Severe Hypertriglyceridemia and Pancreatitis Following Hormone Replacement Prior to Cryothaw Transfer

Jane Ruman,^{1,3} Steven Brenner,¹ and Mark V. Sauer²

Submitted September 11, 2001; accepted September 17, 2001

Purpose: A case of acute pancreatitis with severe hypertriglyceridemia occurred following use of intramuscular estradiol valerate during endometrial preparation for cryopreserved embryos.

Methods: A 30-year-old woman with primary infertility and a past history of well-controlled hypothyroidism, underwent endometrial development with intramuscular estradiol valerate in preparation for the transfer of cryopreserved embryos.

Results: Initial hospitalization, discontinuation of all estrogens, aggressive intravenous fluid hydration, and initiation of low-fat diet with additional gemfibrozil treatment resulted in complete resolution of all symptoms related to the pancreatitis including the hyperlipidemia. A subsequent cryothaw cycle using oral estradiol resulted in a viable pregnancy with only mild increases in the patient's triglyceride and cholesterol levels noted throughout her 38-week gestation.

Conclusion(s): Estradiol valerate, a commonly used form of estrogen for endometrial preparation during cryothaw cycles, may cause severe hypertriglyceridemia and acute pancreatitis in certain predisposed individuals. Oral and transdermal estrogens should be the preferred method of endometrial preparation in patients at high risk for lipid metabolism disorders, such as patients with polycystic ovarian syndrome and familial hypertriglyceridemia. These estrogens are more rapidly metabolized and have a shorter half life compared to that of estradiol valerate.

KEY WORDS: Estradiol valerate; hypertriglyceridemia; infertility; pancreatitis.

INTRODUCTION

Severe hypertriglyceridemia and pancreatitis is a rare, potentially fatal complication of both pregnancy and exogenous estrogen use. The first reported cases of estrogen-induced pancreatitis (1) involved a

woman prescribed oral contraceptives and a 53-year-old man on mestranol therapy. Subsequently, there have been other documented cases of massive hypertriglyceridemia in patients during pregnancy (2), and in women receiving hormone replacement (HRT), oral contraceptives (3), and tamoxifen (4). All cases involved patients with underlying abnormalities of lipid metabolism, usually diagnosed after the initial episode of hyperlipidemia. Recently, a case was reported in which triglyceride levels rose to >5000 mg/dL after clomiphene citrate was used to treat an infertile woman with polycystic ovarian syndrome (PCOS) (4).

Estradiol valerate, a long-acting estrogen in sterile oil solution for intramuscular use, is commonly prescribed for endometrial development in preparation

¹ Department of Obstetrics and Gynecology, Long Island Jewish Medical Center, New Hyde Park, New York.

² Department of Obstetrics and Gynecology, Division of Reproductive Endocrinology, New York-Presbyterian Hospital, Columbia University College of Physicians and Surgeons, New York, New York.

³ To whom correspondence should be addressed at Department of Obstetrics and Gynecology, New York-Presbyterian Hospital, Columbia University College of Physicians and Surgeons, 622 West 168th Street, PH16-69, New York, New York 10032; e-mail: jruman6129@aol.com.

for transfer of thawed, cryopreserved embryos and embryos of donor oocytes. This paper describes a woman with no underlying history of a lipid metabolism disorder who developed marked hyperlipidemia and acute pancreatitis after estradiol valerate usage during preparation for a cryothaw cycle. This case represents one of the first reported hypertriglyceridemias caused by the use of infertility medications.

CASE REPORT

A 30-year-old female, para 0010, complained of a 3-year history of primary infertility. She had a history of hypothalamic amenorrhea (FSH < 1 mIU/mL, LH < 1 mIU/mL). Cranial MRI was normal. Two years earlier, the patient was diagnosed with hypothyroidism secondary to Hashimoto's thyroiditis and placed on Synthroid 50 mcg q.d. The patient had failed multiple cycles of superovulation with human menopausal gonadotropin (hMG) and intrauterine insemination. A baseline fasting triglyceride level and a total cholesterol level were 166 mg/dL and 178 mg/dL, respectively. She denied any past history of hypertriglyceridemia or abnormal lipid profiles. The patient was unaware of any family members with lipid metabolism disorders, premature atherosclerosis, liver disease, or pancreatic disease. Her family history was significant only for a sister who had primary hypothalamic amenorrhea.

The patient underwent a successful GIFT procedure with a resultant pregnancy that was lost in the second trimester because of incompetent cervix. During that assisted reproductive technique (ART) cycle, embryos were cryopreserved and the patient elected to undergo cryothaw transfer several months after the loss. The patient was initially begun on the Estraderm patch (Novartis) which was promptly discontinued secondary to a local skin reaction. Subsequently, she was prescribed oral Estrace (Bristol-Myers), 2 mg p.o.t.i.d., to which estradiol valerate was added, 6 mg i.m. biweekly, to maintain estradiol levels above 200 pg/dL.

Four days after the patient's third injection, she presented with lower abdominal pain, nausea, vomiting, and low grade fever. On physical exam, she appeared slim but well-nourished with a body mass index of 21.5 kg/m². She had a normal blood pressure of 104/60 mm Hg and an oral temperature of 100.6°F. The patient had no evidence of jaundice or eruptive xanthomas. Abdominal exam revealed a soft, nondistended abdomen, hypoactive bowel sounds,

and diffuse right quadrant tenderness with voluntary guarding but no rebound. No hepatosplenomegaly was appreciated. Pelvic exam was unremarkable, and pelvic ultrasound demonstrated normal bilateral ovaries and an endometrial thickness of 5–6 mm corresponding to her present serum estradiol level of 220 pg/dL. Initial bloodwork was drawn, revealing milky, lipemic serum with a significantly elevated triglyceride level of 8062 mg/dL and total cholesterol level of 1186 mg/dL. All estrogen treatment was discontinued, prophylactic subcutaneous heparin was begun, and the patient was sent directly to the hospital for supportive care.

Upon admission to the hospital, laboratory tests showed mild leukocytosis (white blood cell count of $17.1 \times 10^9/L$), an amylase of 212 U/L (reference range, 30–110 U/L), lipase level of 1511 U/L (reference range, 23–300 U/L), a normal glucose level of 93, and normal transaminase and bilirubin levels. Computed tomography with contrast of the abdomen showed streaky inflammatory changes in the pancreatic head and tail, with thickening of the anterior pararenal fascia and wall of the transverse colon, and a localized ileus in the region of the pancreas. The liver, spleen, and kidneys were free of lesions, and a radionuclide hepatobiliary system scan showed no evidence of acute cholecystitis. The patient was hydrated aggressively and kept n.p.o. for 24 h. She was maintained on sq heparin for deep vein thrombosis (DVT) prophylaxis. On Day 2 of hospital admission, her cholesterol level dropped to 514 mg/dL and her triglyceride level to 1016 mg/dL. The patient was begun on a low-fat diet (<15% of total caloric intake from fat) and gemfibrozil, 600 mg p.o.b.i.d. She was discharged on hospital Day 4 after complete resolution of her clinical symptoms, with a total cholesterol level of 300 mg/dL and a moderately elevated triglyceride level of 780 mg/dL. After 2 months on the low-fat diet and gemfibrozil therapy, she was able to maintain a normal total cholesterol level under 200 mg/dL and triglyceride levels of 300–500 mg/dL. Both amylase and lipase levels had returned to normal. A 75-g glucose tolerance test performed 2 months after discharge demonstrated mild glucose intolerance, and the patient was begun on a diabetic diet in addition to her low-fat diet.

Six months following this episode of pancreatitis, the patient elected to undergo a second cryothaw transfer cycle. Oral micronized estradiol was used for endometrial stimulation, but the cycle did not result in pregnancy. Two months later (8 months postdischarge), she underwent another cryothaw

transfer with similar medications. An embryo transfer with three embryos was performed resulting in a single viable intrauterine gestation. Gemfibrozil had been discontinued prior to the transfer, and a pre-transfer lipid profile revealed a total cholesterol level of 181 mg/dL and triglyceride level of 353 mg/dL. After transfer, estrogen support was slowly tapered. Peak total cholesterol and triglyceride levels reached 224 mg/dL and 450 mg/dL, respectively, during the first trimester and subsequently remained mildly elevated throughout the second and third trimester. The patient underwent cerclage placement at 13 weeks gestation without complication. She was maintained on a diabetic, low-fat diet throughout her pregnancy, with excellent glucose and serum lipid control. She delivered a healthy male infant weighting 7 pounds and 6 ounces at 38 weeks gestation.

DISCUSSION

Estradiol valerate is a long-acting injectable estrogen commonly used by infertility specialists to stimulate endometrial growth in preparation for transfer of embryos during a cryothaw cycle or donor oocyte cycle. The effects of estrogen on lipid metabolism are well known. Exogenous estrogen administration has been shown to increase the endogenous production of triglycerides by increasing very low-density lipoprotein (VLDL) secretion from the liver while simultaneously reducing triglyceride catabolism by lowering lipoprotein lipase (LPL) and hepatic triglyceride lipase (5). In normal pregnancies, serum triglyceride levels increase between two- and four-fold, while plasma cholesterol levels increase approximately 50% by the end of the third trimester (6). This effect is thought to be attributable to the rise of endogenous estradiol during pregnancy, causing an estrogen-induced increase in VLDL synthesis and inhibition of LPL activity (2,7). Massive hypertriglyceridemia occurs in women with preexisting, often covert, abnormalities of lipid metabolism during periods of increased estrogen exposure, such as pregnancy or exogenous estrogen administration. Acquired hypertriglyceridemia from prescribed estrogens combined with familial hypertriglyceridemia, may result in triglyceride levels over 2000 mg/dL, causing symptoms of the chylomicronemia syndrome: lipemia retinalis, hepatosplenomegaly, eruptive xanthomas, abdominal pain, and acute pancreatitis (2,8). Several cases of severe chylomicronemia have been reported in patients previously undiagnosed with familial

hypertriglyceridemia both during pregnancy, and with HRT, tamoxifen, and oral contraceptive use (1–4). In addition, clomiphene citrate, a nonsteroidal estrogen analog similar in structure to tamoxifen, has also been shown to induce severe hypertriglyceridemia and pancreatitis in an infertile woman with PCOS (7). This was the first documented case of the chylomicronemia syndrome in women undergoing an ART.

The patient described in this report developed massive hypertriglyceridemia and pancreatitis within 2 weeks of therapy. Although her chylomicronemia was severe (triglyceride levels reaching 8000 mg/dL), she responded well to management. Both the discontinuation of estrogen therapy and interruption of oral intake with intravenous administration of 5% dextrose solution enabled her triglyceride levels to decrease below 1000 mg/dL within 48 h. Gestational hypertriglyceride-induced pancreatitis carries an estimated 21% mortality for the fetus and 20% mortality for the mother (2,7). Early intervention by reducing triglyceride levels usually consists of fasting, low-fat diet, lipid-free total parental nutrition, and in refractory cases, plasma exchange (9). Maintenance of low lipid levels in the patient was achieved by low-fat diet and gemfibrozil treatment. The use of oral estradiol during her subsequent cryothaw pregnancies did not produce the same degree of hyperlipidemia as did treatment with the injectable estrogen. Estradiol valerate has a potent and prolonged estrogenic effect compared to oral estrogen, the latter of which is extensively metabolized by the liver during the first-pass effect. A single intramuscular injection of estradiol valerate bypasses the first-pass metabolism, and is absorbed over several weeks. Because of its rapid metabolism, we recommend the use of oral estradiol during endometrial stimulation for women with known familial hypertriglyceridemia or other conditions associated with lipid metabolism disorders such as PCOS. The use of oral estradiol in these patients will decrease the risk of severe hypertriglyceridemia and pancreatitis.

REFERENCES

1. Zorrilla E, Hulse J, Hernandez A, Gershberg H: Severe endogenous hypertriglyceridemia during treatment with estrogens and oral contraceptives. *Clin Endocrinol* 1968;22:755–760
2. Hsia SH, Connelly PW, Hegele RA: Successful outcome in severe pregnancy-associated hyperlipemia: A case report and literature review. *Am J Med Sci* 1995;309:213–218
3. Molitch ME, Oill P, Odell WD: Massive hyperlipemia during estrogen therapy. *JAMA* 1974;227:522–525

4. Hozumi Y, Kawano M, Miyata M: Severe hypertriglyceridemia caused by tamoxifen-treatment after breast cancer surgery. *Endocr J* 1997;44:745–749
5. Glueck CJ, Lang J, Hamer T, Tracy T: Severe hypertriglyceridemia and pancreatitis when estrogen replacement therapy is given to hypertriglyceridemic women. *J Lab Clin Med* 1994;123:59–64
6. Potter JM, Nestel PJ: The hyperlipidemia of pregnancy in normal and complicated pregnancies. *Am J Obstet Gynecol* 1979;133:165–170
7. Castro MR, Nguyen TT, O'Brien T: Clomiphene-induced severe hypertriglyceridemia and pancreatitis. *Mayo Clin Proc* 1999;74:1125–1128
8. Chait A, Brunzell JD: Severe hypertriglyceridemia: Role of familial and acquired disorders. *Metabolism* 1983;22:209–214
9. Swoboda K, Derfler K, Koppensteiner R, Langer M, Pamberger P, Brehm R, Ehringer H, Druml W, Widhalm K: Extracorporeal lipid elimination for treatment of gestational hyperlipidemic pancreatitis. *Gastroenterology* 1993;104:1527–1531