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In vitro fertilization-induced extreme hypertriglyceridemia with secondary acute pancreatitis in emergency department: A case report and literature review

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Abstract:

Acute pancreatitis is one of the severe complications of hypertriglyceridemia, which needs to be recognized early to provide appropriate treatment. Hypertriglyceridemia-induced pancreatitis has several causes, in which *in vitro* fertilization (IVF) is a rare etiology that is becoming increasingly popular. We report a 33-year-old female patient with a history of hypertension who has failed an IVF cycle and started a new IVF procedure 1 month before admission. She was diagnosed with severe triglyceridemia-induced acute pancreatitis with extremely high serum triglycerides (TGs) levels (18,547 mg/dL). We combined plasmapheresis and intravenous (IV) insulin and significantly reduced blood TG over a short time. She was discharged with a TG level of 366.7 mg/dL on the 10th day. It is essential to monitor serum TG levels in plasma before, during, and after this therapy, especially in the 1st month after initiating IVF. Although plasmapheresis combined with IV insulin is not officially recommended for acute triglyceridemia-induced pancreatitis, the therapy can be considered in cases with extremely high serum TG levels.

Keywords:

Acute pancreatitis, estrogen, hypertriglyceride, *in vitro* fertilization

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Introduction

Hypertriglyceridemia is one of the leading causes of severe acute pancreatitis, especially when blood triglyceride (TG) levels are >1000 mg/dL.[1] Acute pancreatitis is a disease that needs to be detected early and treated promptly with appropriate measures because it can cause extremely serious consequences, even death. There are many different causes of elevated TG, one of which is the use of estrogen, especially during *in vitro* fertilization (IVF) procedures.

Regarding the associated medications, exogenous estrogen is recognized as a factor that raises TG levels.[2] Estrogen increases the synthesis of hepatic TGs, then secretes very low-density lipoprotein (VLDL) into circulation, resulting in an increase in the level of serum TGs.[3]

High estrogen levels are often maintained in patients with infertility treatment. Estrogen therapies are administered for endometrial preparation during thawed transfer and cryopreservation of embryos and oocytes. IVF cycle, ethinyl estradiol is

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among the oral estrogen medications utilized to promote endometrial preparation in readiness for embryo transfer.[4] Furthermore, IVF has recently become more and more common.

There are few case reports of IVF associated with hypertriglyceridemia and acute pancreatitis.[5,6] However, it is still unknown how estrogen therapy in infertility treatment impacts a lipid panel. Therefore, prescreening people at risk of acute pancreatitis before IVF is essential. Here, we report a case of acute pancreatitis due to IVF-induced hypertriglyceridemia.

Case Report

A 33-year-old woman presented to our hospital due to a 6-h history of epigastric pain. She had a history of hypertension, no previous history of acute pancreatitis, no trauma, no drugs or substance use, and no family history of dyslipidemia. She has had two healthy girls and wants a boy, guiding her to IVF. She had failed at her first IVF cycle 7 months ago and started a new cycle 1 month ago. Her TGs before the first IVF were in the NR and were not checked this time. She had taken estradiol oral 8 mg daily and progesterone intravaginal 800 mg daily for 1 month before this presentation.

The patient suddenly had abdominal pain after lunch and the pain radiated to the back with a Visual Analog Scale of 8–9 out of 10 and was associated with nausea and vomiting. During an initial evaluation, she was afebrile and had a blood pressure of 140/80 mmHg, a pulse of 120 beats/min, a respiratory rate of 16 breaths/min, and a body mass index of 27.3. Her physical examination was only significant for tenderness on the epigastric and right upper quadrant on palpation with no guarding signs. The laboratory results revealed an elevated white blood cell count of 14.34 G/L (NR: 4–10 G/L), hemoglobin of 10.3 mg/dL (NR: 12–14 mg/dL), hematocrit of 30.3% (NR: 33%–45%), elevated serum level of lipase of 306 U/L (NR: 0–160 U/L), amylase of 264 U/L (NR: 30–110 U/L), TG of 18,547 mg/dL (NR <150 mg/dL), blood glucose 260 mg/dL (NR: 74–106 mg/dL), sodium of 98 mmol/L (NR: 135–145 mmol/L), potassium of 2.9 mmol/L (NR: 3.5–5.2 mmol/L), aspartate transaminase of 139 U/L (NR: 10–40 U/L), alanine transaminase of 11.4 U/L (NR: 7–50 U/L), total bilirubin of 12.7 umol/L (NR 5.1–17 umol/L), total calcium 2.47 mmol/L (NR: 2.13–2.55 mmol/L), beta-hCG <2 mIU/mL (NR: <5 mIU/mL), lactate dehydrogenase 155 U/L (NR: 140–280 U/L), arterial bicarbonate of 21.5 mmol/L (NR: 22–26 mmol/L), and lactate of 3.4 mmol/L (NR: 0.5–2.2 mmol/L). Ultrasound did not clearly observe the pancreatic head and the end of the biliary tract. A computed tomography (CT) scan of the abdomen was performed to exclude the serious underlying causes. It revealed acute edematous pancreatitis with peri-pancreatic fluid (Balthazar D) and no sign of biliary dilation or obstruction [Figure 1]. Although her Ranson's criteria score for pancreatitis mortality was 1, her levels of TGs were remarkably high, and her pain was severe. The patient was admitted to the intensive care unit and treated with aggressive intravenous (IV) hydration, pain control, electrolyte management, and IV insulin and plasmapheresis two times. On the 2nd day, her TG dropped to 8326 mg/dL, and 3963.6 mg/dL on the 3rd day. She has undergone a CT scan of the abdomen after 72 h with no evidence of developing necrosis and thrombosis. After confirmation of the absence of pregnancy, she started fibrate and statin on Day 4. Her symptoms improved gradually, and she was discharged with a TG level of 366.7 mg/dL on Day 10 [Figure 2].

Discussion

Acute pancreatitis is an inflammatory condition of the pancreas. The diagnosis requires at least two over three criteria: typical pain, elevated amylase or lipase at least three times the normal upper limit, and imaging findings of acute pancreatitis. The three most common causes of acute pancreatitis are gallstones, alcohol, and hypertriglyceridemia.

TGs cause acute pancreatitis through several mechanisms, including increased free fatty acids toxicity and increased plasma viscosity,[1] in an acute pancreatitis patient, diagnosis of hypertriglyceridemic pancreatitis is definitive when serum TGs levels are >1000 mg/dL at onset but still probable with TGs levels >500 mg/dL.[7] Our case met the criteria with TGs level at the onset of 18,547 mg/dL. Hypertriglyceridemia is commonly developed during pregnancy or estrogen therapies, including IVF, due to increasing the synthesis of hepatic TGs, followed by secreting VLDL into the circulation, hypersecretion of TGs, and apoprotein B,[3] and reduction of the breakdown of circulating TGs.[8] Even so, hypertriglyceridemia is usually mild to moderate and rarely causes acute pancreatitis. Through the

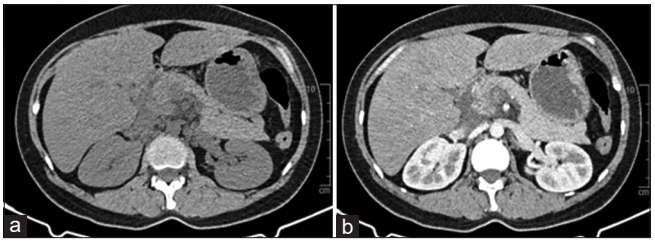

Figure 1: The abdominal computed tomography scan on admission revealed the enlargement and irregular margin of the pancreatic head, which was covered with fluid collection (Axial view: (a) no contrast; (b) with contrast)

Table 1: Characteristics of *in vitro* fertilization-induced hypertriglyceridemic pancreatitis patients in 8 cases report[5,6,9-14]

Author, year of publication	Age	Past medical history	Onset after initiation of IVF	Serum TG (mg/dL)	Treatment	Outcome
Steinmetz OK, 1993	32	Family history of dyslipidemia	8.5 days	3415	NA	NA
Ruman J, 2002	30	No	10 days	8062	Gemfibrozil, heparin for DVT	Treated successfully
Lee J, 2008	33	Hypertension, uterine polyps, and PCOS	1 week (3rd cycle)	2400	N/A	Treated successfully
Reper P, 2014	42	Diabetes	9th weeks of gestation after IVF	9850	Plasmapheresis	Treated successfully
Issa CM, 2017	39	No	10 days	15,050	Insulin	Treated successfully
Aljenedil S, 2017	38	Hypothyroidism, obesity, and type 2 diabetes mellitus	1 month	9070	Insulin	Treated successfully
Reddy S, 2022	41	Acute pancreatitis	15 days	2531	Plasmapheresis	Treated successfully
Shrimanker TV, 2022	36	Prior hypertriglyceridemia-induced pancreatitis	NA	4000	Insulin	Treated successfully

NA: Not available, IVF: *In vitro* fertilization, PCOS: Polycystic ovarian syndrome, DVT: Deep vein thrombosis, TG: Triglyceride

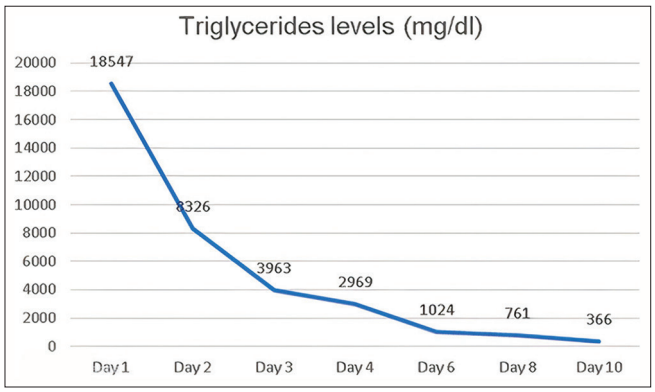

Figure 2: Triglyceride levels during hospitalization

literature review, there are only eight reported cases of IVF induced hypertriglyceridemia with secondary acute pancreatitis [Table 1],[5,6,9-14] our case is the ninth but with an extremely high level of triglyceridemia, treatment includes managing acute pancreatitis in general and reducing serum TG levels. The two most common TG-lowering therapies are plasmapheresis and insulin. Although their effect on outcomes was not fully proven, they were indicated for complicated patients.[15] Between the two methods, few randomized trials are comparing their efficacy; the latest study in 2022 showed no significant difference, but there was a trend toward a greater decrease in TG levels with plasmapheresis (67% compared to 53% with insulin).[16] In this case, due to the exceptionally high serum TG level, we decided to use both methods, resulting in serum TG being halved every day and returning to 366.7 mg/dL after 10 days. As no trial evaluated the efficacy of using both, our rationale was to reduce serum TGs quickly due to the high thrombosis risk.[17]

The pathogenesis of the patient's condition is unclear. She does not have a family history of dyslipidemia or diabetes mellitus. Serum TG s were normal 7 months ago. Thus, IVF and estrogen therapy are only likely the cause of her hypertriglyceridemia. However, the extremely high level of TGs, like our patient, is usually considered to have underlying abnormalities, a remote possibility of familial genetic disease unknown. Among the 8 reported cases of IVF-induced hypertriglyceridemia with secondary acute pancreatitis, there have been 6 cases suggestive of high risk for hypertriglyceridemia, including familial dyslipidemia, active hypertriglyceridemia, polycystic ovarian syndrome, and diabetes mellitus. Two cases did not have clear risks in past medical history.

The onset of acute pancreatitis can be as early as 1 week after initiation of IVF cycles,[11] and most cases present within 1 month after IVF. Our patient had symptoms 1 month after the second cycle of IVF. Anyway, all the cases were treated successfully.

Conclusion

Our patient is only the ninth published about IVF-induced hypertriglyceridemia complicated secondary acute pancreatitis with a remarkably extreme serum TG level. The combination of plasmapheresis and IV insulin might reduce the TG level quickly. Furthermore, with IVF becoming more and more popular, doctors at primary care centers, obstetricians, especially fertility doctors should be aware to prevent its complications by screening lipid profile before and after IVF, especially in the 1st month, even with patients not at high risk, including diabetes mellitus, obesity, personal or familial history of dyslipidemia, and polycystic ovarian syndrome.

Author contributions statement

Conceptualization (Pham Dang Hai, Nguyen Huu Thanh); writing – original draft (Nguyen Huu Thanh, Trinh Van Duong, Nguyen Thu Huyen); writing – review and editing (Pham Dang Hai). All the authors read and approved the final manuscript.

Conflicts of interest
None Declared.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that her name and initials will not be published and due efforts will be made to conceal her identity, but anonymity cannot be guaranteed.

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