkaline phosphatase returned to normal [5].

Anabolic steroids are characterized by the substitution of a phenyl-amino-dimethyl group at the 11P-position of the steroid ring as well as radicals located at the C17 position. Cholestasis due to the C17 variable androgens was observed in some animal models where the possible mechanism of action could have been reduced bile salt transporter proteins and disruption of the intrahepatic microfilaments [4]. In this setting, cholestatic injury is typically reversible upon discontinuation of the glucocorticoid. The similar clinical phenotype reported by Funke et al [6] and our patient's case support this mechanism as an underlying pathological process.

In summary, there are two possible mechanisms to explain our patient's cholestatic injury. Mifepristone could have inhibited the metabolism of estrogen when the mifepristone dose was escalated, which could have precipitated hepatic cholestasis. Alternatively, mifepristone could have acted like an anabolic steroid to cause liver injury. Therefore, our case report highlights the importance of the knowledge of concomitant drug use, particularly those that behave as CYP3A4 substrates or inhibitors, when considering mifepristone therapy. Close liver function monitoring when patients start mifepristone treatment and during dose escalation is advisable, especially when the patient is on other drugs that may act as CYP3A4 substrates or inhibitors.

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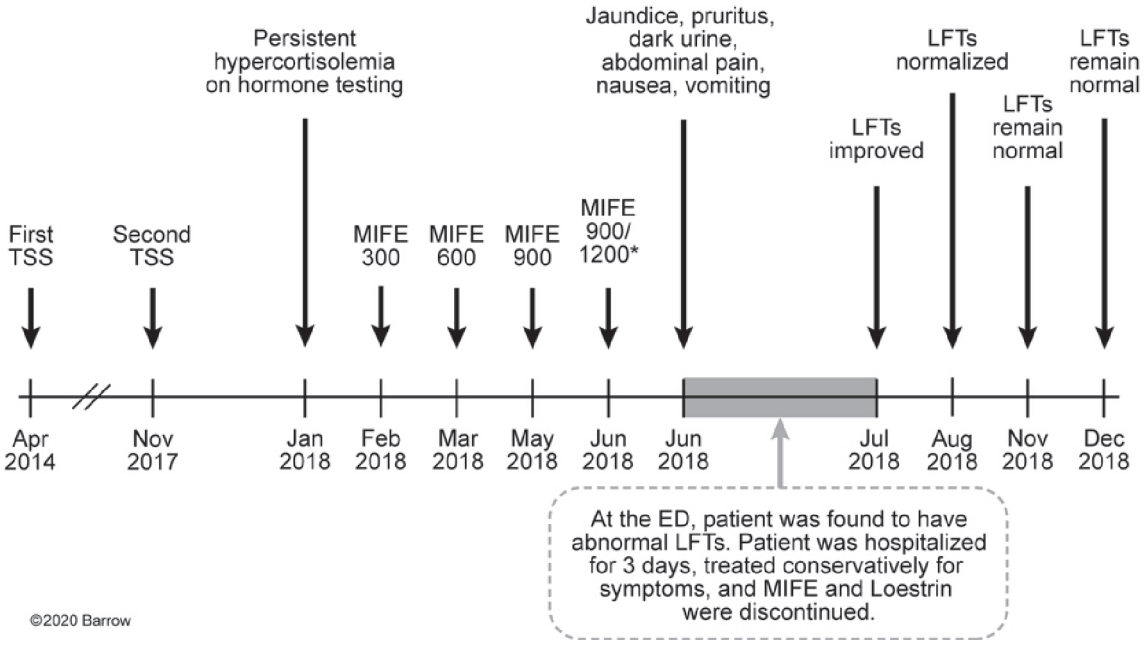

Figure 1. Sequence of events and mifepristone dosage schedule (mg/day). *Dosage alternated between 900 and 1,200 mg daily. ED: emergency department; LFTs: liver function tests; MIFE: mifepristone; TSS: transsphenoidal surgery. Used with permission from Barrow Neurological Institute, Phoenix, Arizona.

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