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Hypertriglyceridemia-induced pancreatitis created by oral estrogen and *in vitro* fertilization ovulation induction

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Abstract

Hypertriglyceridemia is one of the known causes of pancreatitis. Estrogen treatment can aggravate hypertriglyceridemia by increasing very low density lipoprotein secretion and reducing hepatic triglyceride lipase. In this paper, we present 3 patients who developed severe hypertriglyceridemia with conditions that increased estrogen. Two patients were found to have genetic lipoprotein lipase deficiency and were treated with birth control pills. The third was a patient with polycystic ovary disease who was receiving ovulation induction therapy for *in vitro* fertilization.

Introduction

Although estrogens can lead to increased blood levels of triglyceride, this is usually harmless in patients whose baseline triglycerides are within normal limits. Common estrogen-containing treatments and conditions include birth control pills, hormone replacement therapy for menopause, tamoxifen treatment, clomiphene treatment for polycystic ovary syndrome and pregnancy.[1–5] In males, hypertriglyceridemia was reported in postprostatectomy estrogen therapy [6] and high dose estrogen therapy as a preparatory step for sex change surgery.[7]

Estrogen-induced severe hypertriglyceridemia can sometimes lead to severe pancreatitis. This necessitates the investigation of other possible risk factors (e.g. covert genetic hyperlipoproteinemias) [6; 8]. Physicians should be cognizant of whether an individual is at risk of this severe complication prior to interventions that alter estrogen. Such patients include those who have genetic deficiencies of lipoprotein lipase (LpL), the rate-limiting enzyme for catabolism of plasma triglycerides. Homozygous LpL deficiency often presents in childhood and leads to severe hypertriglyeridemia and pancreatitis. These patients must avoid dietary fat to control their triglyceride levels. Heterozygous deletion of this enzyme becomes evident in others later in life when either diabetes or pregnancy leads to unexpected and severe forms of the above ailments [9; 10]

Other circumstances are associated with treatments that lead to a marked increase in plasma estrogen. Patients with polycystic ovary syndrome (PCOS) have low HDL and increased triglyceride levels in addition to exhibiting insulin resistance [11]. Such patients are often treated with hormone replacement in order to normalize their menstrual cycles. Patients with PCOS are often candidates for *in vitro* fertilization because of associated decreased fertility. Ovulation induction required for multiple ovulations is rarely associated with pancreatitis. Only a single

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such case was found in the literature [12]. Thus, this complication is either very rare or is under reported.

In this paper, we present three patients who have developed pancreatitis associated with interventions that increase estrogen levels. One patient's pancreatitis developed, with triglyceride concentration >2,000 mg/dl, during her third induction cycle for *In vitro* fertilization. The other two are cases of LpL deficiency whose first pancreatitis episodes coincided with the intake of birth control pills. These cases emphasize the importance of pre-screening for blood plasma triglyceride concentrations, careful history-taking and scrupulous physical examination before initiation of estrogen-related treatment.

Case reports

1) The first patient, a 33-year old woman, was referred for hypertriglyceridemia after severe pancreatitis. She had a past medical history significant for hypertension, uterine polyps and PCOS. She was born in the Ukraine and immigrated to the US in 1990. She had no history of childhood hyperlipidemia and food intolerance. Her mother was informed of hypertriglyceridemia, but had no history of pancreatitis. Both of the woman's parents had coronary disease. Her mother and father both suffered myocardial infarction at the ages of 44 and 58, respectively. The patient lived a sedentary lifestyle. She neither drank alcohol nor smokeed cigarettes. She denied a history of cholelithiasis or pancreotoxic drugs. She normally took birth control pills for her irregular menstruation (her periods were every 3 months).

She underwent two previous *in vitro* fertilization cycles: the first led to a successful pregnancy. The second cycle proved unsuccessful and only 3 oocytes were harvested. During a third cycle the patient developed acute abdominal pain after 1 week of ovulation induction. Pancreatitis was diagnosed at that time. Her triglyceride levels were recorded as >2,400 mg/dl. Her physical exam was significant for obesity. She was 5'5" in heighth and weighed 184 lbs (BMI 31). Her weight had reached as high as 220 lbs at one point in her life. She had no xanthomas, lipemia retinalis, arcus, or xanthelasma. The abdomen was soft, non-tender without hepatomegaly nor splenomegaly. The chest was within normal limits and pulses were palpable and of equal strength in all extremities. Thyroid, carotid, heart, and skin exams were unremarkable. Follow-up laboratory test results [4–6] months after the pancreatitis included a triglycerideconcentrations of 420 and 262 mg/dl, cholesterolconcentrations of 148 and 178 and normal liver and pancreatic enzymes as well as normal thyroid function tests.

2) The second patient was a 22-year-old woman with a past medical history of cholecystectomy secondary to multiple gall bladder stones. She developed pancreatitis and hypertriglyceridemia (triglycerides >7,000 mg/dl) while on a birth control pill regimen. Her father's biological family is French Canadian. She experienced no significant illnesses during childhood and cites no obvious difficulties in terms of recurrent pain following the consumption of fatty foods. She was breast fed without difficulty. Her mother notes that she was a poor eater and small for her age. There is no known history of marked hypertriglyceridemia. She did not drink alcoholic beverages or take oral estrogen. She was athletic throughout high school and continues to frequent the gym 6 days per week. She indicated a family history of gall bladder disease, in the maternal line (e.g. mother, grandmother). She has a brother and sister, neither of whom had elevated blood triglyceride concentrations. Her father had a history of increased triglycerides, although his recent triglyceride level was recorded as 123 mg/dl. Her mother's triglyceride and HDL levels were within normal limits.

The patient avoided high fat foods and refined sugars. Her therapy for the past year had included daily intake of 6 fish oil capsules, 145 mg of fenofibrate, carnitine, vitamin B, and folic acid. The patient's periods were reported as regular. She was 5'1.5" and 117 lbs. She had no

xanthomas, xanthelasma, nor arcus, but had a small abdominal scar from a laparoscopic cholecystectomy. Her medical records indicate the following triglyceride levels in the past: 1678, 3420 3212 and 815 mg/dl. Serum antinuclear antibodies and the erythrocyte sedimentation rate were unremarkable.

Seven months after her initial visit she complained of left upper quadrant fullness. She was diagnosed with splenic vein thrombosis from pancreatitis and gastric varices. Now on a low-fat diet, her most recent triglyceride reading was 1083 mg/dl. LpL activity in postheparin plasma was <10% of normal.

3) The third patient was a 28-year-old woman with a history of pancreatitis that developed after oral contraceptive therapy began. The diagnosis of LpL deficiency was made at age 3 when her pediatrician noted lipemic plasma. A postheparin assay confirmed LpL deficiency and she was placed on a low-fat diet. This diagnosis was subsequently confirmed by genetic analysis [13]. A younger brother was also diagnosed with LpL deficiency. The patients' family is of Italian descent. The parents' families originated from neighboring villages in Calabria. Except for adherence to diet, the patient had an uneventful childhood and adolescence. However, as a college student she was prescribed an oral estrogen preparation for contraception and for the first time, developed pancreatitis that resulted in a 3-week hospitalization.

She was referred for assessment of lipid control during an IVF induction. Her initial triglyceride was 585 mg/dl on fenofibrate (160 mg) and fish oil (2 g/day). Her triglyceride was monitored every other day during this cycle and increased to 1500 mg/dl at ovulation. After fertilization, to avoid the possibility of pregnancy-induced pancreatitis, several fertilized embryos were transferred to a surrogate carrier. At 2 months of age, triglyceride levels for the baby were obtained from a heel stick, which were normal, <80 mg/dl.

Discussion

The mechanism of pancreatitis induced by hypertriglyceridemia or estrogen is not known. In this article we will review systemic and local effects of lipids on the pancreas as well as possible direct effects of estrogen. Both mechanisms might have caused the disease in our three patients. There are several possible reasons for the increased triglyceride levels that occur with estrogen therapy. Estrogen decreases hepatic lipase (HL) activity.[14] Although HL is generally viewed as a regulator of HDL levels, this enzyme has *in vitro* [15] and *in vivo* actions [16] that include hydrolysis of VLDL, LDL and HDL triglyceride. This is best illustrated in HL-deficient patients. Although HDL is inappropriately not decreased, the most striking lipoprotein phenotype is increased LDL/IDL triglyceride and cholesterol [17, 18].

The effect of estrogen on LpL is controversial. Although Murata et al. reported that estrogens can inhibit the LpL promoter activity causing LpL deficiency[19], others have not found similar effects.[14] Most germane to these cases, estrogen does not alter postheparin LpL activity in humans [14]. However, it should be noted that LpL is also expressed in the pancreatic islet cells. [20] and it is conceivable that regulation of LpL in this location is altered by estrogen.

Estrogen also increases triglyceride by promoting synthesis of triglyceride in the liver and secreting this lipid into the circulation as VLDL.[21] After estrogen injection in turkeys Kelly et al. showed increased hepatic fatty acid synthesis, increased newly synthesized triglyceride in the liver, and hypersecretion of triglyceride and apoprotein B.[21] Estrogen was shown to stimulate both triglyceride and VLDL secretion by isolated perfused livers.[22]

The mechanism by which hypertriglyceridemia causes pancreatitis is not completely understood. One hypothesis is that high concentrations of toxic-free fatty acids derived from plasma triglyceride induce local inflammation, leading to pancreatitis.[23; 24] There are several

studies that show inflammatory effects of triglyceride-rich lipoproteins. Ting et al. increased expression of leukocyte adhesion molecules and monocyte adherence in response to the inflammatory cytokine tumor necrosis factor-α(TNF-α) by treating the endothelial cells with triglyceride-rich lipoproteins. [25; 26]. Dandona et al. also observed that FFA in the plasma positively correlates with NF-κand ROS generation.[27] Locally-produced fatty acids might also alter endothelial reactivity by inhibiting the actions of eNOS[28].

It is possible that estrogen, aside from producing an alteration in plasma triglyceride concentrations, has toxic effects within the pancreas itself. Pancreatic acinar cells have significant amounts of an estradiol-binding protein. [29] Estrogen increases LDL receptors [18; 30] in some situations and conceivably could promote lipid uptake into acinar cells. Sufficient excess lipid uptake leads to lipotoxicity and cellular apoptosis, a process that is best characterized in muscle cells.[31] Direct effects of estrogens on pancreatic function is supported by the observation that pancreatic amylase release in the rat is stimulated by estrogen.[32]

Due to these or other mechanisms, estrogen alone has been reported to induce pancreatitis without increased lipid level.[33] Estrogen-induced pancreatitis sometimes unmasks otherwise covert hyperlipoproteinemias.[6] There is a report of a patient with type III hyperlipoproteinemia developing severe hypertriglyceridemia during pregnancy and after taking birth control pills.[8]

Two of our patients suggest that new cautions are in order for those with plasma triglyceride transport abnormalities during the use of technologies for assisted reproduction. The increasingly widespread use of assisted reproduction makes this a more pressing issue. The first of our two patients, a woman with a tendency toward hypertriglyceridemia due to her underlying PCOS developed pancreatitis during a routine IVF stimulation cycle. Only one such other case appears in the literature. [12] Therefore, this complication is either extremely rare or simply underreported. Others have noted that patients with PCOS often have lipid abnormalities, especially low levels of plasma HDL. [34] There are cases in which women with LpL deficiency have successful pregnancies.[35] However, there is a danger of severe pancreatitis — as reported in the published literature [10] – and which has been shared with us through discussions with several directors of lipid referral clinics. Our second patient illustrates an option for a successful and relatively risk-free approach for reproduction by mothers with LpL deficiency. Although not legal in all states, the use of a surrogate carrier after a carefully monitored ovulation induction cycle allowed our patient — who was appropriately fearful of another occurrence of pancreatitis – to have a biologically-related child. Moreover, her husband had a normal lipoprotein profile. Thus, the patient could also be assured that it was highly unlikely that her child would also be LpL-deficient.

These cases again emphasize the importance of pre-screening for triglyceride levels, careful history-taking and meticulous physical examination before initiation of estrogen-related medical treatment. This includes, quite rightly, identifying risk groups in preparation for *in vitro* fertilization to prevent life-threatening side effects like severe pancreatitis. Patients with known hypertriglyceridemia necessitate vigilant surveillance for complications and should receive appropriate management of hypertriglyceridemia before and during estrogen-related treatment.

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