

Norethisterone–induced cholestasis: the hidden alarm

Abstract

Combined oral contraceptives have a well-known side effect of causing a reaction similar to intrahepatic cholestasis of pregnancy. This has been thought to be largely due to the estrogen component of contraceptives. However, in this case report, we delineated the case of cholestasis in a middle-aged woman who has been receiving norethisterone, a progestogen only pill, for symptomatic fibroids. Within 2 months of starting norethisterone, this patient developed hepatomegaly and jaundice. Her labs showed abnormalities of liver function indicative of a cholestatic picture. Upon discontinuation of norethisterone and starting ursodeoxycholic acid, her liver functions began to trend down and returned to normal within a month. There have been similar case reports; however, the data is lacking with regards to establishing a correlation. Awareness of unanticipated side effects of a drug such as norethisterone is crucial in the prompt recognition and treatment of cholestasis should it arise. Moreover, knowledge is lacking with regards to the effect of progesterone on the liver in general and on developing cholestasis in particular.

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; ALP, alkaline phosphatase; ANA, anti-nuclear antibodies; AMA, antimicrobial antibodies; RF, rheumatoid factor; ANCA, antineutrophil cytoplasmic antibodies; TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy SAAG, serum ascites albumen gradient.

Background

The relationship between sex steroids and hepatic function has historically been described.¹ Specifically, rare cases of estrogen containing contraceptives causing a presentation similar to intrahepatic cholestasis of pregnancy have been described.² The estrogen component of combined oral contraceptives is thought to interfere with bile acid transport through the canaliculi, particularly through multidrug resistance-associated transporter 2.³ However, progestogen only pills have not been as implicated in the development of hepatic cholestasis. However, it has been noted that levels of progesterone sulfate are elevated in patients with intrahepatic cholestasis of pregnancy.⁴

Norethisterone is a progestin only medication commonly used in birth control pills. There have been previous cases describing patients who had a presentation similar to intrahepatic cholestasis of pregnancy after use of norethisterone.^{5,6} In this case report, we delineate the presentation of a middle-aged female who complained of cholestatic symptoms after starting norethisterone.

Case

A 47-year-old Jordanian woman was suffering from abnormal uterine bleeding requiring multiple visits to the Emergency Department. During workup, she was found to have a bulky uterus with multiple sub-serosal and mural fibroids. She was given norethisterone 10 mg PO for symptomatic treatment of her bleeding with the dosage given with tapering; TID then BID then once a day for 2 months. The patient had no other past medical history. She had a laparoscopic cholecystectomy for symptomatic gallstones prior to her gynecological complaint. She was not previously on any other medications particularly other contraceptives. She never drank alcohol and was never sexually active.

After 2 months of norethisterone treatment, the patient was planned for total abdominal hysterectomy and bilateral salpingo-oophorectomy when her preoperative workup revealed total bilirubin: 54umol/L, direct bilirubin: 43umol/L Calcium: 2.71mmol/L, albumin: 23g/L, and ALP: 319U/L. ALT was 34U/L and AST was 26U/L. On physical examination, she had jaundice and hepatomegaly which was also demonstrated on abdominal ultrasound. Hematology team was consulted and they ruled out hemolytic anemia through peripheral smear and LDH and haptoglobin levels. Autoimmune workup was done and was negative for ANA, AMA, RF, ANCA. She also had normal C3 and C4 levels. Norethisterone was stopped and she was started on Ursodeoxycholic acid BID for 5 days. Thirty days later, her total bilirubin which had peaked to 139 gradually dropped to 21 and eventually returned to normal. Her ALP; however, remained persistently high. Her RUCAM score was (8+) indicative of probable drug-induced liver injury.⁷ The patient had her planned TAH+BSO 4 months later.

Interestingly, a year later, the patient developed bouts of abdominal pain and low SAAG ascites with features of peritonitis and mild omental nodularity with enlarged abdominal and pelvic lymph nodes revealed by MR enteroclysis, as well as skin leukocytoclastic vasculitis proven by skin biopsy. Extensive workup was done which ruled out Tuberculosis, Viral or Autoimmune hepatitis and lymphoma. When evaluated by the rheumatology team, their working diagnoses were undifferentiated autoimmune disease, sarcoidosis and possible Familial Mediterranean Fever. She was initially started on steroids but the bouts of abdominal pain did not cease. She was then started on hydroxychloroquine due to its immunomodulatory effect, and colchicine for a presumptive diagnosis of Familial Mediterranean Fever. A month later, she stopped both hydroxychloroquine and colchicine because of nausea, and she has been in remission since then on small dose of steroids.

Discussion

In our case, the patient's history and investigations ruled out any other causes for the cholestasis particularly the use of any other drugs. The development of Familial Mediterranean Fever is also of note because it can be coincidental or exist as a predisposing factor

to developing cholestasis from progestogen. The course of symptom development and their resolution with relation to norethisterone use and discontinuation is highly suggestive of a correlation.

The development of jaundice after taking estrogen containing oral contraceptives is a well-established clinical correlation. However, there is no data in the literature describing the frequency of developing cholestasis or jaundice secondary to norethisterone. The current literature consists of case reports dating as early as the 1960's. One of the earliest case reports, dating back to 1968, described the development of jaundice in 2 sisters who received norethisterone for irregular bleeding and contraception, respectively.⁸ Additionally, a case was described in which a patient, who as a teenager, developed cholestasis that was thought to be secondary to norethisterone use, developed intrahepatic cholestasis of pregnancy 8 years later.⁹ Due to the paucity of data on the effects of norethisterone on hepatic function, the mechanism through which cholestasis occurs remains unclear.

One article of note is a recent study on the effect of sex steroids on the development of halothane-induced liver injury in mice. The study concluded that pre-treatment of mice with estradiol mitigated the effects of halothane induced liver injury while progesterone exacerbated it.¹⁰ Another study described the effects of treating immature male mice intraperitoneally with progesterone to observe its effect on liver cells. It was observed that treatment with progesterone did not have a cytotoxic effect on the cells, but cellular proliferation and spindle disturbances were observed.¹¹

The importance of gathering more data on the effect of progestin only pills on the liver lies in the possibility of prescribing them to women with underlying medical conditions. For example, one article described 2 cases of multiple hepatic adenomas in patients receiving renal dialysis who received norethisterone for dysfunctional uterine bleeding.¹² Another article described 4 cases of hepatic adenomas in patients with inherited platelet disorders.¹³ In all these cases, life-threatening hemorrhage can occur from the adenomas due to the coagulopathy, so progestin only pills must be prescribed with caution in such patients.

Conclusion

In conclusion, norethisterone does not have a well-established clinical correlation with the development of cholestasis. Despite the presence of a few case reports, there is yet a lot to be known about the mechanism of the liver changes, as well as, the clinical setting in which they occur. There is also lack of knowledge regarding patient factors that predispose to developing cholestasis from progesterone. Recognition of the presence of such a side effect can aid in the diagnosis and treatment of cholestasis when it occurs.

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Conflicts of interest

The author declares there are no conflicts of interest.

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