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Hyperlipidemia: A Rare Complications Following *in Vitro* Fertilization (IVF)

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Abstract
Although estrogens can lead to increased blood levels of triglyceride, this is usually harmless in patients whose baseline triglycerides are within normal limits. Estrogen-induced severe hypertriglyceridemia can sometimes lead to severe pancreatitis. Few cases of hypertriglyceridemic pancreatitis have been reported in women during a vitro fertilization treatment (IVF) cycle. Here, we describe a 34-year-old female with secondary infertility who was on hormone replacement therapy (HRT), exogenous estrogen and progesterone to prepare for transfer of cryopreserved embryos. She subsequently presented with nausea, vomiting, and abdominal painto an emergency room and was found to have hypertriglyceridemic pancreatitis. Our case highlights the possibility that estrogen, which is commonly used for endometrial preparation during IVF cycles, may cause severe hypertriglyceridemia and acute pancreatitis. Our case, demonstrate hypertriglyceridemic pancreatitis can occur during IVF. Further work is needed to understand the effects of exogenous estrogen on lipids for women undergoing IVF.

Keywords: *In vitro* fertilization Hyperlipidemia, pancreatitis, Estrogen-induced, IVF.

Introduction

Acute pancreatitis during pregnancy is a severe condition that increases mortality and morbidity both for mother and fetus. Acute pancreatitis is potentially a fatal complication of severe hypertriglyceridemia, and severe hypertriglyceridemia is the third most common cause of acute pancreatitis. 1 Hypertriglyceridemia occurs in patients with both an underlying disorder of lipoprotein metabolism as well as an associated condition such as uncontrolled diabetes, excessive alcohol intake, or use of certain drugs. 2 Among the drugs causing pancreatitis, 3 exposure to exogenous estrogen is known to increase triglyceride levels. 4 Exogenous estrogen administration both overstimulation and even within range stimulation-has been shown to increase the endogenous production of triglycerides by increasing very low-density lipoprotein secretion from the liver while simultaneously reducing triglyceride catabolism by lowering lipoprotein lipase (LPL) and hepatic lipase activity. 5,6 Women who undergoes fertility treatments are exposed to high levels of estrogen. Compared to oral contraceptive pills (OCPs), much higher doses of estrogen are used for endometrial preparation during transfer of thawed, cryopreserved embryos and embryos of donor oocytes. Despite the exposure to high doses of estrogen, it remains unknown what effect estrogen has on lipid levels during fertility treatments, and few prior cases of hypertriglyceridemic pancreatitis have been reported in women undergoing IVF.

Case Presentation

34 year old female presented to obstetric ER with sudden onset pain abdomen, non-bilious vomiting and chest pain at 5th week of pregnancy with a background history of Type 2 Diabetes mellitus, hypothyroidism and secondary infertility and was on HRT for infertility. Patient was admitted with provisional diagnosis of Hyperemesis Gravidarum. Examination revealed BP130/80mmHg and pulse rate of 130/min. Patient was kept NPO. IV fluids were started. Investigations revealed.

Table 1: Initial Investigations at the time of Admission

FBS	227
Hb	14.30 gm/dL
Sodium	132 mEq/L (136-146)
Potassium	3.8 mEq/L (3.5-5.10)
Chloride	85.8 mEq/L (101-109)
Calcium	6.90 mg/dL (8.5-10.5)
CRP	218 (5mg/L)
Triglycerides	10101 mg/dL (<150)
Amylase	174 U/L (<100)
Lipase	435 U/L (13-60)
LFT and RFT	Within normal limits
USG whole abdomen revealed	Bulky and heterogenous pancreas

Differential Diagnosis that were Considered are the Following

A. Pancreatitis
B. Heterotrophic pregnancy (?Hemoperitoneum)

Immediate repeat haemoglobin was advised and it was 14.1 gm/dL ruling out the possibility of intraperitoneal hemorrhage (Heterotrophic pregnancy).

Decision was taken not to operate on the patient and to shift the patient to medical ICU. All medications related to pregnancy (exogenous estrogens and progesterones) were stopped. Patient and patient party were counseled regarding possibility of abortion and priority was given for the well-being of the patient.

In the ICU patient was started on IV fluids, Insulin infusion and omega 3 fatty acids. Patient responded well to the treatment and got symptomatically better day by day. Serum triglycerides levels were monitored serially and showed a decreasing trend as follows in mg/dl:

Table 2: Day wise fasting Triglyceride Report (mg/dl)

Day 1	Day 2	Day 3	Day 4	Day 5
10,101	4500	1500	847	519

Patient started bleeding vaginally on day 4. Tran's vaginal sonography revealed irregular gestational sac. Vaginal Misoprostol 600 mg was given and abortion induced. Patient started accepting orally was and started on subcutaneous insulin and shifted out of ICU to ward.

Patient got better symptomatically and was discharged subsequently in hemodynamically stable condition.

Discussion

While the risk of acute pancreatitis in the general population is about 0.5 to 1 percent, and about 5 percent in people with alcoholism, the risk increases to 10 percent in those with serum TG above 1,000 mg/dL.7

The pathogenesis of hypertriglyceridemic pancreatitis is not clear, but likely involves free fatty acid-mediated cellular damage. Large TG-rich lipoprotein particles, primarily chylomicrons, impede capillary circulation and cause ischemic damage to pancreatic acinar cells. Damaged cells release lipase and other enzymes into the interstitium, leading to TG hydrolysis and free fatty acid release. Free fatty acid aggravates cellular damage through a variety of mechanisms, including endothelial damage, vascular leak, mitochondrial toxicity, platelet aggregation and activation of coagulation cascade.

Homozygous deficiency of lipoprotein lipase causing familial chylomicronemia syndrome is the most common primary monogenic disorder responsible for hypertriglyceridemic pancreatitis.

Secondary exacerbating factors in patients with an underlying lipid disorder, often polygenic, are more commonly responsible for hypertriglyceridemic pancreatitis.8 It is therefore very important to seek and address these secondary causes for elevated TG, which include uncontrolled diabetes, alcohol use, weight gain, and high intake of saturated fats and refined carbohydrates. Drug-induced hypertriglyceridemia is another important cause for acute pancreatitis. The list of offending agents includes estrogen, retinoic acid derivatives, sirolimus, L- asparaginase, capecitabine, protease inhibitors and propofol.

The management of hypertriglyceridemia-induced pancreatitis in the acute phase is similar to other causes of acute pancreatitis with the addition of various other modalities that target specifically hypertriglyceridemia such as insulin, heparin, fibric acid derivatives, and in extreme cases plasmapheresis.9 The patient presented above responded to aggressive IV hydration in addition to fibrates and IV insulin that was helpful also in controlling her ketoacidosis. IV insulin infusion is an effective but underutilized intervention to reduce serum TG. Insulin is not only an activator of lipoprotein lipase but also suppresses free fatty acid release, thus limiting further generation of TG-rich lipoproteins from the liver.10

Conclusion

In conclusion, our patient is one of the rare cases of reported IVF-induced severe hypertriglyceridemia with secondary acute pancreatitis. The occurrence of hypertriglyceridemia is a serious complication of IVF, due to hormone replacement, particularly during pregnancy, which might lead to further increase in triglyceride level, and consequently an increased risk on both the mother and the fetus. As such, with the increasing popularity of IVF, and aiming at the prevention of such life-threatening complications, prescreening of patients with lipid levels before IVF should be highly considered, especially in those who might be at a higher risk such as patients with diabetes mellitus, polycystic ovaries syndrome, obesity, and family and personal history of dyslipidemia.

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