

## CASE REPORT

# Hypertriglyceridemia-induced pancreatitis after egg retrieval for in vitro fertilization and fenofibrate cessation

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**Funding information**

The authors received no funding for this project

**Abstract**

A 36-year-old woman with prior hypertriglyceridemia-induced pancreatitis presented with a recurrence of pancreatitis after beginning in vitro fertilization (IVF). Her primary care physician had discontinued fenofibrate due to concerns for teratogenicity. This case illustrates the importance of fibrate therapy for high-risk women undergoing IVF, despite limited evidence regarding its teratogenicity.

**KEYWORDS**

gastroenterology, medicine, obstetrics, pharmacology

## 1 | INTRODUCTION

Clinicians searching IBM's Micromedex database for information about the effects of fenofibrate in women who are pregnant or trying to conceive learn that available evidence is inconclusive for determining fetal risk.<sup>1</sup> UpToDate recommends that in pregnant women who are at risk for pancreatitis, the use of fenofibrate beginning in the second trimester may be considered but provides no guidance regarding its safety in the first trimester.<sup>2</sup> Therefore, primary care physicians may be tempted to stop prescribing fenofibrate to any patients who express a desire to become pregnant in the near future. However, the in vitro fertilization (IVF) process involves hormonal treatments that can affect triglyceride concentrations, so patients with known predisposition to hypertriglyceridemia require careful management when undergoing IVF. We present a case of hypertriglyceridemia-induced pancreatitis in a woman undergoing IVF after fenofibrate cessation was recommended by her primary care physician due to concerns for teratogenic sequelae.

## 2 | CASE HISTORY/EXAMINATION

A 36-year-old woman presented to the emergency department (ED) with one day of periumbilical abdominal pain radiating through to her back and loose stools. Her past medical history was notable for body mass index of 28.60 kg/m<sup>2</sup> and prior hypertriglyceridemia-induced pancreatitis 4 years prior, requiring hospitalization. She had no history of polycystic ovarian syndrome. At the time of her prior hospitalization, her triglycerides were greater than 4000 mg/dl (normal range 30–200 mg/dl). She was managed medically with insulin infusion and intravenous fluids without need for invasive procedures. She was started on fenofibrate and had no further flares. Her serum triglyceride levels remained consistently <100 mg/dl on annual outpatient testing performed over the next 4 years.

Sixteen months prior to this most recent episode of illness, her primary care physician discontinued her fenofibrate after she expressed intent to become pregnant.

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Her serum triglycerides at that time were 70 mg/dl. She stopped following up regularly with her primary care physician, in part due to the COVID-19 pandemic, so her serum triglycerides were not checked again after fenofibrate cessation. After a year of failing to conceive, she was diagnosed with infertility and began the IVF process. She took the oral contraceptive pill desogestrel and ethinyl estradiol 0.15 mg–0.03 mg tablet. She underwent transvaginal, ultrasound-guided oocyte aspiration without complications 2 weeks prior to this hospitalization that retrieved nine eggs. Three days prior to this admission, she was celebrating her sister's birthday and consumed over eight alcoholic beverages per day over the weekend as well as fried foods.

At baseline, she reported consuming alcohol once a week, usually no more than 3 drinks. She denied prior episodes of alcohol withdrawal, and she denied ever using tobacco or illicit drugs. She worked as a business developer for an advertisement agency. She had been married for 2 years and was monogamous with her male partner. Her menses began at age 13, and she had never been pregnant. She had no known family history of pancreatitis, pancreatic cancer, biliary disease, or autoimmune conditions. Her family history was significant for hypertriglyceridemia, a paternal aunt with Down syndrome and a maternal uncle with unprovoked deep vein thrombosis.

Once she developed abdominal pain, she suspected the recurrence of pancreatitis, so she took one fenofibrate 145 mg tablet from an old prescription along with a dose of bismuth subsalicylate. She reported taking no other medications, supplements, or minerals. Her symptoms worsened over the subsequent 24 h, prompting presentation to the ED. Her observation was notable for tachycardia at 130 beats per minute and blood pressure 156/112 mmHg, but other vitals within normal limits. She was tender to palpation peri-umbilically and in the right upper quadrant, but her examination was otherwise unremarkable. She had negative SARS-CoV-2 PCR tests from the day prior to her recent egg retrieval procedure and for this ED visit.

### 3 | INVESTIGATIONS, DIFFERENTIAL DIAGNOSIS, AND TREATMENT

Her initial differential diagnosis included diverticulitis, pancreatitis, cholecystitis, appendicitis, hepatitis, ovarian hyperstimulation syndrome (OHSS), and ovarian torsion. Pregnancy was unlikely given her known infertility and negative serum pregnancy test.

Her blood tests revealed leukocytosis with predominant neutrophilia, with a total white blood cell count of  $16.5 \times 1000/\mu\text{l}$  (normal range  $3.8\text{--}10.6 \times 1000/\mu\text{l}$ ), an

absolute neutrophil count (ANC) of  $13.6 \times 1000/\mu\text{l}$  (normal range  $1.8\text{--}7.3 \times 1000/\mu\text{l}$ ), 82.2% neutrophils (normal range 38.0–74.0%), hemoglobin 14.2 g/dl (normal range 11.9–16.0 g/dl), and platelet count  $275 \times 1000/\mu\text{l}$  (normal range  $140\text{--}446 \times 1000/\mu\text{l}$ ). Complete metabolic panel was unremarkable aside from sodium 133 mmol/L (normal range 136–145 mmol/L) and glucose 125 mg/dl with liver function tests including alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase all within normal limits. Hemoglobin A1c was 4.8% (normal range <5.7%), and urinalysis and thyroid stimulating hormone were both unremarkable. Two peripherally drawn blood cultures showed no growth after 5 days. Serum lactic acid was within normal limits. However, serum lipase was 1183 U/L (normal range 73–393 U/L), and her serum triglyceride level was 3,296 mg/dl (normal range 30–200 mg/dl) with total cholesterol 325 mg/dl (normal range 50–200 mg/dl) and direct low-density lipoprotein 57 mg/dl (normal range 0–130 mg/dl). C-reactive protein was 2.4 mg/dl (normal range 0.0–1.0 mg/dl), and lactate dehydrogenase was 205 U/L (35–190 U/L).

Computed tomography (CT) of the abdomen showed moderate peripancreatic fat stranding and fluid consistent with acute pancreatitis. Given the above workup and her clinical history, the likeliest etiology of the pancreatitis in this episode was secondary to hypertriglyceridemia, with multiple contributory factors. She was admitted to the intensive care unit and managed with intravenous hydration and an insulin drip. She responded well, so plasmapheresis was deferred. Within 4 days, she was discharged home on fenofibrate, with triglyceride level on the day of discharge 314 mg/dl.

### 4 | OUTCOME AND FOLLOW-UP

The patient was discharged home with instructions to follow up with maternal–fetal medicine (MFM) specialist and gastroenterology. One week after discharge, her triglyceride level had improved to 250 mg/dl on fenofibrate. The MFM specialist attributed her recent episode of pancreatitis to receiving IVF treatments and recommended the continuation of the fenofibrate, but the patient was reluctant due to concerns about teratogenicity. Gastroenterologists recommended magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) with secretin to rule out ductal etiology. Imaging revealed unremarkable appearance of the pancreas with normal appearance of the main pancreatic duct after secretin administration, but evidence of diffuse hepatic steatosis. Bloodwork found triglycerides 99 mg/dl, as well as normal amylase and lipase. MFM and gastroenterologists recommended to continue fenofibrate until

the patient became pregnant, at which time they would discontinue the medication during the first trimester of pregnancy with monthly triglyceride testing and nutrition follow-up. As yet, the patient has not achieved conception.

## 5 | DISCUSSION

There are several reported cases of hyperlipidemia during pregnancy causing pancreatitis, but there have been only six reported cases of IVF-induced hypertriglyceridemia.<sup>3-8</sup> Postulated mechanisms include oral estrogen therapies increasing hepatic triglyceride synthesis and its inhibitory effects on lipoprotein lipase. Estrogen therapy can cause latent effects ranging from 2 months to 2 years and may lower the threshold for developing severe hypertriglyceridemia in those with an underlying predisposition to dyslipidemia.<sup>9</sup> Among the six reported cases of IVF-related hypertriglyceridemia-induced pancreatitis, there have been suggestions of remote history of familial dyslipidemia or active hypertriglyceridemia in three cases, diabetes mellitus in four cases, or polycystic ovarian syndrome in two cases, all of which can cause secondary triglyceridemia. Similar to our case, the six patients all survived.<sup>3-8</sup>

Internists should be aware that obstetricians generally recommend the continuation of fibrate therapy in women at risk for severe hypertriglyceridemia who plan to become pregnant. In our case, there were several factors contributing to her exacerbation, including cessation of triglyceride-lowering therapy, initiation of IVF therapy with recent egg retrieval procedure, and recent dietary indiscretions. While concern exists about the potential teratogenicity of fenofibrate in the first trimester of pregnancy, these concerns must be balanced against potentially life-threatening complications of hypertriglyceridemia that are more likely to affect patients like ours who are undergoing IVF and also find it difficult to adhere to low-fat diet chronically. The mortality rate of pancreatitis secondary to hypertriglyceridemia (10%) is similar to the rate of pancreatitis attributed to other causes (8%).<sup>10</sup> This balancing act must continue even after the patient becomes pregnant as pancreatitis is associated with significant maternal and fetal morbidity and up to 24% of cases presenting in the first trimester.<sup>11</sup> Chibber and Gibson describe the case of a woman with familial hypertriglyceridemia and prior pancreatitis who discontinued all lipid-lowering medications upon becoming pregnant and later died from abdominal compartment syndrome due to severe triglyceride-induced pancreatitis in early pregnancy.<sup>12</sup> In addition to pancreatitis, hypertriglyceridemia can cause other severe complications including chylomicronemia syndrome, which is a hyperviscosity state that can cause

abdominal or neurologic symptoms.<sup>13</sup> In our case, the patient's care team elected to recommend continuation of fenofibrate until the patient became pregnant, with close monitoring off fenofibrate after conceiving, for the first trimester. The safest option for lipid-lowering therapy in a woman likely to become pregnant is omega-3 fatty acids, but the effect on triglycerides is modest and may not be sufficient in a woman with strong predisposition to hypertriglyceridemia.<sup>14</sup>

Another learning point from this case is the diagnostic consideration of OHSS when the patient presented for her most recent hospitalization. OHSS is a complication from IVF caused by cystic enlargement of the ovaries and third-space fluid shifts due to vascular changes.<sup>15</sup> Risk factors include polycystic ovarian syndrome, young age, and prior episodes of OHSS, and symptoms can include abdominal pain, nausea, vomiting, ascites, and dyspnea. The diagnosis is determined by imaging findings and clinical history that typically includes after ovarian stimulation followed by hCG injection. In our case, the patient's presentation was more consistent with pancreatitis, but OHSS should be on the differential diagnosis of any patient with similar history of abdominal pain after beginning IVF therapy.

In conclusion, this case and our review of the literature illustrate the unique management considerations of hypertriglyceridemia with secondary acute pancreatitis in the setting of IVF therapy. Our case is only the seventh published and illustrates the need to maintain lipid-lowering therapy until the patient becomes pregnant, as the process of becoming pregnant may take months, during which time the patient is vulnerable to complications from hypertriglyceridemia. Patient concern about teratogenicity is to be expected, so patient education and shared decision-making should be utilized to ensure patient adherence to recommended management with omega-3 fatty acids a viable if less effective option.

## AUTHOR CONTRIBUTION

Tushaar V. Shrimanker served as first author, reviewed all cited literature, wrote initial draft of discussion section, and made revisions to all sections for clarity, accuracy, and inclusion of additional intellectual content. Zachary Retalis served as second author, reviewed cited literature, wrote initial drafts of clinical summary sections, revised initial drafts of all sections, and acquired relevant clinical data. Khalil I. Hussein served as final author, was responsible for the initial design of this work, reviewed all cited literature, acquired relevant clinical data, wrote initial draft of introduction section, and revised drafts of all sections for important intellectual content.

## ACKNOWLEDGEMENTS

None.

## CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

## DATA AVAILABILITY STATEMENT

Data are not available due to privacy/ethical restrictions.

## ETHICAL APPROVAL

Our institutional review board (IRB) does not require that case reports be submitted for IRB approval.

## CONSENT

This study was published with the written consent of the patient.

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**How to cite this article:** Shrimanker TV, Retalis Z, Hussein KI. Hypertriglyceridemia-induced pancreatitis after egg retrieval for in vitro fertilization and fenofibrate cessation. *Clin Case Rep*. 2022;10:e05874. doi: [10.1002/ccr3.5874](https://doi.org/10.1002/ccr3.5874)