THE JOURNAL OF
Obstetrics and Gynaecology Research

doi:10.1111/jog.13859 J. Obstet. Gynaecol. Res. Vol. 45, No. 2: 477–481, February 2019

Suggestive hypothesis on a case report: Patient presenting with cyclical ovarian cysts coupled to increased cholestatic enzymes

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Abstract

We describe the case of a childbearing-age woman presenting with spontaneous recurrent functional ovarian cysts and, more interestingly, chronic and asymptomatic elevation of cholestatic parameters. The patient showed no history of chronic viral infections, immunological and metabolic disorders, alcohol abuse and environmental toxins exposition. Hepatic ultrasonography and cholangio-pancreatography-magnetic-resonance excluded any morphological and structural abnormalities, while liver biopsy evidenced only minimal and not specific features of inflammation. Cholestasis indices obtained prompt recovery after each cycle of synthetic hormone therapy, implanted to treat functional ovarian cysts. She has continuously experienced the off-therapy asynchronous recurrence of liver laboratory abnormalities and functional ovarian cysts. The favorable effect of the synthetic hormone therapy to obtaining a stable recovery of this unexplained long-lasting *cholestatic syndrome* could be likely explained by downregulation of an endogenous ovarian overproduction, although estrogen-regulated local intracellular transduction pathways cannot be excluded.

Key words: functional ovarian cyst, liver enzymes, synthetic hormone treatment.

Introduction

Functional ovarian cysts (FOC) are benign and generally asymptomatic disorders, with an occurrence in about 7% of asymptomatic childbearing-age women and an occasional discovery varying from 14% to 18% in postmenopausal women.[1,2] FOC can occur during the ovarian hyperstimulation syndrome (OHSS), as complication of ovarian stimulation to induce pregnancy; in OHSS setting, FOC cause overproduction of ovarian hormones, such as oestrogens and progesterone, potentially determining liver damage.[3] In addition, synthetic hormone therapy (SHT), widely used to treat several gynecological disorders, is a well-known risk factor for drug-induced liver injury, determining in animal models marked congestion blood vessels, distended sinusoids with dilated central veins as well as degeneration, necrosis of hepatocytes and distinct fibrosis.[4] In this paper, we reported the case of a young, lean woman presenting with experienced history of liver biochemical alterations, mostly including cholestasis abnormalities, and recurrent FOC, both responsive to SHT and off-therapy relapsing. Her FOC were spontaneous and not associated with OHSS. This *cholestatic syndrome* was asymptomatic and showed a poor benefit from ursodesossicholic acid (UDCA) therapy. SHT was prolonged to suppress the repeated FOC. We have compared this case with scarce evidence from literature, hypothesizing possible etio-pathogenetic mechanisms and potential clinical implications.

Received: February 28 2018.
Accepted: October 14 2018.
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Case Report

On February 2009, an asymptomatic 28-year-old woman presented with high serum aminotransferases (prevalence of alanine aminotransferase [ALT], 1.6 × upper of normal limit [unl]) and cholestasis indices (gamma glutamyl transpeptidase [GGT], 6.6 × unl; alkaline phosphatase [ALP], 1.9 × unl; direct bilirubin was 0.40 mg/dL and total bilirubin was 1.46 mg/dL), lasting since 2003 and discovered in occasion of a CMV infection. A previous liver biopsy performed in 2004 evidenced only 'minimal and not significant alterations', such as small spots of intralobular inflammation and lipofuscin pigment occurrence in centrolobular zone and in Kupffer cells. Markers of hepatotropic viruses were repeatedly negative, as well as antinuclear, antiextractable nuclear antigen, anti-smooth muscle, antimitochondrial, antiliver-kidney microsomal type 1, antineutrophil cytoplasmic, anti-gliadin and antiendomysium antibodies. Patient did not present with deficit of alpha1 antitrypsin or ceruloplasmin and signs of iron overload. Personal information did not reveal noticeable assumption of alcohol, nor exposition to environmental or professional toxics. BMI was stable around 21 with a waist circumference between 72 and 74 cm. The age at menarche was 12 years, followed by regular menses. Familial history evidenced biliary lithiasis, nonalcoholic fatty liver and hepatocarcinoma. Previous treatment by UDCA at a dosage of 15 mg/Kg/die/9 months ended up in no significant improvement.

On April 2009, a liver ultrasonography (US) followed by a without intravenous contrast cholangiopancreatography-magnetic-resonance confirmed the absence of morphological and structural abnormalities. A pelvic US, performed during a gynecological screening, showed an ovarian cyst. Breasts at US did not demonstrate any morpho-structural alteration.

From December 2009 to December 2010, the patient showed unexpected, rapid recovery of aminotransferases and cholestasis indices in occasion of the SHT with chlormadinone acetate (2 mg)/ethinyl estradiol (0.03 mg), scheduled for a 21-day cicle/month starting from the first day of the next menstrual cycle, to treat the ovarian cyst (a diameter of 6 cm at US on the left ovary). Increase of liver enzymes persistently relapsed after 8 weeks from completion of previous SHT cycle associated with the ovarian cyst reoccurrence on July 2011 (Table 1). A second cycle of alternative SHT from October to December 2011, by Drospirenone (3 mg)/ethinyl estradiol (0.03 mg), was attempted to gain a prolonged response, again obtaining normalization of liver indices and FOC regression. However, the patient manifested a new relapse of FOC and, of more interest, a rapid increase of aminotransferases and cholestatic indices off therapy, similar to what happened after the first SHT interruption (Table 2). In prevision of future SHT cycles to treat recurrent FOC, she received a complete thrombophilic risk status survey, which resulted absent. Furthermore, the patient underwent a hysteroscopic polypectomy on November 2012. During the next SHT cycles (January–March and December 2013–May 2014), she reshowed analogous clinical and biochemical features, as at the first referral (Table 2). Particularly, in coincidence of every cycle of SHT, the patient needed about 8 weeks to normalize liver indices and 4–8 weeks for regression of FOC. On the other hand, she always experienced hepatic biochemical abnormalities and FOC relapse, respectively, after 4 to 8 weeks and 6 to 8 months off-SHT. FOC had diameter varying from 5 to 7.5 cm, singly occurring at both the ovaries. She was never pregnant.

Table 1 Laboratory and instrumental data throughout the SHT (the initial approach)

	Chlormadinone acetate (2 mg)/Ethinyl estradiol (0.03 mg)†					
	Basal	After 4 weeks on therapy	After 8 weeks on therapy	Up to the end of therapy	4–8 weeks off therapy	6–8 months off therapy
GGT	6.6 × unl	1.6 × unl	inr	inr	6.7 × unl	6.4 × unl
ALP	1.9 × unl	1.1 × unl	inr	inr	2.2 × unl	2.1 × unl
Bilirubin total/conjugated	1.46/0.40	inr	inr	inr	1.55/0.46	1.5/0.44
AST	1.1 × unl	inr	inr	inr	1.2 × unl	1.2 × unl
ALT	1.6 × unl	inr	inr	inr	1.3 × unl	1.6 × unl
FOC (diameter)	6 cm	np	np	np	np	6.5 cm

†Overall treatment from November 2009 to December 2010 for 21 day/month cycle. and ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FOC, functional ovarian cyst, detected at ultrasonography; GGT, gamma glutamyl transpeptidase; inr, in normal range; np, not present; unl, upper normal limit.

Table 2 Laboratory and instrumental data throughout the SHT (the stable approach)

	Drospirenone (3 mg)/Ethinyl estradiol (0.03 mg)†					
	Basal	After 4 weeks on therapy	After 8 weeks on therapy	Up to the end of therapy	4–8 weeks off therapy	6–8 months off therapy
GGT	5.8 × unl	1.5 × unl	inr	inr	6.4 × unl	7.2 × unl
ALP	1.6 × unl	1.3 × unl	inr	inr	2.1 × unl	1.7 × unl
Bilirubin total/ conjugated	1.5/0.45	inr	inr	inr	1.58/0.45	1.54/0.44
AST	1.2 × unl	inr	inr	inr	1.2 × unl	1.4 × unl
ALT	1.6 × unl	inr	inr	inr	1.35 × unl	1.5 × unl
FOC (diameter)	7.5 cm	np	np	np	np	7 cm

†First cycle, from October 2011 to December 2011; second cycle, from January 2013 to March 2013; third cycle, from December 2013 to May 2014; fourth cycle, from December 2014 up to today. All cycles were administered for a 21 day/month cycle. The off-therapy results were a mean value of those registered during the breaks among the several cycles. and ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FOC, functional ovarian cyst, detected at ultrasonography; GGT, gamma glutamyl transpeptidase; inr, in normal range; np, not present; unl, upper normal limit.

In recent years, until 2018, she has continued to take SHT to keep long-suppressed the recurrence of the FOC, also on the advice of the gynecologist; throughout the hormonal treatment liver indices persisted normal. As confirmative investigation, at the time of the enzyme elevation, the total bile acid levels resulted to be increased, i.e., 10 μmol/L (n.v. < 6). Finally, acoustic radiation force impulse (ARFI) imaging, a new and promising ultrasound-based diagnostic technique evaluating the wave propagation speed, allows the assessment of the tissue stiffness. Recently, ARFI revealed a significant liver fibrosis (F2). The patient provided informed written consent authorizing use and disclosure of her health information.

Discussion

First of all, we would like to offer readers available literature data, although not recent and concerning a similar condition, i.e., an induced hormone hyperstimulation, such as that appearing during OHSS.

Nawroth *et al*.[5] described a case of icterus during a severe OHSS; a 33-year-old woman developed an aminotransferases increase, without cholestatic damage, after 7 days from stimulation with human chorionic gonadotrophin (HCG) to induce ovulation; no dilatation of bile ducts on liver US imaging was observed and hepatic laboratory abnormalities resolved after 6 days from normalization of blood levels of HCG. Obrutz *et al*.[6] detailed a severe liver injury during OHSS; a 32-year-old patient developed a 100-fold-increase of aminotransferases levels, ascites, pleural and pericardial effusion. Similar features were observed in a 26-year-old woman who manifested OHSS, presenting with massive ascites, pain at upper abdomen and dark urine; laboratory data showed increase of aspartate aminotransferase (AST) and ALT, and serum estradiol concentration was much higher than normal values during the early stages of pregnancy.[7] Borgaonkar and Marshall[8] reported a marked increase of aminotransferases in association with OHSS: after 23 days from induction of ovulation, their patient developed ascites and pleural effusion; aminotransferases reached values of ALT 1472 IU/L and AST 908 IU/L 4 days following stimulation; ALP and GGT reached 186 and 908 IU/L, respectively, while serum bilirubin was normal. Ryley *et al*.[9] described a patient suffering from severe OHSS, who showed a sustained increase of aminotransferases persisting at high levels for a period of 2 months; enzymatic abnormalities were associated with several histologic (zonal fatty degeneration and inflammation) and cytological (mitochondrial crystalline inclusions and dilated endoplasmic reticulum) alterations. An observational prospective study, conducted on 50 women with severe OHSS, evidenced an increase of aminotransferases from mild to moderate in a third of the population. In these latter patients, there was also an increase of cholestatic indices. All liver alterations resolved after the ovarian syndrome recovery.[10] Indeed, the only reported data addressing an eventual link between liver and ovarian cysts focus on insulin resistance, key mechanism of nonalcoholic fatty liver disease and common feature among women with polycystic ovary syndrome (PCOS), especially in those patients with hyperandrogenism and chronic anovulation; particularly, PCOS women are at risk for developing metabolic syndrome, impaired glucose tolerance and type II diabetes mellitus.[11]

According to our case, several evidences documented possible alterations of liver enzymes because of an unopposed ovarian hormonal overproduction. Hepatic alterations included a very wide spectrum of severity varying from mild–moderate forms[10] to more severe ones.[5–9] According to Delvigne and Rozenberg, oestrogens probably cause microvascular alterations such as vasodilatation, increased vascular permeability and consequent hepatocyte swelling, to which follows an amplified cellular permeability with consequent release of AST and ALT; alternatively, the estrogen-induced production of mediators such as IL-6 may cause microvascular thromboses and hepatic ischemia.[3] Chen *et al*.[12] highlighted that oestrogens can hamper transport of bile acids from hepatocyte to biliary canaliculi because of inhibition of transporters such as the bile salt export pump and multidrug resistance-associated transporter 2; in addition, they inhibit uptake of bile acids by counteracting cotransport systems, sited in the basolateral membrane of hepatocyte, such as Na^+ –taurocholate cotransporting polypeptide and Na^+ –independent organic anion-transporting polypeptides.[12] Surprisingly, in our patient, SHT normalized liver biochemical alterations in contrast to what commonly observed.[4] So, we think that in this patient a low-dose of SHT therapy could act on the hypothalamus-pituitary-ovary axis and counteract a probable endogenous ovarian hormonal overproduction. Finally, our patient developed an endometrial polypus. FOC and endometrial polypus were signs of the probable unopposed estrogenic stimulation.

SHT may play a hepatic protective role in other settings different from ovarian hyperfunction. Callejon *et al*.[13] reported a selective reduction of cholestasis indices and follicle-stimulating hormone, without aminotransferases variation, in a population of 30 postmenopausal women; of note, these patients assumed transdermal estradiol, which could reduce the effect of first hepatic passage. On the contrary, Perry and Wiseman[14] found that a hormonal therapy produced only a modest and not significant improvement of aminotransferases levels in a wider population of postmenopausal women.

On the other hand, oestrogens can act as important promoter of cell growth and differentiation on specific alfa- and beta-receptors; as far as the liver is concerned, the cholangiocytes express both alfa- and beta-subtypes, while hepatocytes only the alfa-ones; thus, oestrogens induce cholangiocyte proliferation by synergistically acting through both genomic and nongenomic pathways and an estrogenic deficiency could occur in the terminal, ductopenic stage of cholangiopathies, as basis for the inefficacy of cholangiocyte proliferation to balance the loss of intrahepatic bile ducts.[15]

Finally, both SHT combinations were similarly effective and the choice of continuing the SHT by using different progestin, i.e., drospirenone, was made, in agreement with gynecologist, on the basis of shorter half-life, presence of antiandrogenic activity and absence of glucocorticoid activity, characteristics potentially less 'dangerous' in the long-term administration, as confirmed by following research.[16]

As limitation to this study, we should stress that liver biopsy was not reperformed due to ethical issues. Hormone profile was not checked, having the patient not accepted stopping the therapy according to the gynecological advice. In this setting, we would like to further stress the patient's satisfaction and compliance, which led to a good quality of life.

In conclusion, we hypothesize that the favorable effect of the 'low-dose' SHT to obtaining a stable recovery of this unexplained long-lasting *cholestatic syndrome* is likely due to downregulation of an endogenous ovarian overproduction, although estrogen-regulated local intracellular transduction pathways cannot be excluded.

Further mechanistic studies are needed to better clarify the exact role of oestrogens in liver metabolism and their role in developing new therapeutic modalities.

Disclosure

The authors declare no conflict-of-interest related to this report.

Author contributions

Conca P and Tarantino G conceived the Case report study, managed the decisional making, such as clinical, instrumental and laboratory data during the overall study period. Literature searching and analysis of the data were performed by Cafaro G. Savastano S, Coppola A and Cimino E supervised the study and contributed to the decisional making. All the authors read the manuscript and approved the final version.

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