CASE REPORT

Journal of Anatolian Medical Research
JAMER 2024;9(1):30-32
DOI:10.55694/jamer.1400753

A Case of Hypertriglyceridemic Pancreatitis Secondary to Tacrolimus and Estradiol Use for In Vitro Fertilization

İn Vitro Fertilization Amaçlı Takrolimus ve Estradiol Kullanımına Sekonder Hipertrigliseridemik Pankreatit Olgusu

Merve Civan[1], Ramazan Ozan[2], Alparslan Demiray [1], İsmail Koçyiğit[1]

[1] Erciyes University, Department of Internal Medicine, Kayseri, Turkey
[2] Erciyes University, Department of Nephrology, Kayseri, Turkey

ABSTRACT

Hypertriglyceridemia is a metabolic condition with a multifactorial etiology that may cause life-threatening complications, such as pancreatitis. In pregnant women, hypertriglyceridemia may be secondary to physiological changes during pregnancy or may be exacerbated by medications. The combination of tacrolimus and estradiol is sometimes used in In Vitro fertilization (IVF) for women with a history of recurrent implantation failure. This case report discusses a case of acute pancreatitis caused by hypertriglyceridemia secondary to the use of tacrolimus and estradiol.

Keywords: *Tacrolimus, estradiol, in vitro fertilization, hypertriglyceridemia, pancreatitis*

ÖZET

Hipertrigliseridemi, pankreatit gibi yaşamı tehdit eden komplikasyonlara neden olabilen çoklu etiyolojiye sahip bir metabolik durumdur. Hamile kadınlarda hipertrigliseridemi, gebelik sırasındaki fizyolojik değişikliklere sekonder olabilir veya ilaçlar tarafından kötüleştirilebilir. Tacrolimus ve östradiol kombinasyonu, tekrarlayan implantasyon başarısızlığı öyküsü olan kadınların in vitro fertilizasyon (IVF) tedavisinde kullanılmaktadır. Bu vaka raporu, tacrolimus ve östradiol kullanımına bağlı gelişen hipertrigliseridemiye sekonder akut pankreatit vakasını ele almaktadır.

Anahtar Kelimeler: *Tacrolimus, östradiol, in vitro fertilizasyon, hipertrigliseridemi, pankreatit*

INTRODUCTION

Hypertriglyceridemia during pregnancy may be related to the physiological changes that occur during pregnancy, and this effect may be intensified by the medications administered. Acute pancreatitis due to hypertriglyceridemia is known to pose significant maternal and fetal mortality and morbidity risks in pregnant women (1). In Vitro fertilization (IVF), T helper 1 (Th1) and Th1/Th2 ratios have been found to be elevated in women with a history of recurrent implantation failure (2). Therefore, immunosuppressive agents such as tacrolimus have been increasingly used, as they have been shown to improve implantation rates and pregnancy outcomes, especially in women with an elevated Th1 immune response (2). Additionally, estradiol use has been shown to have a positive impact on pregnancy rates in IVF studies (3). Both tacrolimus and estradiol are known to cause hypertriglyceridemia (4,5). Severe gestational hypertriglyceridemia can lead to acute pancreatitis, with a maternal mortality rate of approximately 20%. Fasting triglycerides >500 mg/dL, despite a strict dietary and lifestyle modifications, should prompt treatment with omega-3-fatty acids and continue a fat-restricted diet (<20g total fat/d or <15% total calories) under the guidance of a registered dietitian. The use of fibrates should be considered as a second-line therapy due to their unclear risk versus benefit and potential teratogenic effects. Plasmapheresis should be considered early in asymptomatic pregnant women with fasting triglyceride

Corresponding Author: Merve Civan, Erciyes University, Internal Medicine Kayseri, Turkey,
Email: mervecivan@hotmail.com
Cite this article as: Civan M, Ozan R, Demiray A, Koçyiğit. A Case of Hypertriglyceridemic Pancreatitis Secondary to Tacrolimus and Estradiol Use for In Vitro Fertilization. JAMER 2024;9(1):30-32.

Received: 05.12.2023
Accepted: 24.02.2024
Online Published: 15.04.2024

levels >1000 mg/dL or in pregnant women with clinical signs and symptoms of pancreatitis and triglyceride levels >500 mg/dL despite maximal lifestyle changes and pharmacologic therapy (6). A MEDLINE search (1950-2018) of the English language literature was performed to identify all adult (≥17 years old) human case reports where medication/drug-induced acute pancreatitis was the causative factor. The included case reports were required to provide the name of the drug, and the diagnosis of AP must have been strictly established based on the revised Atlanta Classification criteria. A total of 183 medications were found to be implicated in 577 DIAP cases (7).

This case report presents the first instance of acute pancreatitis caused by hypertriglyceridemia resulting from the combined use of estradiol and tacrolimus in a pregnant woman with recurrent implantation failure.

CASE REPORT

A 32-year-old woman with a known history of polycystic ovary syndrome, hypertension, and nephrolithiasis, who had experienced two previous failed IVF attempts, achieved a 7-week pregnancy with her third IVF attempt.

Due to her previous failures, the patient was administered tacrolimus 1 mg/day, subcutaneous progesterone 225 mg, and estradiol 32 mg/day starting one week before the IVF attempt. Her laboratory results revealed amylase levels of 215 U/L (normal range: 28-100 U/L), lipase levels of 711 U/L (normal range: 13-60 U/L), triglyceride levels of 1228 mg/dL (normal range: 40-160 mg/dL), cholesterol levels of 740 mg/dL (normal range: 70-200 mg/dL), LDL levels of 609 mg/dL (normal range: 100-130 mg/dL), and HDL levels of 18 mg/dL (normal range: 35-55 mg/dL) (Table 1).

Possible causes of hypertriglyceridemia, such as alcohol use, obesity, hypothyroidism, chronic inflammatory disease, and chronic kidney disease, were ruled out. The patient's lipid panel had been within the normal range prior to the IVF attempt. Abdominal ultrasonography revealed normal choledochal and intrahepatic bile ducts, pancreatic edema, peripancreatic fluid collection, and a diagnosis of pancreatitis. Computed tomography was not recommended due to the patient's pregnancy, and magnetic resonance cholangiopancreatography was not advised because she was in her first trimester. Echocardiography was performed to assess coronary artery disease due to the existing hyperlipidemia, revealing an ejection fraction of 60% and left ventricular hypertrophy.

Consultations were obtained from the fields of gastroenterology, gynecology, and endocrinology based on the current findings and complaints.

Due to the presence of pancreatitis, oral intake was discontinued, and the patient was managed with hydration. Tacrolimus and estradiol were discontinued based on the obstetrics and gynecology team's assessment that the pancreatitis was related to drug-induced hyperlipidemia. Apheresis for hyperlipidemia was not considered, as it could potentially result in fetal miscarriage. After discontinuation of tacrolimus and estradiol, the clinical signs of pancreatitis regressed, and amylase and lipase levels returned to normal on the fourth day. A combination of omega-3 fatty acids and fibrates was planned to address hyperlipidemia.

Table 1. Tacrolimus and estradiol treatment cessation-related biochemical parameter alteration.

Parameters:	Day 1	Day 2	Day 3	Day 4	Day 5
Amylase (28-100 U/L)	225	70	46	41	50
Lipase (13-60 U/L)	711	252	190	135	120
Triglyceride (40-160mg/L)	1228	990	989	856	611

DISCUSSION

In both the general population and pregnant women, the most common cause of pancreatitis is of biliary origin (8). Drug use and hypertriglyceridemia are other contributing factors. Tacrolimus, an estradiol and calcineurin inhibitor, has been increasingly used in recent years to enhance implantation success in pregnant women undergoing IVF. Studies have indicated that elevated blood tacrolimus concentrations in the early stages are associated with hyperlipidemia (9). Although the exact impact of tacrolimus on lipid metabolism is not fully understood, it may lead to hypertriglyceridemia through impaired triglyceride clearance due to reduced lipoprotein lipase biosynthesis (10). Additionally, it can elevate triglyceride levels by inducing insulin resistance through beta-cell dysfunction and disruptions in insulin signaling (10). Estrogen contributes to hypertriglyceridemia through various mechanisms. Research has shown that estrogen enhances the secretion of very low-density lipoprotein (VLDL) from the liver while reducing triglyceride catabolism by decreasing levels of hepatic lipase and lipoprotein lipase. Furthermore, in a study conducted on rats, estrogen-induced increase in pancreatic amylase enzyme levels had a direct toxic effect on pancreatic cells (11). In this case, pancreatitis resulted from hypertriglyceridemia, exacerbated by the combined effects of tacrolimus and estradiol, along with the physiologically elevated triglyceride levels during pregnancy. The pancreatitis resolved after discontinuation of both drugs, which were implicated in the etiology. In most cases of hypertriglyceridemia-induced. Acute pancreatitis, conservative management (nothing by mouth, intravenous fluid resuscitation and analgesia) is sufficient to achieve triglyceride levels less than 500 mg/dl. Intravenous insulin and plasmapheresis are sometimes

used, although prospective studies demonstrating clinical benefits, it is still commonly used. Pharmacological management of hypertriglyceridemia (HTG) should start early and target triglyceride levels of less than 500 mg/dL to reduce the risk of recurrent acute pancreatitis. In addition to the currently used fenofibrate and omega-3 fatty acids, several novel agents are being studied for the long-term treatment of HTG (12,13).

Conclusion

For individuals predisposed to hyperlipidemia, close monitoring of lipid profiles and symptoms that may arise due to complications is recommended. It should be noted that the concurrent use of drugs known to cause hyperlipidemia, such as tacrolimus and estradiol, may lead to serious complications such as acute pancreatitis.

Informed Consent: Written informed consent was obtained from the patient for the publication of the study

Conf ict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has no financial support.

REFERENCES

1. Montgomery WH, Miller FC. Pancreatitis and pregnancy. Obstet Gynecol. 1970;35(4):658-664.
2. Bahrami-Asl Z, Farzadi L, Fattahi A, Yousefi M, Quinonero A, Hakimi P, et al. Tacrolimus improves the implantation rate in patients with elevated Th1/2 helper cell ratio and repeated implantation failure (RIF). Geburtshilfe Frauenheilkd. 2020;80(8):851-862.
3. Florêncio RS, Meira MSB, Cunha MVD, Camarço MNCR, Castro EC, Finotti MCCF, et al. Plasmatic estradiol concentration in the mid-luteal phase is a good prognostic factor for clinical and ongoing pregnancies, during stimulated cycles of in vitro fertilization. JBRA Assist Reprod. 2018;22(1):8-14.
4. Sanada M, Tsuda M, Kodama I, Sakashita T, Nakagawa H, Ohama K. Substitution of transdermal estradiol during oral estrogen-progestin therapy in postmenopausal women: effects on hypertriglyceridemia. Menopause (New York, NY). 2004;11(3):331-336.
5. Tory R, Sachs-Barrable K, Goshko CB, Hill JS, Wasan KM. Tacrolimus-induced elevation in plasma triglyceride concentrations after administration to renal transplant patients is partially due to a decrease in lipoprotein lipase activity and plasma concentrations. Transplantation. 2009;88(1):62-68.
6. Gupta M, Liti B, Barrett C, Thompson PD, Fernandez AB. Prevention and management of hypertriglyceridemia-induced acute pancreatitis during pregnancy: A systematic review. Am J Med. 2022;135(6):709-714.
7. Simons-Linares CR, Elkhouly MA, Salazar MJ. Drug-induced acute pancreatitis in adults: An update. Pancreas. 2019;48(10):1263-1273.
8. Eddy JJ, Gideonsen MD, Song JY, Grobman WA, O'Halloran P. Pancreatitis in pregnancy. Obstet Gynecol. 2008;112(5):1075-1081.
9. Li HY, Li B, Wei YG, Yan LN, Wen TF, Zhao JC, et al. Higher tacrolimus blood concentration is related to hyperlipidemia in living donor liver transplantation recipients. Dig Dis Sci. 2012;57(1):204-209.
10. Liu XH, Chen H, Tan RY, Luo C. Acute pancreatitis due to tacrolimus in kidney transplant and review of the literature. J Clin Pharm Ther. 2021 Feb;46(1):230-235.
11. Aljenedil S, Hegele RA, Genest J, Awan Z. Estrogen-associated severe hypertriglyceridemia with pancreatitis. Journal of clinical lipidology. 2017;11(1):297-300.
12. Soares TS, Moraes-Souza RQ, Carneiro TB, Araujo-Silva VC, Schavinski AZ, Gratão TB, et al. Maternal-fetal outcomes of exercise applied in rats with mild hyperglycemia after embryonic implantation. Birth Defects Res. 2021;113(3):287-298.
13. Gligorijevic N, Stefanovic-Racic M, Kershaw EE. Medical management of hypertriglyceridemia in pancreatitis. Curr Opin Gastroenterol. 2023;39(5):421-427.